Editorials
Standardized care enhances patient safety and outcomes: evidence-based multidisciplinary clinical practice guidelines
Perioperative cardiovascular assessment for noncardiac surgery in elderly patients

Review Articles
Korean clinical practice guidelines for diagnostic and procedural sedation
Surgical phleth index monitoring in perioperative pain management: usefulness and limitations

Clinical Research Articles
European anesthesiologists’ experiences with gender-based mistreatment in the workplace: a secondary multilevel regression analysis
The SingHealth Perioperative and Anesthesia Subject Area Registry (PASAR), a large-scale perioperative data mart and registry
Perioperative adverse cardiac events and mortality after non-cardiac surgery: a multicenter study
Reduced side effects and improved pain management by continuous ketorolac infusion with patient-controlled fentanyl injection compared with single fentanyl administration in pelviscopic gynecologic surgery: a randomized, double-blind, controlled study

Effect of local anesthetic volume (20 vs. 40 ml) on the analgesic efficacy of costoclavicular block in arthroscopic shoulder surgery: a randomized controlled trial
Randomized controlled trial of the effect of general anesthetics on postoperative recovery after minimally invasive nephrectomy
Programmed intermittent epidural bolus as an ideal method for labor analgesia: a randomized controlled trial
Comparison of the effects of open and closed aspiration on end-expiratory lung volume in acute respiratory distress syndrome
Electroencephalographic spectrogram–guided total intravenous anesthesia using dexmedetomidine and propofol prevents unnecessary anesthetic dosing during craniotomy: a propensity score–matched analysis
Total postoperative opioid dose is an independent risk factor for prolonged postoperative ileus after laparoscopic colorectal surgery: a case-control study
Comparison of dexametomidine and opioids as local anesthetic adjuvants in patient controlled epidural analgesia: a meta-analysis

Experimental Research Article
Comparison of the median and intermediate approaches to the ultrasound-guided sacral erector spinae plane block: a cadaveric and radiologic study

Letters to the Editor
"Hana Pharm.,"
the manufacturer of
all kinds of anesthetic agents,
will be with you!
-Everlastung Partner-

Sevofran®
Liquid for Inhalation

- The first and only sevoflurane agent manufactured in Korea
- Economic choice for minimizing the burden of medical expenses for patients
- Fast recovery and clinical safety have been proved.

Hana Pharm. Co., Ltd.
www.hanaip.co.kr

Head Office
218, Teheran-ro, Gangnam-Gu, Seoul, Korea
Tel.: (02)577-7667 (Rep.) Fax.: (02)588-6403

Hapjeong Plant
T.S. Hapjeong-dong, Hapjeong-eup, Heeoeun-gu,
Gyeonggi-do, Korea
Tel.: (03)356-4511-4 Fax.: (03)356-5610

Gangneung Plant
J.S. Gangneung-dong 6, Uljung-eup, Hanseo-eup,
Gangneung-si, Gangwon-do, Korea
Tel.: (03)835-9680 Fax.: (03)835-2472
AceScope
VIDEO LARYNGOSCOPE with Touch Screen

Smart easy to use.
Convenient touch screen.
Disposable channeled blade.

Wireless charger
A Quantitative Monitor for Neuromuscular Blockade

Radically innovative. Ridiculously simple.

TECHNICAL SPECIFICATIONS

Electrode Array:
- Single-Patient Use
- Monitors adductor pollicis or first dorsal interosseous muscle

Stimulation:
- Current Range: 10-80 mA
- Pulse Width: 100µs, 200µs, or 300µs
- Frequency: 1Hz - 50Hz ±5%
- Sequences: Train-of-Four, Post-Tetanic Count, Single Twitch, Tetanus

Electromyography:
- Accuracy: ±5%
- Dynamic noise canceling

Battery:
- Type: Lithium Ion, Rechargeable
- Battery Life: At least 6 hours when fully charged

Safety and Efficacy Compliance:
- IEC60601-1, IEC60601-1-2, IEC60601-2-40 (EMG)

Blink Device Company is redefining ease-of-use, dependability and accuracy within the medical device industry. We develop technologies alongside clinicians to solve real clinical problems and enhance patient care. Our devices are practical, intuitive and cost-effective—allowing providers to focus on patient care, not the technology in-hand. Our company is headquartered in Seattle, Washington, and we make our products in the USA.

1530 Westlake Ave N # 600
Seattle, WA 98109
blinkdc.com
T: 206.708.6043
F: 973.215.8175

U.PiNE MED
566-55, Yeonnam-dong, Mapo-gu, Seoul, Korea
Tel : 02-3141-1836 Fax : 02-3143-2320
Does PONV still Remain unsolved?

Feel the difference with Ramosetron
Aims and Scope

The Korean Journal of Anesthesiology (Korean J Anesthesiol; KJA/ISSN: 2005-6419), an official journal of the Korean Society of Anesthesiologists, is an English-language, peer-reviewed journal that publishes articles in the fields of anesthesiology, critical care, and pain medicine. KJA aims to publish high-quality clinical and scientific materials on all aspects of anesthesiology, critical care, and pain medicine. Its regional focus is mainly Korea, but it also welcomes submissions from researchers all over the world.

In addition to publishing original articles, KJA features reviews, editorials, case reports, and letters to the editor. KJA also features statistical rounds to provide its readers with educational fundamentals and practical implications for clinical and experimental statistics. Additionally, KJA gladly publishes negative results, which will benefit clinical practice and promote further research activity.

The primary considerations for publication are clarity, uniqueness, and advancement in design, performance, and knowledge.

The journal has been partly supported by the Korean Federation of Science and Technology Societies. KJA is indexed/tracked/covered by SCIE (Science Citation Index Expanded), KCI (indexed by the National Research Foundation of Korea), PubMed, PubMed Central, EBSCOhost Databases, KoreaMed, KoMCI Web, KoreaMed Synapse, Science Central, SCOPUS, Embase, CAS (Chemical Abstracts Service), WPRIM (Western Pacific Regional Index Medicus), DOIs, DOAJ (Directory of Open Access Journal) and Google Scholar. It has been indexed in MEDLINE by U.S. National Library of Medicine.

Korean Journal of Anesthesiology Volume 77, Number 1, 1 February 2024

The circulation number per issue is 400.

© The Korean Society of Anesthesiologists, 2024
© It is identical to the ‘Creative Commons Attribution Non-Commercial License’
(http://creativecommons.org/licenses/by-nc/4.0/).

Contacting the KJA

All manuscripts must be submitted online through the KJA e-Submission system at http://www.editorialmanager.com/kja. Electronic files of the manuscript contents must be uploaded at the web site. Items pertaining to manuscripts submitted for publication, as well as letters or other forms of communication regarding the editorial management of KJA should be sent to:

Editor in Chief
Younsuk Lee, Young Lan Kwak

Publishing/Editorial Office
101-3503, Lotte Castle President, 109 Mapo-daero, Mapo-gu, Seoul 04146, Korea
Tel: +82-2-792-5128 Fax: +82-2-792-4089 Email: journal@anesthesia.or.kr/anesthesia@kams.or.kr

Printed by M2PI
#805, 26 Sangwon 1-gil, Seongdong-gu, Seoul 04779, Korea
Tel: +82-2-6966-4930 Fax: +82-2-6966-4945 Email: support@m2-pi.com

This work was supported by the Korean Federation of Science and Technology Societies (KOFST) grant funded by the Korean government.

© This paper meets the requirements of KS X ISO 9706, ISO 9706-1994 and ANSI/NISO Z39. 48-1992 (Permanence of paper)
Editorials

1 Standardized care enhances patient safety and outcomes: evidence-based multidisciplinary clinical practice guidelines
   Sangseok Lee

3 Perioperative cardiovascular assessment for noncardiac surgery in elderly patients
   Eunsoo Kim

Review Articles

5 Korean clinical practice guidelines for diagnostic and procedural sedation
   Sang-Hyun Kim, Young-Jin Moon, Min Suk Chae, Yea-Ji Lee, Myong-Hwan Karm, Eun-Young Joo, Jeong-Jin Min, Bon-Nyeo Koo, Jeong-Hyun Choi, Jin-Young Hwang, Yeonmi Yang, Min A Kwon, Hyun Jung Koh, Jong Yeop Kim, Sun Young Park, Hyunjlee Kim, Yang-Hoon Chung, Na Young Kim, Sang Uk Choi

31 Surgical pleth index monitoring in perioperative pain management: usefulness and limitations
   Seok Kyeong Oh, Young Ju Won, Byung Gun Lim

Clinical Research Articles

46 European anesthesiologists’ experiences with gender-based mistreatment in the workplace: a secondary multilevel regression analysis
   Joana Berger-Estilita, Luana Fritsche, Kariem El-Boghdadly, Claudia Camila Dias, Marko Zdravkovic

58 The SingHealth Perioperative and Anesthesia Subject Area Registry (PASAR), a large-scale perioperative data mart and registry
   Hairil Rizal Abdullah, Daniel Yan Zheng Lim, Yuhe Ke, Nur Nasyiah Mohamed Salim, Xiang Lan, Yizhi Dong, Mengling Feng

66 Perioperative adverse cardiac events and mortality after non-cardiac surgery: a multicenter study
   Byungjin Choi, Ah Ran Oh, Jungchan Park, Jong-Hwan Lee, Kwangmo Yang, Dong Yun Lee, Sang Youl Rhee, Sang-Soo Kang, Seung Do Lee, Sun Hack Lee, Chang Won Jeong, Bumhee Park, Soobeen Seol, Rae Woong Park, Seunghwa Lee

77 Reduced side effects and improved pain management by continuous ketorolac infusion with patient-controlled fentanyl injection compared with single fentanyl administration in pelviscopic gynecologic surgery: a randomized, double-blind, controlled study
   Inssan Park, Seukyoung Hong, Su Yoon Kim, Jung-Won Hwang, Sang-Hwan Do, Hyo-Seok Na

85 Effect of local anesthetic volume (20 vs. 40 ml) on the analgesic efficacy of costoclavicular block in arthroscopic shoulder surgery: a randomized controlled trial
   Yumin Jo, Cha hyun Oh, Woo-Yong Lee, Hyung-Jin Chang, Hammi Park, Juyeon Park, Jicoum Lee, Yoon-Hee Kim, Youngkwn Ko, Woosuk Chung, Boohwi Hong

95 Randomized controlled trial of the effect of general anesthetics on postoperative recovery after minimally invasive nephrectomy
   Hyun-Kyu Yoon, Somin Joo, Susie Yoon, Jeong-Hwa Seo, Won Ho Kim, Ho-Jin Lee

106 Programmed intermittent epidural bolus as an ideal method for labor analgesia: a randomized controlled trial
    Doyeon Kim, Jeayoun Kim, Hyeonju Choo, Duck Hwan Choi

115 Comparison of the effects of open and closed aspiration on end-expiratory lung volume in acute respiratory distress syndrome
   Süleyman Yıldırım, Saba Mukaddes Saygı, Onur Süneçli, Cenk Kirakli

122 Electroencephalographic spectrogram–guided total intravenous anesthesia using dexmedetomidine and propofol prevents unnecessary anesthetic dosing during craniotomy: a propensity score–matched analysis
   Feng-Sheng Lin, Po-Yuan Shih, Chao-Hsien Sung, Wei-Han Chou, Chun-Yu Wu
Total postoperative opioid dose is an independent risk factor for prolonged postoperative ileus after laparoscopic colorectal surgery: a case-control study

Hui Ju, Kai Shen, Jiaxin Li, Yi Feng

Comparison of dexmedetomidine and opioids as local anesthetic adjuvants in patient controlled epidural analgesia: a meta-analysis

Yafen Gao, Zhixian Chen, Yu Huang, Shujun Sun, Dong Yang

Experimental Research Article

Comparison of the median and intermediate approaches to the ultrasound-guided sacral erector spinae plane block: a cadaveric and radiologic study

Bilge Olgun Keleş, Necati Salman, Elvân Tekir Yılmaz, Habil Resul Birinci, Alparslan Apan, Selami İnce, Ali Faruk Özçaşar, Aysun Uz

Letters to the Editor

Comment on "Single-shot regional anesthesia for laparoscopic cholecystectomies: a systematic review and network meta-analysis" Raghuraman M Sethuraman

Han scale and difficult facemask ventilation: time to add an "R"? David Lopez-Lopez, Adrián García-Romar, Patricia Neira-Somoza, Pablo Casas-Reza, Rocío Mato-Bua

Serratus posterior superior intercostal plane block: novel block for minimal invasive cardiac surgery - A report of three cases- Bora Bilal, Bahadir Ciftci, Selcuk Alver, Ali Ahiskaloglu, Serkan Tulgar

Comment on "The novel diagonal suprascapular canal block for shoulder surgery analgesia: a comprehensive technical report" Raghuraman M Sethuraman

Response to "Comment on The novel diagonal suprascapular canal block for shoulder surgery analgesia: a comprehensive technical report" Carlos Rodrigues Almeida

Lipophilicity of drugs, including local anesthetics, and its association with lipid emulsion resuscitation Susanne K Wiedmer, Ju-Tae Sohn

ⓒ The Korean Society of Anesthesiologists, 2024
한편 안전하고 효과적인 진정을 위한 진정 임상진료지침

Sang-Hyun Kim, Young-Jin Moon, Min Suk Chae, Yea-Ji Lee, Myong-Hwan Karm, Eun-Young Joo, Jeong-Min, Bon-Nyeo Koo, Jeong-Hyun Choi, Jin-Young Hwang, Yeonmi Yang, Min A Kwon, Hyun Jung Koh, Jong Yeop Kim, Sun Young Park, Hyunjee Kim, Yang-Hoon Chung, Na Young Kim, Sung Uk Choi

Department of Anesthesiology and Pain Medicine, Soonchunhyang University Bucheon Hospital, Soonchunhyang University College of Medicine, Bucheon, Asan Medical Center, University of Ulsan College of Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Konkuk University Medical Center, Department of Dental Anesthesiology, School of Dentistry and Dental Research Institute, Seoul National University, Department of Anesthesiology and Pain Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Anesthesiology and Pain Research Institute, Yonsei University College of Medicine, Kyung Hee University College of Medicine, SMG-SNU Boramae Medical Center, Seoul National University College of Medicine, Seoul, Department of Pediatric Dentistry, Jeonbuk National University School of Dentistry, Jeonju, Department of Anesthesiology and Pain Medicine, Dankook University Hospital, Cheonan, Ajou University School of Medicine, Suwon, Soonchunhyang University Seoul Hospital, Soonchunhyang University College of Medicine, Seoul, Kyungpook National University School of Medicine, Daegu, Korea University College of Medicine, Seoul, Korea

한편 안전하고 효과적인 진정은 진정제의 선택, 진정 기법, 진정 제공자의 경험, 진정 관련 교육 및 수련의 수준, 적절한 장비와 의료인력, 환자의 기저질환 및 시행되는 시술의 종류 등과 같은 다양한 요인에 영향을 받는다. 본 근거기반 다학제적 임상진료지침의 목적은 진정시행의 안전성과 효능을 담보함으로써 환자의 안전에 기여하고 궁극적으로는 공공보건을 개선하는 데 있다. 본 임상진료지침은 진정 제공자, 사용가능한 약물 및 장비, 적절한 환자 선택, 고위험 환자에 대한 마취과 전문의 의뢰, 진정 전 급식, 성인과 소아 환자에게 사용되는 대표 진정약물의 비교, 진정 중 호흡기계, 심혈관계 및 진정깊이 모니터링, 소아 환자의 진정 중 호흡기 합병증 관리 및 적절한 퇴원 기준과 같은 다양한 주제를 포함하는 15개의 핵심 문항으로 구성된다.

본 임상진료지침의 권고 내용들은 검사 및 시술에 대한 진정 임상진료지침, 심혈관계 및 진정깊이 모니터링, 소아 환자의 진정 중 호흡기 합병증 관리 및 적절한 퇴원 기준과 같은 다양한 주제를 포함하는 15개의 핵심 문항으로 구성된다. 본 임상진료지침의 권고 내용들은 검사 및 시술에 대한 진정 임상진료지침, 심혈관계 및 진정깊이 모니터링, 소아 환자의 진정 중 호흡기 합병증 관리 및 적절한 퇴원 기준과 같은 다양한 주제를 포함하는 15개의 핵심 문항으로 구성된다.

한편 안전하고 효과적인 진정은 진정제의 선택, 진정 기법, 진정 제공자의 경험, 진정 관련 교육 및 수련의 수준, 적절한 장비와 의료인력, 환자의 기저질환 및 시행되는 시술의 종류 등과 같은 다양한 요인에 영향을 받는다. 본 근거기반 다학제적 임상진료지침의 목적은 진정시행의 안전성과 효능을 담보함으로써 환자의 안전에 기여하고 궁극적으로는 공공보건을 개선하는 데 있다. 본 임상진료지침은 진정 제공자, 사용가능한 약물 및 장비, 적절한 환자 선택, 고위험 환자에 대한 마취과 전문의 의뢰, 진정 전 급식, 성인과 소아 환자에게 사용되는 대표 진정약물의 비교, 진정 중 호흡기계, 심혈관계 및 진정깊이 모니터링, 소아 환자의 진정 중 호흡기 합병증 관리 및 적절한 퇴원 기준과 같은 다양한 주제를 포함하는 15개의 핵심 문항으로 구성된다. 본 임상진료지침의 권고 내용들은 진정제의 선택, 진정 기법, 진정 제공자의 경험, 진정 관련 교육 및 수련의 수준, 적절한 장비와 의료인력, 환자의 기저질환 및 시행되는 시술의 종류 등과 같은 다양한 요인에 영향을 받는다. 본 근거기반 다학제적 임상진료지침의 목적은 진정시행의 안전성과 효능을 담보함으로써 환자의 안전에 기여하고 궁극적으로는 공공보건을 개선하는 데 있다. 본 임상진료지침은 진정 제공자, 사용가능한 약물 및 장비, 적절한 환자 선택, 고위험 환자에 대한 마취과 전문의 의뢰, 진정 전 급식, 성인과 소아 환자에게 사용되는 대표 진정약물의 비교, 진정 중 호흡기계, 심혈관계 및 진정깊이 모니터링, 소아 환자의 진정 중 호흡기 합병증 관리 및 적절한 퇴원 기준과 같은 다양한 주제를 포함하는 15개의 핵심 문항으로 구성된다.
Surgical pleth index monitoring in perioperative pain management: usefulness and limitations

Seok Kyeong Oh†, Young Ju Won†, Byung Gun Lim

Department of Anesthesiology and Pain Medicine, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Korea

Received: March 2, 2023
Revised: March 16, 2023
Accepted: March 16, 2023

Corresponding author:
Byung Gun Lim, M.D., Ph.D.
Department of Anesthesiology and Pain Medicine, Korea University Guro Hospital, Korea University College of Medicine, 148 Gurodong-ro, Guro-gu, Seoul 08308, Korea
Tel: +82-2-2626-3231
Fax: +82-2-2626-1438
Email: bglim9205@korea.ac.kr
ORCID: https://orcid.org/0000-0002-3302-1831

†Seok Kyeong Oh and Young Ju Won have contributed equally to this work as first authors.

Keywords: Analgesia; Autonomic nervous system; General anesthesia; Intraoperative monitoring; Nociception test; Pain measurement; Photoplethysmography.
European anesthesiologists’ experiences with gender-based mistreatment in the workplace: a secondary multilevel regression analysis

Joana Berger-Estilita,1,2,3 Luana Fritsche,4 Kariem El-Boghdady,5 Claudia Camila Dias3,6 Marko Zdravkovic7,8

1Institute of Anesthesiology and Intensive Care, Salemspital, Hirslanden Medical Group, Bern, Switzerland, 2Institute for Medical Education, University of Bern, Bern, Switzerland, 3CINTESIS@RISE, Center for Health Technology and Services Research, Faculty of Medicine, University of Porto, Porto, Portugal, 4Medical Faculty, University of Bern, Bern, Switzerland, 5Department of Anesthesia, Guy’s and St Thomas’ NHS Foundation Trust, London, UK, 6Knowledge Management Unit and Department of Community Medicine, Information and Health Decision Sciences (MEDCIDS), Faculty of Medicine of the University of Porto (FMUP), Alameda Prof. Hernâni Monteiro, Porto, Portugal, 7Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia, 8Department of Anesthesiology, Intensive Care and Pain Management, University Medical Center Maribor, Maribor, Slovenia

배경: 직장에서의 성 차별적인 학대(gender-based mistreatment, GBM)는 직원을 향한 부정적이거나 해로운 행동을 가리킨다. 의료 환경에서는 이로 인해 직무 불만족 및 업무 성과 저하로 이어질 수 있으며, 환자 결과에 잠재적으로 영향을 미칠 수 있다. 본 연구의 목표는 유럽 마취의사들 사이에서 직장에서의 GBM을 조사하고 유럽 마취학에서의 성 차별적 학대 순위를 작성하는 것이다.

방법: 우리는 직장 태도와 관련된 항목 중 하나로 성 차별적 편견을 탐구하는 46개 항목 설문 조사 데이터베이스의 이차 분석을 수행했다. 설문 조사 완료율은 80.8%였다. 모든 응답자는 유럽 국가에서 선정되었다. 학대와 나머지 변수 간의 관련성은 일변량 및 다변량 로지스틱 회귀 분석을 사용하여 분석되었다. 이후 일반화된 선혼합 모델을 사용하여 각 유럽 국가에서 학대의 영향을 양적으로 측정했다. 통계적 유의성은 \( P < 0.05 \)로 설정되었다.

결과: 본 연구에는 43개의 유럽 국가에서 5,795명의 응답자가 포함되었다. GBM의 독립 예측 변수는 다음과 같다: 여성 성별, 나이가 어린 경우, 리더십에서 성별을 불이익으로 인식하고 연구에서 성별을 불이익으로 인식하는 것이, 전체 모델은 통계적으로 유의하며, GBM을 경험한 사람과 그렇지 않은 사람을 구별할 수 있는 능력을 나타낸다(\( P < 0.001 \)). 따라서 26개의 유럽 국가가 학대의 유발된 발생률을 기반으로 순위가 배경되었으며, 이탈리아가 가장 우수한 성적(가장 낮은 발생률)을 보였다.

결론: 본 연구의 목표는 유럽 마취학자의 GBM에 대한 초기 통찰력을 제공하고 성평등에 대한 주요 기준 역할을 하며, 시간이 지남에 따른 병변들의 진화를 기록하는 것이었다.

Keywords: Anesthesiology; Gender bias; Gender equity; Occupational stress; Perceived discrimination; Sexism; Working conditions; Workplace violence.
The SingHealth Perioperative and Anesthesia Subject Area Registry (PASAR), a large-scale perioperative data mart and registry

Hairil Rizal Abdullah¹,², Daniel Yan Zheng Lim²,³,*, Yuhe Ke¹, Nur Nasyitah Mohamed Salim⁴, Xiang Lan⁵, Yizhi Dong⁵, Mengling Feng⁵

¹Department of Anesthesiology, Singapore General Hospital, ²Duke-NUS Medical School, ³Department of Gastroenterology, Singapore General Hospital, ⁴Health Services Research Unit, Singapore General Hospital, ⁵Saw Swee Hock School of Public Health and Institute of Data Science, National University of Singapore, Singapore

Keywords: Anesthesia; Big data; Data science; Intraoperative care; Perioperative care; Postoperative care; Preoperative care; Statistical data interpretation.

배경: 수술 전후 결과를 개선하기 위해 수술 전후 기간 동안 고품질의 실제 데이터를 통합하는 수술 전후 등록체계 마련이 필수적이다. 싱가포르 종합병원(SGH)은 수술 전, 중, 후의 단계에서 자료를 통합하고자 주술기 마취과 부문 등록체계(Perioperative and Anesthesia Subject Area Registry, PASAR)를 구축하였다. 이 연구에서는 이 데이터베이스를 구축하는 데 사용된 방법론을 소개한다.


결과: 2022년 12월 현재, PASAR는 153,312건의 환자 입원과 168,977건의 수술 진수를 포함하는 26개의 데이터lox 구성되어 있다. 이 기간 동안 환자의 연령의 중위수는 60.0세이고 성별 분포는 균형을 이루었으며, 대다수가 중국인이다. 고혈압과 심혈관계 동반 질환이 많았다. 수술 유형과 시간, 중환자실(ICU) 입원 기간, 30일 및 1년 사망률 등의 정보를 수집했다. 수술 및 수술은 선택수술보다 중환자실 체류기간이 길었지만 수술시간은 더 짧았다.

결론: PASAR는 수술기 환자들에 대한 고품질의 자료를 수집할 수 있는 포괄적이고도 자동화된 접근 방식을 제공한다.
Perioperative adverse cardiac events and mortality after non-cardiac surgery: a multicenter study

Byungjin Choi¹,², Ah Ran Oh¹,²,³, Jungchan Park¹,², Jong-Hwan Lee², Kwangmo Yang⁴,⁵, Dong Yun Lee⁶, Sang Youl Rhee⁷, Sang-Soo Kang⁸, Seung Do Lee⁷, Sun Hack Lee⁸, Chang Won Jeong⁹, Bumhee Park¹,¹⁰, Soobeen Seol¹, Rae Woong Park¹,², Seunghwa Lee¹

¹Department of Biomedical Sciences, Ajou University Graduate School of Medicine, Suwon, ²Department of Anesthesiology and Pain Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, ³Department of Anesthesiology and Pain Medicine, Kangwon National University Hospital, Chuncheon, ⁴Center for Health Promotion, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, ⁵Department of Endocrinology and Metabolism, Kyung Hee University School of Medicine, Seoul, ⁶Department of Anesthesiology and Pain Medicine, Kangdong Sacred Heart Hospital, Seoul, ⁷Division of Cardiology, Department of Internal Medicine, Gyeongsang National University Hospital, Jinju, ⁸Division of Cardiology, Department of Internal Medicine, Pusan National University Hospital, Busan, ⁹Central Research Center of Biomedical Research Institute, Wonkwang University Hospital, Iksan, ¹⁰Office of Biostatistics, Medical Research Collaborating Center, Ajou Research Institute for Innovative Medicine, Ajou University Medical Center, Suwon, ¹¹Department of Cardiology, Wiltse Memorial Hospital, Suwon, Korea

Keywords: Cardiac arrhythmias; Cardiovascular diseases; Embolism; General surgery; Mortality; Myocardial infarction.
배경: 마약성 진통제 관련 부작용을 최소화하기 위해 마약성 진통제와 보조 약물들을 병용하여 정맥 주입 환자 자가조절 진통제 (patient-controlled analgesia, PCA)로써 사용할 수 있다. 부인과 골반경 수술에서 이중 챔버 PCA를 통해 두 가지 진통제를 따로 투여하는 것이 단일 펜타닐 PCA를 사용하는 것보다 진통 효과는 충분하면서도 부작용은 더 적은지를 조사하였다.

방법: 본 전향적, 이중맹검, 무작위 배정, 대조군 시험에는 골반경 부인과 수술을 받은 68명의 환자가 포함되었다. 환자들은 병용투여 그룹(케토롤락과 펜타닐을 두 개의 챔버 PCA로 투여) 또는 단일(펜타닐 단독) 투여그룹에 배정되었다. 두 그룹에 대하여 수술 후 2시간, 6시간, 12시간, 24시간 후의 수술 후 오심과 구토 (PONV) 및 진통의 질을 비교하였다.

결과: 병용투여 그룹은 수술 후 2~6시간 (p = 0.011) 및 6~12시간 (p = 0.009) 동안 PONV 발생률이 유의하게 낮게 나타났다. 최종적으로, 병용 그룹에서는 2명(5.7%)의 환자가, 단일 그룹에서는 18명(54.5%)의 환자가 수술 후 24시간 동안 PONV를 경험하였고, 정맥 PCA를 유지할 수 없었다 (odd ratio: 0.056, 95% CI [0.007~0.229], P < 0.001). 단일투여 그룹보다 병용투여 그룹이 수술 후 24시간 동안 만성 PONV를 보였으며, 펜타닐을 투여한 환자들은 더 적게 투여하였음에도 불구하고 (66.0 ± 77.8 µg vs. 383.6 ± 70.1 µg, P < 0.001) 수술 후 통증은 그룹간에 유의한 차이가 없었다.

결론: 골반경 수술을 받는 부인과 환자를 대상으로 두 가지 진통제인 이중 챔버 정맥주사를 통해 케토롤락과 펜타닐을 부작용으로 투여하고 간헐적으로 펜타닐을 투여한 결과, 기존의 펜타닐 정맥주사와 비교하여 진통 효과는 충분하고 부작용이 더 적었다.

Keywords: Analgesia; Fentanyl; Ketorolac; Patient-controlled analgesia; Postoperative nausea and vomiting; Postoperative pain.
Effect of local anesthetic volume (20 vs. 40 ml) on the analgesic efficacy of costoclavicular block in arthroscopic shoulder surgery: a randomized controlled trial

Yumin Jo1,*, Chahyun Oh1,*, Woo-Yong Lee2, Hyung-Jin Chung2, Hanmi Park1, Juyeon Park1, Jieun Lee1, Yoon-Hee Kim1, Youngkwon Ko1,3, Woosuk Chung1, Boohwi Hong1,3

Departments of 1Anesthesiology and Pain Medicine, 2Orthopedic Surgery, Chungnam National University Hospital, Chungnam National University College of Medicine, 3Biomedical Research Institute, Chungnam National University Hospital, Daejeon, Korea

배경: 횡격막을 보존할 수 있는 다양한 횡격막 차단 방법 중 늑쇄골 차단술(costoclavicular block, CCB)은 관절경 어깨 수술에서 반횡격막 마비(hemidiaphragmatic paresis, HDP) 발생률은 낮지만, 진통 효과는 일관되지 않은 것으로 보고되었다. CCB에 대한 더 높은 용량의 국소 마취제를 사용하면 쇄골 상부에 퍼짐으로써 충분한 진통효과를 얻을 수 있다는 가설을 세웠다.

방법: 관절경 회전근개 수술이 예정된 환자 60명을 대상으로 두 가지 용량의 국소 마취제(CCB20, 0.75% 로피바카인 20 ml; CCB40, 0.375% 로피바카인 40 ml) 중 하나에 무작위 배정하여 CCB를 시행하였다. 일차평가변수는 수술 후 1시간이 지났을 때의 완전 진통 비율(통증 수치 평가 척도에서 0점)이었다. 이차평가변수는 수술 후 24시간 이내에 국소 마취제 확산에 대한 초음파 평가, 횡격막 기능, 폐 기능, 수술 후 마약성 진통제 사용 및 기타 통증 관련 경험 등이었다.

결과: 두 그룹의 완전 진통 비율의 차이는 유의하지 않았다(CCB20 및 CCB40 두 그룹에서 각각 23.3% [7/30] 및 33.3% [10/30]; 위험 차이 10%, 95% CI [-13, 32], P = 0.567). 기타 통증관련 평가변수에서도 유의한 차이가 없었다. 평가한 임상인자들 중 수술 후 통증과 유의한 연관성을 보인 인자는 초음파로 관찰한 쇄골 상부 확산 여부가 유일하였다. HDP 발생률 및 페기능 변화에 있어서 두 그룹 사이에 유의한 차이가 없는 않았다.

결론: 국소 마취제 40 ml를 사용하는 것이 쇄골 상부 확산을 보장하지 못한다. 또한, 관절경 어깨 수술에 있어서 국소 마취제 20 ml를 사용한 것과 비교하여 완전 진통 비율도 더 높게 나타나지 않았다.

Keywords: Analgesia; Arthroscopy; Brachial plexus block; Nerve block; Regional anesthesia; Shoulder.
Randomized controlled trial of the effect of general anesthetics on postoperative recovery after minimally invasive nephrectomy

Hyun-Kyu Yoon1,2, Somin Joo1, Susie Yoon1,2, Jeong-Hwa Seo1,2, Won Ho Kim1,2, Ho-Jin Lee1,2

Department of Anesthesiology and Pain Medicine, 1Seoul National University Hospital, 2Seoul National University College of Medicine, Seoul, Korea

Background: Various kinds of systemic and regional anesthetic techniques have been evaluated to improve the perioperative outcomes of patients undergoing surgery. However, the optimal technique for patients undergoing minimally invasive surgery remains to be determined. In this study, we compared the effects of total intravenous anesthesia (TIVA) and desflurane (DES) on the recovery period after surgery.

Methods: This was a prospective, randomized controlled trial involving 150 patients who were randomly assigned to receive DES or TIVA. Postoperative recovery was evaluated using the Korean version of the Quality of Recovery (QoR-15K) score at 24, 48, and 72 hours postoperatively. The general estimating equation (GEE) was used to analyze the differences in the QoR-15K score between the two groups. Other outcomes such as the use of pentazocine, pain intensity, nausea and vomiting, and discharge status 3 weeks after surgery were also compared.

Results: The data from 70 patients in each group were analyzed. The TIVA group showed significantly higher QoR-15K scores than the DES group at 24 and 48 hours postoperatively (P = 0.029; 0.022, respectively). However, there were no significant differences at 72 hours (P = 0.400). The GEE analysis indicated that DES was associated with a significantly lower QoR-15K score compared to TIVA (P = 0.037). There were no significant differences in the use of pentazocine, pain intensity, nausea and vomiting, or discharge status among the two groups.

Conclusion: TIVA is associated with a superior recovery outcome compared to DES after surgery. This finding suggests that TIVA could be a better choice for patients undergoing minimally invasive surgery.

Keywords: Enhanced recovery after surgery; General anesthetics; Inhalation anesthesia; Intravenous anesthesia; Perioperative medicine; Postoperative period.
Programmed intermittent epidural bolus as an ideal method for labor analgesia: a randomized controlled trial

Doyeon Kim¹, Jeayoun Kim², Hyeonju Choo³, Duck Hwan Choi⁴

Department of Anesthesiology and Pain Medicine, ¹CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, ²Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, ³Inha University Hospital, Inha University School of Medicine, Incheon, ⁴Dongtan Sacred Heart Hospital, Hallym University School of Medicine, Hwaseong, Korea

배경: 프로그램된 간헐적 경막 외 주입(PIEB)이 분만 진통에 이상적인 방법이지만, 적절한 주입 유속은 아직 밝혀지지 않았다. 그러므로, 우리는 여러 다른 경막 외 주입 유속에 따른 진통 효과를 조사하였다.

방법: 본 무작위 대조시험에는 자연분만이 예정된 미출산 여성들을 등록하였다. 참가자들에게 0.2% 로피바카인 3 mg과 펜타닐 20 μg를 경막 내 주입한 후, 세 개의 시험군으로 무작위 배정하였다. 환자 자가조절 경막 외 진통제(PCEA) 1시간 동안 10 ml을 다음과 같이 투여하였다. (0.2% 로피바카인 60 ml, 펜타닐 180 μg, 0.9% 생리식염수 40 ml): 연속(n = 28, 연속 주입시 10 ml/h), PIEB (n = 29, 10 ml의 정맥 주입시 240 ml/h) 또는 수동 주입시(n = 28, 10 ml의 정맥 주입시 1,200 ml/h). 일차점가 변수는 시간당 경막 외 진통제 두여량이었다. 분만 진통과 첫 돌발 통증 사이의 시간 간격을 조사하였다.

결과: 경막외 마취제의 시간당 사용량 중앙값[사분위수 범위]은 그룹 간에 유의미한 차이가 있었다(연속 주입: 14.3 [8.2] ml; PIEB: 9.4 [3.6] ml; 및 수동 주입: 10.0 [2.3] ml; P < 0.001). PIEB 그룹의 동반 통증까지의 시간은 다른 그룹보다 길었다(연속주입: 149.2 min; PIEB: 200.0 [35.3] min; 및 수동 주입: 60.5 [124.7] min, P = 0.027).

결론: 유속이 느린 PIEB는 연속적인 경막외 주입이나 유속이 빠른 수동 주입보다 분만 진통 효과가 더 적절하였다.

Keywords: Analgesia; Anesthesia; Injections; Obstetrics; Pain; Pregnancy.
Comparison of the effects of open and closed aspiration on end-expiratory lung volume in acute respiratory distress syndrome

Süleyman Yildirim¹, Saba Mukaddes Saygili¹, Onur Süneçli², Cenk Kirakli¹

¹Intensive Care Unit, ²Department of Physiotherapy, University of Health Sciences Turkey, İzmir School of Medicine, Dr. Suat Seren Chest Disease and Surgery Training and Research Hospital, İzmir, Turkey

배경: 급성호흡곤란증후군(acute respiratory distress syndrome, ARDS) 환자에서는 폐포 허탈이 쉽게 일어난다. 기관 내 흡인은 호기말 폐용적(end-expiratory lung volume, EELV) 감소로 폐포 허탈을 증가시킬 수 있다. 본 연구에서는 ARDS 환자를 대상으로 개방형 흡인과 폐쇄형 흡인 후 EELV 손실량을 비교하고자 하였다.

방법: 본 무작위배정 교차 연구는 비침습적 기계환기를 받고 있는 20명의 ARDS 환자를 대상으로 진행하였다. 개방형 흡인과 폐쇄형 흡인은 무작위로 진행하였다. 폐 임피던스는 전기 임피던스 단층 촬영을 사용하여 측정하였다. 흡인 후와 흡인 후 1분, 10분, 20분, 30분 후 호기말 폐 임피던스의 변화를 이용하여 EELV 변화량을 평가하였으며, 동맥혈 가스 분석과 호흡기계통의 고원압(Pplat), 구동압(Pdrive), 순응도(CRS)와 같은 환기 매개변수도 기록하였다.

결과: 개방형 흡인보다 폐쇄형 흡인 후 용적 손실이 더 적었다(평균 ΔEELV: –2661 ± 1937 vs. –4415 ± 2363; 평균 차이: –1753; 95% CI [-2662, –844]; P = 0.001). 폐쇄형 흡인의 경우 흡인 후 10분에 EELV가 회복된 반면, 개방형 흡인의 경우 30분이 지나도 회복되지 않았다. 폐쇄형 흡인 후 Pplat 및 Pdrive는 감소한 반면 CRS는 증가하였다. 반대로, 개방형 흡인 후에는 Pplat 및 Pdrive는 감소하고 CRS는 감소하였다.

결론: 기관 내 흡인은 EELV 손실로 인한 폐포 허탈을 초래할 수 있다. 폐쇄형 흡인은 환기 매개변수의 악화 없이 호기말 용적 손실이 적다는 점에서 ARDS 환자는 개방형 흡인보다는 폐쇄형 흡인을 시행하는 것이 좋다.

Keywords: Critical care; Electric impedance; Lung volume measurements; Positive-pressure respiration; Respiratory distress syndrome; Suction.
배경: 텍스메데토미딘 투여시 이중분광지수(BIS)를 이용한 마취 심도의 평가의 신뢰도가 낮다. 반면, 뇌파 전위(EEG) 스펙트로그램은 마취제에 대한 뇌의 반응을 바로 시각적으로 확인할 수 있기 때문에 마취 심도를 더 적절히 평가함으로써 불필요한 마취제의 사용을 예방할 가능성이 있다.

방법: 본 연구는 프로포폴과 덱스메데토미딘이 이용한 전정맥 마취 하 정규 개두술을 받은 성인 환자 140명을 후향적으로 분석하였다. 환자들은 나이와 수술 유형에 따른 성향 점수를 기준으로 스펙트로그램 그룹(수술 중 강력한 EEG 알파 신호 유지) 또는 인덱스 그룹(수술 중 BIS 점수 40–60점 유지)으로 동일하게 매칭되었다. 본 연구의 1차 평가 변수는 프로포폴의 전체 사용 용량이었으며, 2차 평가 변수는 수술 후 환자의 신경학적 프로파일었다.

결과: 스펙트로그램 그룹의 환자들에서 프로포폴의 사용량이 유의하게 적었다(1585 ± 581 vs. 2314 ± 810 mg, P < 0.001). 또한, 스펙트로그램 그룹에서 각성 지연 환자가 더 적었다(1.4% vs. 11.4%, P = 0.033). 수술 후 성망 프로파일은 두 그룹 간에 다소 차이가 있었다(프로포폴, P = 0.227) 스펙트로그램 그룹 환자들의 입원 중 바벨 지수 점수가 더 우수했다(입원 시: 83.6 ± 27.6 vs. 91.6 ± 17.1; 퇴원 시: 86.4 ± 24.3 vs. 85.1 ± 21.5; 근심시 시간 간 상호작용 P = 0.008). 그러나 수술 후 신경학적 합병 증후군 발생률은 두 그룹간 차이가 없었다.

결론: 정규 개두술을 받는 환자들에게 정맥 백 마취를 시행 시 뇌파 전위 스펙트로그램 모니터링을 통해 불필요한 마취제 사용을 줄일 수 있을 것이다. 그러나 아니라 각성 지연을 방지하고 수술 후 바벨 지수 점수를 개선할 가능성도 있다.

Keywords: Anesthesia adjuvants; Bispectral index monitor; Consciousness monitors; Craniotherapy; Dexmedetomidine; Electroencephalography; Intravenous anesthesia.
Total postoperative opioid dose is an independent risk factor for prolonged postoperative ileus after laparoscopic colorectal surgery: a case-control study

Hui Ju¹, Kai Shen², Jiaxin Li¹, Yi Feng¹

Departments of¹ Anesthesiology, ²Gastroenterologic Surgery, Peking University People's Hospital, Beijing, China

배경: 수술 후 장기간의 장폐색(prolonged post-operative ileus, PPOI)은 대장결장 수술의 주요 합병증이다. 마약성 진통제 사용량 증가는 PPOI의 위험을 증가시키는 것으로 알려져 있다. 이 연구의 목적은 수술 후 총 마약성 진통제 사용량(total postoperative opioid dose, TPOD)의 증가는 PPOI의 발생률 증가와 관련이 있다는 가설을 검증하기 위한 것이다.

방법: 이 환자-대조군 짝짓기 연구는 2018년 1월부터 2020년 6월까지 북경대학교 인민병원에서 정규 복강경 대장결장 수술을 받은 환자들을 후향적으로 자료를 수집하였다. PPOI 환자는 장폐색증 그룹에 배정하고, PPOI가 없는 환자(대조군)는 연령, 미국마취과학회 신체상태 분류점수(ASA class), 수술 유형에 따라 장폐색증 그룹과 1:1 비율로 매칭을 시행하였다. 일차 평가변수는 장폐색증군과 대조군 사이의 TPOD였다. 이차 평가변수는 PPOI의 위험인자였다.

결과: 총 267명의 환자가 최종 분석에 포함되었다. 환자 인구통계학적(demographic data) 데이터나 수술인자에 있어서 두 군간의 차이는 없었다. TPOD, 수술 후 1일차(POD1)의 수선타릴 정맥 투여량, 정맥내 자가통증조절법(patient-controlled analgesia, PCA) 사용은 PPOI와 관련이 있었다(OR < 0.05). 다변량 로지스틱 회귀 분석에서는 TPOD 증가는 복강경 대장결장 수술 후 PPOI 발생의 독립적인 위험 인자임을 확인하였다(OR: 1.67, 95% CI [1.03–2.71], P = 0.04).

결론: TPOD는 복강경 대장결장 수술 후 PPOI 발생의 독립적인 위험 인자이다. TPOD를 줄이기 위해 수술 후 진통제에 대한 새로운 전략을 모색해야 한다.

Keywords: Case-control studies; Colorectal surgery; Ileus; Nerve block; Opioid-induced constipation; Postoperative pain.
Comparison of dexmedetomidine and opioids as local anesthetic adjuvants in patient controlled epidural analgesia: a meta-analysis

Yafen Gao††, Zhixian Chen‡‡, Yu Huang§§, Shujun Sun††, Dong Yang‡‡,††

†Department of Anesthesiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, ‡Department of Pathology, Block T, Queen Mary Hospital, Hong Kong, §Department of Urology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, †Department of Pain, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Background: In the past, patient-controlled epidural analgesia (PCEA) has been used as a local anesthetic adjuvant for postoperative pain management. However, the use of dexmedetomidine (DEX), a short-acting and non-sedating adjuvant, has been investigated for its potential role in reducing opioid consumption and improving pain control in the postoperative period.

Methods: A systematic review and meta-analysis were conducted to compare the efficacy and safety of DEX and opioids as local anesthetic adjuvants in PCEA. Literature searches were performed in PubMed, Embase, Cochrane Library, and China Biology Medicine databases until December 2022.

Results: A total of 636 patients were included in the analysis, and the results showed that patients receiving DEX had lower postoperative pain scores (VAS) and less opioid consumption compared to those receiving opioids alone. The incidence of nausea and vomiting was also lower in the DEX group.

Conclusion: The use of dexmedetomidine as a local anesthetic adjuvant in PCEA can effectively reduce postoperative pain and opioid use, and may decrease the incidence of nausea and vomiting. Further studies are needed to confirm these findings and explore the optimal dosing and administration methods.

Keywords: Conduction anesthesia; Dexmedetomidine; Meta-analysis; Opioid analgesics; Patient-controlled epidural analgesia; Postoperative pain; Regional anesthesia.
Comparison of the median and intermediate approaches to the ultrasound-guided sacral erector spinae plane block: a cadaveric and radiologic study

Bilge Olgun Keleş¹, Necati Salman², Elvan Tekir Yılmaz¹, Habip Resul Birinci¹, Alparslan Apan¹, Selami İnce³, Ali Faruk Özyaşar⁴, Aysun Uz⁵

*¹Department of Anesthesiology and Reanimation, Giresun University Faculty of Medicine, Giresun, ²Department of Anatomy, University of Health Sciences Türkiye, Gülhane Faculty of Medicine, Ankara, ³Department of Radiology, Beytepe Murat Erdi Eker State Hospital, Ankara, ⁴Department of Anatomy, Karadeniz Technical University Faculty of Medicine, Trabzon, ⁵Department of Anatomy, Ankara University Faculty of Medicine, Ankara, Turkey

**Keywords**: Cadaver; Conduction anesthesia; Dissection; Nerve block; Pain management; Regional anesthesia; Sacrococcygeal region.

Background: The use of ultrasound-guided sacral erector spinae plane block (ESPB) for postoperative pain management is well established, with sacral ESPB (sacral ESPB, SESPB) often being used in this setting. The current study aimed to compare the diffusion of the mixture of local anesthetic solutions following application using ultrasound-guided SESPB in cadavers using radiological methods.

Methods: Four cadavers were studied, with the median and intermediate approach used to inject the mixture of radiopaque and dye solutions. CT imaging was used to verify the solution distribution, followed by dissection to visualize the distribution.

Results: In the median approach, the radiopaque solution was seen in the perineurial space of S1 and S5, with a spread to the transverse process of the sacrum. In the intermediate approach, the radiopaque solution was seen in the erector spinae muscle plane of L2 and S3, with no anterior spread. Dissection showed that the dye was present in the subcutaneous tissues in the median approach, with no spreading to the superficial tissues.

Conclusion: Both approaches resulted in the presence of the mixture in the erector spinae plane, with anterior spread only seen in the intermediate approach. This study provides valuable information for the optimal use of ultrasound-guided sacral erector spinae plane block.

Keywords: Cadaver; Conduction anesthesia; Dissection; Nerve block; Pain management; Regional anesthesia; Sacrococcygeal region.
The safety and effectiveness of diagnostic and procedural sedation are influenced by various factors, including patient characteristics (e.g., age, comorbidities, obesity, obstructive sleep apnea, and American Society of Anesthesiologists [ASA] classification), procedural aspects (type, duration, and setting), and sedation-related factors (choice of sedatives, dosage, provider’s expertise, and monitoring). The risks increase with extremes in age, the presence of multiple health issues, and longer and more invasive procedures. Additionally, method of administration are also critical. Effective monitoring and adherence to guidelines are thus essential for minimizing complications.

Standardized guidelines are necessary in clinical practice as they play a major role in improving the quality and efficiency of patient care, maintaining consistency among healthcare professionals, and enhancing patient safety. Standardized guidelines reflecting the latest research and best clinical practices aid in improving care and patient outcomes. Healthcare providers who adhere to these standardized procedures and guidelines can maintain consistency in medical practice and optimize their workflow. Utilizing these guidelines enables the effective management and treatment of patients and can reduce medical costs. Compliance with evidence-based standardized guidelines also offers better legal protection for healthcare professionals. Additionally, the development and maintenance of these guidelines present opportunities for new research and improvements.

Several studies have emphasized the importance of clinical practice guidelines for procedural sedation. The 2002 guidelines published by the ASA Task Force on Sedation and Analgesia by Non-Anesthesiologists provide clinical guidance on the use of sedation and analgesics by non-anesthesiologists [1]. The 2018 guidelines on moderate procedural sedation and analgesia, which included a multidisciplinary team, offer recommendations for sedation management in specific clinical situations and patient groups [2].

In this issue of the Korean Journal of Anesthesiology, the Korean Clinical Practice Guidelines presented by Kim et al. [3] are noteworthy for several reasons. First, these guidelines focus on the Korean healthcare system and practices and were developed using a multidisciplinary approach that reflects various specialties and emphasizes the importance of a multidisciplinary approach in managing sedation in various clinical situations. Second, the authors recognize the reality that sedation is performed by non-anesthesiologists in Korea and thus provide specific guidelines for this target group. Additionally, as these are recent guidelines, they include guidance on the latest drugs being used in clinical settings, which may differ from guidelines available in other countries. Finally, these guidelines also pay greater attention to sedation management in pediatric patients compared with other guidelines.
However, interpreted in another way, the fact that these guidelines reflect the reality of Korean society means that they may not be directly applicable to other medical environments, especially where drug usage, medical infrastructure, and legal/regulatory environments vary. Although providing guidance on the increasing use of sedation by non-anesthesiologists is crucial, a clear delineation of the roles and expertise of anesthesiologists is still necessary.

Guidelines should be based on the best available evidence; however, research on certain sedation-related topics can be limited, particularly for new drugs or technologies for which long-term efficacy and safety data are limited. These guidelines adopt a modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assigning evidence levels and recommendation grades [4]. When the research available was insufficient for evidence assessment, surveys of expert opinions of sedation providers were conducted. Final recommendations were determined through two rounds of committee voting, user feedback surveys, and external expert reviews.

Several limitations necessitate caution in the application and interpretation of these guidelines in clinical practice. However, the validity of these guidelines can be maintained through continuous reviews and updates, and their applicability in various clinical settings must be considered.

Funding

None.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

References

Perioperative cardiovascular assessment for noncardiac surgery in elderly patients

Eunsoo Kim

Department of Anesthesia and Pain Medicine, Pusan National University School of Medicine, Biomedical Research Institute, Pusan National University Hospital, Busan, Korea

Population aging refers to the increase in the proportion of elderly individuals in a population resulting from longer life expectancy and declining fertility and tends to characterize upper-middle and high-income countries, such as Organization for Economic Cooperation and Development (OECD) member countries. Statistics Korea reported that 18.4% of the total population was elderly (aged > 65 years) in 2023 [1]. If this trend continues, the elderly population will constitute over 20% of the population and Korea will become a super-aged society by 2025. The number of surgeries performed on elderly individuals continues to rise as the population ages. As the elderly population has age-related organ reserve decline and various medical comorbidities, surgery can provide a conclusive approach to treating several diseases related to aging. Although symptom relief and life extension are undeniable benefits of surgery, the risk of postoperative complications is more remarkable for the elderly than for the young [2].

Over 300 million people undergo major surgery annually, 85% of which undergo noncardiac surgery (NCS) [3]. Elderly patients are more vulnerable to perioperative adverse cardiac events (PACEs) and major adverse cardiac events, such as myocardial infarction or injury, cardiac arrest, or congestive heart failure, are firmly associated with perioperative death [4]. Adverse cardiac events can also result in significant complications, prolonged hospital stays, and increased medical costs [5]. In a national cohort of the United States, cardiovascular risk factors (e.g., hypertension, dyslipidemia, diabetes mellitus, obesity, and chronic kidney disease) and atherosclerotic cardiovascular disease (CVD), including coronary artery disease, peripheral artery disease, and prior stroke, increased over time among surgical patients undergoing major NCS [6]. However, the incidence of perioperative major adverse cardiovascular and cerebrovascular events declined from 3.1% to 2.6% in the same national cohort database [7]. These results suggest that the surgical population is getting older and sicker over time and that advancements in cardiovascular medicine, surgical techniques, and anesthetic management during the perioperative period are related to the decline in fatal cardiac events and mortality.

The current issue of the Korean Journal of Anesthesiology includes a nationwide multicenter retrospective cohort study conducted by Choi et al. [8] that uses Common Data Model data from seven tertiary hospitals and demonstrates an association between PACEs, defined as a composite of heart failure, arrhythmic attack, acute pulmonary embolism, cardiac arrest, myocardial infarction, coronary revascularization, or stroke within 30 days of surgery, and mortality after NCS. This study showed that the overall incidence of PACEs was 2.88% and PACEs were associated with increased 1-year and 3-year mortality. After 1:4 propensity score matching, the mortality rate was higher in the PACE group at the 1-year (6.0% vs. 4.4%; hazard ratio [HR]: 1.33, 95% CI [1.10, 1.60], P =
0.005) and 3-year (8.6% vs. 7.3%; HR: 1.18, 95% CI [1.01, 1.38], P = 0.038) follow-ups. The subgroup analyses of patient demographics and comorbidity showed that statistically significant risks were present in the older age group, emergency surgery group, and high surgical risk group. The event-specific analysis also revealed that all PACEs except stroke (HR: 1.22, 95% CI [0.90, 1.64], P = 0.194) were substantially linked to a higher risk of mortality. PACEs include not only major adverse cardiac events but also arrhythmic attacks, which are common and have previously been considered minor events. Thus, PACEs may offer a more precise assessment of the overall risk of cardiac events after NCS and may be an acceptable composite outcome for future clinical research.

The incidence of adverse cardiovascular events after NCS is influenced by both the surgical risk and patient-related risk factors, such as advanced age, CVD, or other risk factors (e.g., smoking, hypertension, diabetes, dyslipidemia, family disposition), and other existing medical conditions. For elderly patients, frailty, a frequent and critical geriatric condition defined by age-related reductions in multiorgan system physiologic reserve and function, increases the risk of adverse outcomes after surgery. European guidelines on cardiovascular assessments for NCS have been revised to include the recommendation that all patients aged ≥ 65 should undergo a heart examination before undergoing intermediate- or high-risk NCS [9]. For patients with established CVD or risk factors for CVD (including aged ≥ 65 years) or those presenting symptoms or signs indicating CVD (newly detected cardiac murmur, chest pain, dyspnea, or peripheral edema), the European guidelines recommend that a preoperative 12-lead electrocardiogram be obtained and high-sensitivity cardiac troponin levels be measured before and at 24 h and 48 h after intermediate- or high-risk NCS. The guidelines also provide a comprehensive set of recommendations for patients to mitigate the risk of cardiovascular problems before and after surgery. Prior to surgery, the application of risk reduction strategies, including smoking cessation, as well as the management of conditions such as hypertension, dyslipidemia, and diabetes are recommended. To minimize perioperative morbidity and mortality, conducting an individualized preoperative assessment and implementing general risk-reduction strategies are essential.

Funding

None.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

References

1. 2023 Statistics on senior citizens [Internet]. Daejeon: Statistics Korea; 2023 [modified 2023 Sep 26; cited 2024 Jan 15]. Available from https://kostat.go.kr/synap/skin/doc.html?fn = 96c9a9b9ef-5f5578593837e7726b3db8e096b08d647ce92139bd644198165 a738rs = /synap/preview/board/10820/
Safe and effective sedation depends on various factors, such as the choice of sedatives, sedation techniques used, experience of the sedation provider, degree of sedation-related education and training, equipment and healthcare worker availability, the patient’s underlying diseases, and the procedure being performed. The purpose of these evidence-based multidisciplinary clinical practice guidelines is to ensure the safety and efficacy of sedation, thereby contributing to patient safety and ultimately improving public health. These clinical practice guidelines comprise 15 key questions covering various topics related to the following: the sedation providers; medications and equipment available; appropriate patient selection; anesthesiologist referrals for high-risk patients; pre-sedation fasting; comparison of representative drugs used in adult and pediatric patients; respiratory system, cardiovascular system, and sedation depth monitoring during sedation; management of respiratory complications during pediatric sedation; and discharge criteria. The recommendations in these clinical practice guidelines were systematically developed to assist providers and patients in sedation-related decision making for diagnostic and therapeutic examinations or procedures. Depending on the characteristics of primary, secondary, and tertiary care institutions as well as the clinical needs and limitations, sedation providers at each medical institution may choose to apply the recommendations as they are, modify them appropriately, or reject them completely.

Keywords: Anesthesiologist; Capnography; Clinical practice guideline; Fasting; Patient monitoring; Procedural sedation; Recovery.
Introduction

Purpose, levels, and continuity of sedation

The purpose of sedation is to reduce or minimize patient discomfort, anxiety, fear, and pain associated with diagnostic tests or therapeutic procedures, thereby allowing scheduled examinations and treatments to be safely and effectively performed. Sedation is classified into four levels according to the patient's response to verbal commands or pain-inducing stimuli, adequacy of airway maintenance and spontaneous ventilation, and maintenance of cardiovascular function as follows: mild/minimal sedation, moderate sedation, deep sedation, and general anesthesia (Table 1).

Diagnostic and therapeutic examinations and procedures are often performed under moderate sedation. Although sedation is classified into distinct and independent stages, it is a continuum, meaning patients can transition rapidly between deeper and lighter levels in the clinical setting. Additionally, accurate prediction of an individual patient's response to a sedative is not always possible.

If a deeper level of sedation or a state of general anesthesia beyond the intended moderate sedation level is reached, the risk of cardiovascular or respiratory depression increases. Therefore, sedation providers must promptly identify and intervene to prevent serious risks and adverse events such as hypoxic brain damage, cardiac arrest, or death [1].

Conversely, insufficient sedation can lead to patient discomfort and injury, difficulties in performing scheduled procedures owing to a lack of patient cooperation, and adverse physiological or psychological reactions caused by stress. Sedation providers must respond appropriately based on the level of sedation achieved instead of the level of sedation attempted.

Safe and effective sedation depends on factors such as the choice of sedatives, sedation techniques used, experience of the sedation provider, degree of sedation-related education and training, equipment and healthcare worker availability at the healthcare institutions (primary, secondary, and tertiary care institutions) where sedation is performed, the patient's underlying diseases, appropriate patient selection, and specific requirements and limitations of the procedure being performed.

Current status and problems associated with sedation in Korea

During examinations and procedures for diagnostic and therapeutic purposes, sedation is increasingly performed not only by anesthesiologists but also by non-anesthesiologist sedation providers from various clinical specialties. According to data from the Healthcare Big Data Hub (https://opendata.hira.or.kr/home.do), the number of prescriptions for monitored anesthesia care increased from 60,000 in 2017 to 90,000 in 2020. The absolute number of endoscopy procedures performed under sedation increased from 860,000 in 2017 to 1.57 million in 2020, and the rate of increase was even higher for sedative endoscopy procedures. As the use of sedation per year increases, the risk of adverse effects from inadequately performed sedation and, though rare, of serious complications will increase. When sedation (such as moderate sedation) is performed by non-anesthesiologists, special attention must be paid to patient safety for the following reasons.

First, sedation is predominantly performed in settings outside the operating room, such as wards; outpatient departments; or emergency, computed tomography, magnetic resonance imaging, electroencephalography (EEG), ultrasound examination, endoscopy,

| Table 1. Definitions of Sedation Levels and Continuity of Sedation Depth |
|-------------------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Responsiveness | Normal response to verbal commands | Purposeful* response to verbal or tactile stimulation | Purposeful* response following repeated or painful stimulation | Unarousable, even with painful stimulus |
| Airway | Unaffected | No intervention required | Intervention may be required | Intervention often required |
| Spontaneous ventilation | Unaffected | Adequate | May be inadequate | Frequently inadequate |
| Cardiovascular function | Unaffected | Usually maintained | Usually maintained | May be impaired |

or interventional procedure rooms, where sufficient patient monitoring devices, emergency equipment, medications, and personnel may not be as readily available as in the operating room where anesthesia professionals familiar with patient monitoring are present. Second, the quality of sedation and patient safety can vary significantly according to the systematic education and training required of the sedation providers, their experience with sedation procedures, and their degree of involvement in sedation.

An analysis of medical disputes related to anesthesia between July 2009 and June 2014 in Korea revealed that sedation accounted for 37.1% of the total cases. In sedation-related dispute cases, the majority of procedures were performed by the responsible physician administering sedation (92.3%), with insufficient attention during sedation (69.2%), failure to perform a preoperative evaluation for sedation (82.1%), absence of sedation records (89.7%), and inadequate monitoring during procedures (15.4%). The main causes of permanent damage and fatalities were respiratory events, such as hypoxemia resulting from airway obstruction or respiratory depression [2].

Preventable factors such as inadequate patient monitoring have been identified as causes of serious harm to patients undergoing procedures under sedation. Ideally, procedures conducted under sedation should be performed at a separate facility equipped with appropriate monitoring devices and emergency medications and equipment, with a dedicated healthcare team (physicians/nurses) that continuously monitors the patient’s condition.

**Background for the development of sedation guidelines**

One method of providing safe and effective sedation in clinical practice is the development of sedation-related practice guidelines. Several organizations have developed domestic clinical guidelines. The Korean Society of Anesthesiologists developed the Practice Guidelines for Propofol Sedation by Non-anesthesiologists in 2016 [3] and the Pediatric Sedation Guidelines (Korean) in 2017. In 2012, the Korean Society of Emergency Medicine developed the Korean Guidelines for Pediatric Procedural Sedation and Analgesia (Korean) [4]. In addition, the Korean Academy of Dental Science developed the Clinical Practice Guidelines for Dental Sedation for General Practitioners (Korean) in 2015. However, officially recognized evidence-based multidisciplinary clinical practice guidelines for sedation have not been developed in South Korea. The Korean Society of Anesthesiologists, therefore, recognized the need to develop evidence-based multidisciplinary clinical practice guidelines for sedation performed by anesthesiologists and non-anesthesiologists.

To encourage the participation of stakeholders involved in sedation, the Korean Society of Anesthesiologists proposed the development of evidence-based multidisciplinary clinical practice guidelines for sedation to representative academic societies, such as the Korean Association of Internal Medicine, Korean Society of Radiology, Korean Academy of Dental Science, Korean Society of Plastic and Reconstructive Surgeons, Korean Ophthalmological Society, and Korean Pediatric Society. On August 12, 2019, members of these societies and the Clinical Practice Guidelines Committee of the Korean Society of Anesthesiologists discussed the direction of the development of multidisciplinary clinical practice guidelines.

Consequently, under the leadership of the Korean Society of Anesthesiologists, the Korean Academy of Dental Science, Korean Society of Radiology, and Korean Ophthalmological Society participated in the development process, while the remaining societies were involved in external expert reviews after the guidelines were drafted. This laid the foundation for the development of these multidisciplinary clinical practice guidelines.

**Purpose and scope of these clinical practice guidelines**

**Purpose**

The purpose of these clinical practice guidelines is to provide multidisciplinary evidence-based recommendations that assist both anesthesia providers specializing in moderate sedation and non-anesthesia providers in decision making to provide safe and effective moderate sedation to patients at medical institutions (primary, secondary, or tertiary). This is achieved by offering clear levels of evidence and a balanced risk-benefit analysis of each topic. Information on patients’ values and preferences are also included in these guidelines to assist providers with decision-making for effective sedation. However, before applying individual recommendations, sedation providers should exercise their judgment based on the specific circumstances of their medical institutions. Additionally, this study aims to provide information to providers on the benefits of performing safe sedation while minimizing anxiety and pain during diagnostic testing or procedures. Finally, these guidelines aim to enhance patients’ and healthcare policy experts’ understanding of sedation practices. Therefore, the proposed guidelines are not mandatory. Depending on the characteristics of primary, secondary, and tertiary care institutions as well as the clinical needs and limitations, sedation providers at each medical institution may choose to apply the recommendations as they are, modify them appropriately, or reject them. These guidelines are also not intended to replace the current sedation-related policies at each medical institution.
Intended users
The expected users of these clinical practice guidelines include sedation providers in primary, secondary, and tertiary care institutions who provide moderate sedation (as defined in Table 1) for diagnostic and therapeutic examinations or procedures (including outpatient and inpatient procedures); patients who receive sedation; and policy experts.

Target populations covered
These clinical practice guidelines are intended to target adult and pediatric patients undergoing moderate sedation for diagnostic or therapeutic examinations or procedures (including outpatient and inpatient procedures). According to the age guidelines of the Korean Pediatric Society, pediatric patients are individuals aged < 19 years, excluding newborns.

Scope
These guidelines focus on moderate sedation before, during, and after diagnostic and therapeutic examinations or procedures. As the risk of transitioning from moderate to deep sedation varies depending on the medications used and individual patient characteristics, guidelines on monitoring for and managing complications that may arise from deep sedation, such as cardiovascular and respiratory depression, are included. These clinical practice guidelines comprise 15 key questions covering various topics related to the following: the sedation providers (including their education); medications and equipment available, appropriate patient selection; anesthesiologist referrals for high-risk patients; pre-sedation fasting; comparison of representative drugs used in adult and pediatric patients; respiratory system, cardiovascular system, and sedation depth monitoring during sedation; management of respiratory complications during pediatric sedation; and discharge criteria. These guidelines do not cover topics such as pre-medication before general anesthesia, local anesthesia during sedation, sedation without accompanying diagnostic or therapeutic procedures, or minimal sedation. These guidelines also do not address general anesthesia.

Determining the level of evidence and grade of recommendation
A modified Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach was adopted to assign the level of evidence and grade of recommendation [5]. The levels of evidence are listed in Tables 2 and 3 presents the grades of recommendation based on several rounds of discussion. When the current research available was insufficient to evaluate the level of evidence, experts’ opinion surveys of sedation providers were collected (261 respondents). Final version of recommendation was confirmed by two-rounds voting of the committee, user opinion survey (120 respondents) and 5 external experts’ review.

<table>
<thead>
<tr>
<th>Table 2. Levels of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level of evidence</strong></td>
</tr>
<tr>
<td>High</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Low</td>
</tr>
<tr>
<td>Very low</td>
</tr>
<tr>
<td>Expert consensus/survey</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 3. Grades of Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade</strong></td>
</tr>
<tr>
<td>General use</td>
</tr>
<tr>
<td>Elective use</td>
</tr>
<tr>
<td>Limited use</td>
</tr>
<tr>
<td>Limited</td>
</tr>
</tbody>
</table>
Guidelines

Key Question 1. Does periodic formal training of sedation providers improve patient safety?

Recommendation: Sedation providers are recommended to undergo periodic formal training regarding sedation to ensure patient safety.

Recommendation level: Elective use (Do, conditional)

Level of evidence: Expert consensus/survey

Background: A systematic approach to education, supervision, and credentialing can facilitate safe practice of sedation [6]. However, individual healthcare institutions and departments have implemented their own education and training procedures, with variability in the quantity and quality of education and training among individual sedation providers. Therefore, the need for sedation providers to have access to periodic, comprehensive, and systematic education and training for safe and efficient sedation administration is increasing [7].

Evidence summary: Relevant research on whether regular education for sedation providers improves patient safety is lacking. This may be due to the ethical issue of administering sedation without conducting education rather than due to the need for the research itself. As the current research available was insufficient to evaluate the level of evidence, expert opinion surveys of sedation providers were collected. Recommendations were based on the survey results, and the level of evidence was evaluated using expert consensus surveys.

To ensure that patients undergoing procedures experience no distress and that an appropriate level of sedation is achieved without limitations, sedation providers must have sufficient knowledge and training. A significant majority of the respondents to the expert opinion survey agreed (strongly agreed: 76.6%, agreed: 20.7%) that sedation management conducted by appropriately trained sedation providers who have received adequate education can reduce the occurrence of complications and improve effective sedation and pain management, thus enhancing patient safety. The opinion that regular sedation education for sedation providers is feasible in the domestic medical setting was supported by the majority of respondents (strongly agreed: 15.7%, agreed: 41.8%). Regarding the frequency of sedation education for sedation providers, the most common opinion was a two-year cycle (41%), followed by a three-year cycle (28.7%), a cycle of five years or more (12.3%), and a cycle of less than one year (11.9%). Periodic sedation-related education on the characteristics of patients receiving sedation and essential techniques, medications, and monitoring systems is expected to improve providers’ capacity to achieve and maintain appropriate and safe sedation in patient care and treatment settings.

During the decision-making process for recommendations, most members (88.2%) of the attending committee expressed support for the recommended direction in terms of periodic sedation-related regular education recommendations, and all attending members (100%) supported the recommended levels. According to the review by external experts, 80% of them expressed support for the recommendations (strongly agree 40%; agree 40%), and in the user survey, 89.2% expressed support for the recommendations.

Key Question 2. Does performing sedation procedures in a standardized environment appropriately equipped with medications and devices necessary for sedation help to effectively manage sedation and pain and reduce complications?

Recommendation: When administering sedation, a standardized environment equipped with the minimum medications and devices necessary for sedation is recommended for proper management of the patient and to reduce the incidence of complications due to sedation.

Recommendation level: General use (Do, strong)

Level of evidence: Expert consensus/survey

Background: In healthcare settings, the demand for procedures performed outside the operating room is increasing, leading to a growing interest in and demand for sedation and pain management. Sedation and analgesia are sometimes administered by the physicians performing the procedure rather than anesthesiologists. To ensure patient safety, sedation should be performed in an easily accessible and standardized environment with the necessary medications and devices available [8]. The American Society of Anesthesiologists (ASA) also emphasizes the highest level of quality regarding the structural aspects of drug storage and administration and occupational safety during sedation performed in healthcare settings outside the operating room [9].

Evidence summary: No research is currently available on whether providing sedation in an environment equipped with the necessary medications and equipment improves patient safety. Owing to insufficient research to conduct an evidence-based assessment, an expert opinion survey was distributed to experts in sedation-related fields and the results were compiled. Recommendations were made based on the survey results, and the final level of evidence was evaluated through an expert consensus survey.

With the increase in demand for sedation performed outside the operating room (e.g., outpatient or clinical settings), the need
for adequate monitoring of vital signs and management of side effects, complications, and emergency situations outside the operating room has increased. The importance of preventing side effects and complications during sedation is also emphasized. According to the expert survey results, the majority of respondents agreed (strongly agreed: 75.5%, agreed: 22.2%) that performing sedation in an environment equipped with the necessary medications and equipment is effective for managing sedation and pain management and reducing complications. Therefore, providing a consistent working environment for sedation providers that is at least minimally equipped with essential emergency and airway-related equipment and medications is expected to allow for appropriate monitoring of vital signs as well as improve providers’ capacity to handle emergency situations, minimize side effects, and prevent or reduce complications. The minimal essential equipment and drugs necessary for sedation are listed in Table 4.

Therefore, providers are recommended to perform sedation in an environment with appropriate medications and equipment to ensure patient safety. By consistently administering sedation in a systematic work environment equipped with the necessary medication and equipment, proficiency with managing sedation-related situations can be improved, leading to more effective management and prevention of sedation-related side effects and complications.

Table 4. List of Equipment for a Standardized Sedation Environment

<table>
<thead>
<tr>
<th>Airway supplies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supplemental oxygen with regulators (minimum of 2 sources)</td>
</tr>
<tr>
<td>Nasal cannula and face mask</td>
</tr>
<tr>
<td>Oral airways</td>
</tr>
<tr>
<td>Ambu bag</td>
</tr>
<tr>
<td>Laryngoscope (Macintosh and Miller; various sizes)</td>
</tr>
<tr>
<td>Endotracheal tubes and stylets</td>
</tr>
<tr>
<td>Supraglottic airway devices (laryngeal mask airway)</td>
</tr>
<tr>
<td>GlideScope</td>
</tr>
<tr>
<td>Suction equipment to include tubing, catheters, and Yankauer suctions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Additional emergency equipment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compression board</td>
</tr>
<tr>
<td>Tracheostomy/Cricothyrotomy kit</td>
</tr>
<tr>
<td>Charged cardiac defibrillator</td>
</tr>
<tr>
<td>ACLS drugs</td>
</tr>
<tr>
<td>Malignant hyperthermia supplies to include dantrolene 20%</td>
</tr>
<tr>
<td>Lipid emulsion for local anesthetic systemic toxicity</td>
</tr>
<tr>
<td>Emergency power source</td>
</tr>
</tbody>
</table>

At a minimum, the sedation environment should be equipped with oxygen supply, suction, and emergency equipment (including CPR) and ACLS drugs. Detailed equipment and drugs for sedation environment can be optionally provided by referring to the table above. ACLS: advanced cardiac life support.

If a separate space can feasibly be allocated for sedation it should be equipped with the minimal medications and equipment necessary for sedation, and procedures are recommended to be performed under sedation in that space. However, if providing a separate space is not feasible owing to the conditions of the medical institution, providers are recommended to equip the area where the procedure is to be performed with the medications and equipment necessary for sedation to establish a minimal and systematic working environment.

More than 70% of the attending committee members supported the recommendation levels and directions, and there were no dissenting opinions regarding the content of the recommendations. According to the results of the public hearing, the approval rate for the recommended directions was 81.3%, and the approval rate for the recommendation levels was 76.5%. The external experts’ review also showed an approval rate of 80%.

Key Question 3. Do criteria need to be established for selecting eligible patients for moderate sedation?

**Recommendation:** Sedation providers are recommended to establish criteria for selecting eligible patients for moderate sedation based on the environment of each healthcare institution and to implement sedation accordingly.

**Recommendation level:** General use (Do, strong)

**Level of evidence:** Expert consensus/survey

**Background:** Although moderate sedation can be administered to any patient, it is safest for healthy patients. Healthy patients are classified as having an ASA status of I or II in the physical status classification system. Patients are classified as having an ASA status of I or II if they meet the following criteria: no serious behavioral problems, no severe gastrointestinal reflux, or no upper respiratory tract infections; no anticipated difficult airway; and no allergy to the administered drug. Previous studies have assessed moderate sedation in patients with an ASA status of I or II [10–15]. However, sedation must be performed carefully in elderly, and obese, and pregnant patients [12,15]. Adverse effects, including unintended deep sedation, hypotension, and hypoxia, have been reported in patients who are older or obese; those with an ASA status of III or higher, with airway problems (e.g., sleep apnea and respiratory distress syndrome), with cardiovascular risks, with allergies, or with difficulty cooperating such as pediatric patients; those receiving psychiatric medications (including benzodiazepines); and those with a history of gastric bypass surgery (Table 5) [1,16–23].

**Evidence summary:** Few studies have directly compared the benefits and potential risks associated with implementing patient
Patients with ASA status I or II are recommended to perform sedation under the supervision of an anesthesiologist. This guideline was initially conceived to confirm whether there were differences in the risks related to sedation according to the provider (anesthesiologist vs non-anesthesiologist). However, most randomized controlled trials comparing the safety of sedation performed by an anesthesiologist versus a non-anesthesiologist included low-risk patient groups (mostly patients with ASA status of I and II and some patients with an ASA status of III), and only a few studies included high-risk patients. Therefore, most clinical practice guidelines for low-risk patients that have been developed were based on the results of a meta-analysis of randomized controlled trials targeting low-risk patients with an ASA status of I or II.

**Evidence summary:** Through a literature search and screening process, three randomized controlled trials were identified, including 635 patients, to analyze this key question [24–26]. Among them, 330 patients were assigned to the non-anesthesiologist sedation provider group and the remaining 305 were assigned to the anesthesiologist group. In all three studies, the incidence of sedation-related hypoxemia (non-invasive oxygen saturation [SpO₂] < 90% or 85%), need for interventions to improve ventilation (head tilt or chin lift, mask ventilation assistance, increased inhaled oxygen concentration), and frequency of hypotension and bradycardia were measured.

The incidence of hypoxemia (risk ratio [RR]: 0.85, 95% CI [0.50, 1.44]) and the need for airway management interventions (RR: 0.75, 95% CI [0.47, 1.21]) during sedation were not significantly different when sedation was performed by an anesthesiologist than by a non-anesthesiologist.

In a randomized controlled trial conducted by Park et al. [26], no significant difference was noted in the overall incidence of severe complications and rate of mortality with complex and highly invasive procedures.

**Background:** The types of specialists that provide sedation vary according to the healthcare environment and medical regulations in each country, and opinions on the scope of sedation provided by non-anesthesiologists differ across clinical guidelines. According to most clinical practice guidelines for gastrointestinal endoscopic sedation, patients with a high ASA status or difficult airway management have a higher incidence of cardiopulmonary complications and rate of mortality with complex and highly invasive procedures. Therefore, to ensure safety, anesthesiologists are recommended to perform the sedation. This guideline was initially intended to confirm whether there were differences in the risks related to sedation according to the provider (anesthesiologist vs non-anesthesiologist). However, most randomized controlled trials comparing the safety of sedation performed by an anesthesiologist versus a non-anesthesiologist included low-risk patient groups (mostly patients with ASA status of I and II and some patients with an ASA status of III), and only a few studies included high-risk patients. Therefore, most clinical practice guidelines for low-risk patients that have been developed were based on the results of a meta-analysis of randomized controlled trials targeting low-risk patients with an ASA status of I or II.

**Key Question 4. For adult patients, is the incidence of sedation-related complications reduced when sedation is performed by an anesthesiologist rather than a non-anesthesiologist?**

**Recommendation:** For adult patients, providers are recommended to perform sedation under the supervision of an anesthesiologist that specializes in pain management to prevent unintended deep sedation and ensure patient safety.

**Level of evidence: Low**

**Conditions:** Selective use of sedation performed by anesthesiologists is recommended for patients with an ASA physical status of III or higher, those with an anticipated difficult airway or with previous difficulties with anesthesia or sedation, and those undergoing complex or invasive procedures.

**Table 5. Example Criteria for Selecting Patients for Sedation**

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk group</td>
<td>Patients with ASA status I or II</td>
</tr>
<tr>
<td>High-risk group</td>
<td>Patients with ASA III or higher, advanced age, obesity, pregnancy, airway problems (sleep apnea or respiratory distress syndrome), allergies, and cardiovascular problems; those who use psychiatric medications; and those with a history of gastric bypass surgery</td>
</tr>
</tbody>
</table>

ASA: American Society of Anesthesiologists.
dation-related complications among the 154 patients with an ASA status of I or II who underwent sedation by an anesthesiologist or non-anesthesiologist. However, the occurrence of unintentional deep sedation (MOAA/S 0–2) was higher in the group that underwent sedation by a non-anesthesiologist than in the group that underwent sedation by an anesthesiologist (5.1% vs. 17.1%, P = 0.018). Satisfaction with the sedation provider was high among patients who underwent sedation by an anesthesiologist (P = 0.001). Patient-reported satisfaction was not significantly different between the groups (odds ratio [OR]: 1.48, 95% CI [0.45, 4.91]). Additionally, no significant differences were noted in the incidence of hypotension or bradycardia between the groups in the meta-analysis. In two of the included studies [24,26], physicians in the non-anesthesiologist group performed sedation independently of the operating physician and had experience providing sedation. Therefore, undergoing sedation by an anesthesiologist did not reduce the occurrence of sedation-related complications in patients included in the analysis with a low risk of complications (ASA status of I or II). However, most patients with an ASA status of I or II underwent procedures for less than 40 min, and the frequency of unintentional deep sedation was significantly reduced. Therefore, these results may not be applicable to patients who undergo complicated and invasive procedures or high-risk patients.

Ferreira et al. [24] reported that the recovery time was approximately 10 min longer when sedation was performed by an anesthesiologist (58 ± 33 vs. 67 ± 29 min, P = 0.032); however, Park et al. [26] reported no significant difference between the two groups in terms of the recovery time. Guerra et al. [25] reported that patients who received sedation from an anesthesiologist using propofol had a longer total hospital stay than patients who received sedation from a non-anesthesiologist using midazolam (31 vs. 28 h, P = 0.003), resulting in higher total hospitalization costs (677 vs. 562 euros, P = 0.001). Although the cost is expected to vary depending on the type of healthcare expenses and procedures conducted in each country, the use of an anesthesiologist can increase the cost of the hospital stay.

According to the results of our meta-analysis, in adult patients, sedation performed by an anesthesiologist was not found to reduce the frequency of significant complications such as hypoxemia. Additionally, no significant differences were noted in the total number of sedatives used or recovery time, although undergoing sedation by anesthesiologists may result in additional costs associated with hospitalization. The balance between the benefits and harms can be judged according to the characteristics of the patient and the procedure. In low-risk patients undergoing short and simple procedures, the financial burden may be higher; however, even in low-risk patients, the possibility of unintentional deep sedation cannot be completely ruled out. If respiratory depression lasts longer than a few minutes, serious complications, such as hypoxic organ damage or subsequent cardiac arrest or death, may occur.

A study analyzing 105 medical dispute cases in South Korea between 2009 and 2014 reported that 92.4% of disputes were related to sedation performed by non-anesthesiologists. Even if the incidence of sedation-related complications is low in patients in the low-risk group, a serious risk of complications (e.g., hypoxic brain damage, organ damage, cardiac arrest, or death) resulting from respiratory depression secondary to unintentional deep sedation is still present.

Patients and caregivers prefer to receive sedation from an anesthesiologist with specialized knowledge and skills in airway management, hemodynamic monitoring, and emergency responses. When asked, “Do you think a skilled sedation provider who only manages the sedation is necessary for patient safety and successful completion of procedures?”, most patients who had undergone sedation (94%; 43/46 patients) reported that a skilled sedation provider should monitor sedation. When asked, “If the patient’s condition is critical, do you think that sedation by an anesthesiologist will improve patient safety?”, 87% (40/46) of the respondents responded “yes,” and the remaining 13% (6/46) reported that they did not know. According to the results of this survey, patients undergoing sedation prefer to be monitored by a skilled anesthesiologist, especially when the patient’s condition is critical.

Sedation can be safely performed in patients with an ASA status of I or II by a non-anesthesiologist with appropriate monitoring. However, the type of procedure and degree of invasiveness must be considered. Patients undergoing complicated, long, or painful procedures that require deep sedation; those with a history of anesthesia or sedation complications; those with an ASA status of III or higher; and elderly patients is recommended to undergo sedation performed by an anesthesiologist to ensure that deep sedation is prevented, the airway is properly managed, and appropriate emergency responses are performed (Table 6).

<table>
<thead>
<tr>
<th>Table 6. High-risk Groups for Moderate and Deep Sedation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical conditions or comorbidities that potentially increase the risk of sedation-related complications</td>
</tr>
<tr>
<td>ASA score III or higher</td>
</tr>
<tr>
<td>Anticipated difficult airway (compromised neck mobility and mouth opening, facial anomaly, or a history of difficult airway)</td>
</tr>
<tr>
<td>History of anesthesia-related adverse events</td>
</tr>
<tr>
<td>Anticipated high level of procedural complexity and invasiveness</td>
</tr>
<tr>
<td>ASA: American Society of Anesthesiologists.</td>
</tr>
</tbody>
</table>

https://doi.org/10.4097/kja.23745
Consensus on the recommendation level and direction was reached among all participating members of the development committee for patients with an ASA status of III or higher or for high-risk patients with suspected airway management complications. A total of 91.4% of the respondents to the user opinion survey of the draft clinical practice guidelines agreed with the recommendations. However, external expert reviews had a low agreement rate (20%). Therefore, future research must be conducted to provide a clearer definition of high-risk groups and to compare the incidence of complications between high-risk patient groups that undergo sedation performed by anesthesiologists and non-anesthesiologists. However, because of the lack of prospective comparative literature that directly compares sedation-related complications when sedation is performed by an anesthesiologist versus a non-anesthesiologist in high-risk patients, the level of evidence for this practice guideline is low. As most previous research has been conducted on low-risk patients, accurately comparing the incidence of sedation-related complications between different high-risk groups is challenging. However, sedation performed by an anesthesiologist skilled in rapid airway maintenance and hemodynamic management would improve the safety of sedation.

**Key Question 5. Is fasting before the procedure necessary for adult patients undergoing sedation?**

**Recommendation:** Adult patients scheduled for sedation are advised to fast from clear fluids for two hours and from solid foods for six hours prior to the procedure.

**Recommendation level:** Elective use (Do, conditional)

**Level of evidence:** Very low

**Conditions:** Fasting criteria for patients undergoing sedation should be comprehensively analyzed based on the urgency of the procedure and the depth of sedation.

**Background:** Sedation is used to facilitate various procedures. Although pulmonary aspiration is rare, it can result in considerable harm or even death. The aim of this clinical practice guideline is to prevent pulmonary aspiration. Although pulmonary aspiration related to general anesthesia has been extensively studied, only a few studies and publications have reported pulmonary aspiration during sedation. Most previous studies in the field of gastroscopy have been case reports or retrospective audits. Strategies to prevent pulmonary aspiration during sedation are similar to those traditionally recommended for general anesthesia.

**Evidence summary:** Studies related to fasting (including fasting time) in adult patients undergoing sedation were identified through a literature search. Review articles, treatment guidelines, and retrospective studies were excluded. As few studies directly comparing the benefits and harms of fasting were identified, one randomized controlled trial and four non-randomized observational studies on patient risk factors for complications were included in the meta-analysis.

Bell et al. (2007) [27] compared the safety of fasting and non-fasting conditions. However, only the percentage of aspiration, adverse respiratory events, and respiratory interventions, were described; no blinded assessment of outcomes was provided. Koepppe et al. (2013) [28] compared the ease of gastroscopy between fasting and non-fasting patients, although all conditions in the study were considered fasting according to the ASA guidelines. Overnight fasting was compared with fasting from liquids and solids for two hours prior to the procedure in terms of aspiration prevention (benefit) and hunger, weakness, anxiety, and thirst (harms). This study presented only indirect evidence and was therefore considered an observational study. Fasting from liquids for two hours prior to sedation was found to cause patient harm [28]. Hamid [29] and Davies et al. [30] compared the results of surveys conducted after the second and third education sessions. However, the sample sizes were small, and the number of samples was not accurate, as only percentages or average scores were presented. In addition, after the second and third education sessions, all patients fasted according to the ASA guidelines, and only indirect evidence was presented. Finally, as the researchers were not blinded, no blinded assessment of the outcomes was performed in any of these studies. All the studies analyzed cases of participants fasting according to the ASA guidelines, even after the second and third surveys, and analyzed the harm resulting from fasting before sedation. In another study by Manchikanti et al. [31], all patients underwent procedures without fasting, and the incidences of aspiration and vomiting were simply described. Overall, the bias of the study design was low; however, owing to the very small sample size, low incidence of complications, and the inconsistency and indirectness, this recommendation was determined to have a very low level of evidence.

Three of the five studies included in a previous meta-analysis reported no observation of pulmonary aspiration [27,28,31]. Only a few studies have reported pulmonary aspiration during sedation. Based on case reports from 1985 to 2016, only nine cases of aspiration during sedation have been reported, excluding those that occurred during gastrointestinal endoscopy [32–36]. However, estimating the incidence of aspiration during sedation is difficult. Among these reported cases, one death caused by pulmonary aspiration during non-gastroscopic sedation was reported [32]. Fasting from solids for at least 4–6 h and from liquids for at least 2 h were reported in all nine case reports. The patients had significant underlying diseases and propofol was the main sedative ad-

https://doi.org/10.4097/kja.23745
ministered. The results suggest that fasting does not completely prevent pulmonary aspiration.

One prospective non-randomized observational study described the frequency of sedation-related adverse effects based on fasting status. No cases of aspiration were reported among the 400 procedures performed in the emergency department. Respiratory complications occurred in 19.5% of patients who fasted and 22.4% of patients who did not fast. Respiratory interventions were required in 24.6% of the patients who fasted and 33.3% of the patients who did not fast. Vomiting occurred in 0.8% of patients who fasted and in 0.4% of patients who did not fast [27]. Among the 18,472 interventional pain treatment procedures performed under sedation in 3,179 patients, aspiration did not occur, but respiratory depression occurred in two cases [31]. The patients in this study consumed solids for up to 2 h prior to the procedure and liquids for up to 15 min prior to the procedure. Antiemetics were required in 15.4% of the procedures based on previous episodes of nausea and vomiting. Nausea was reported in 1.6% of the procedures, and vomiting occurred in three cases. There was no conclusive or direct evidence supporting the requirement for fasting.

One randomized controlled trial and four observational studies were included in the meta-analysis of the harms of fasting. Fasting from clear liquids for up to 2 h prior to gastroscopy resulted in anxiety in 12% of patients, hunger in 44%, and weakness in 22% [28]. When liquid intake was permitted until 2 h prior to sedation, subjective dehydration was reported in 25% of patients, and clinical and objective dehydration was observed in 25% of patients [30].

Based on the available evidence, we cannot conclude that fasting from clear liquids for 2 h and from solid food for 6 h prior to a procedure requiring sedation reduces sedation-related complications. However, aspiration may result in serious complications, and fasting is believed to reduce the gastric contents, thus minimizing the potential harm that could result from aspiration. In contrast, fasting can cause temporary discomfort, including hunger, anxiety, lethargy, thirst, and dehydration. The harm caused by fasting may be partially alleviated if liquids are permitted until 2 h prior to the procedure.

All members in attendance agreed with the level and direction of these recommendations, and none disagreed with the contents of this clinical practice guideline. In a user opinion survey of the draft of this clinical practice guideline, 94.9% of the anesthesiologists agreed with the recommendation. In the external review, 20% of the experts strongly agreed, 60% agreed, and 20% strongly disagreed with this clinical practice guideline.

Key Question 6. Are there any differences in the efficacy and safety of intravenous propofol versus midazolam monotherapy in adult patients undergoing moderate sedation?

**Recommendation:** The use of intravenous propofol for sedation in adult patients results in a significantly shorter recovery time than that of intravenous midazolam. Both drugs are currently widely used in clinical practice. The choice of sedative can be selected based on the duration of the examination or procedure, experience of the sedation provider, and healthcare environment.

**Recommendation level:** Elective use (Do, conditional)

**Level of evidence:** Moderate

**Conditions:** Propofol can be used to shorten the recovery time, and midazolam can also be used to shorten the recovery time when combined with flumazenil.

**Background:** Commonly used sedative drugs include propofol, midazolam, ketamine, and dexmedetomidine. These medications are also used in combination with other sedatives and narcotic agents based on the clinical situation, examination or procedure time, and level of stimulation. For this guideline, the efficacy and safety of propofol versus midazolam monotherapy, both of which are widely used to achieve moderate sedation in adult patients, were compared. Studies that combined these sedatives with narcotic preparations were excluded from the analysis.

**Evidence summary:** The benefits of propofol compared to midazolam were examined in six prospective randomized studies. These analyses primarily focused on efficacy (patient satisfaction) and safety (frequency of hypoxemia and hypotension and recovery time).

No significant difference in the incidence of hypoxemia (oxygen saturation < 90%) during sedation was noted between the propofol and midazolam groups in the meta-analysis (RR: 0.88, 95% CI [0.56, 1.37]) [37–39]. The lowest peripheral oxygen saturation reported during the procedure was significantly lower when propofol was administered than when midazolam was administered (mean difference [MD]: −1.55%, 95% CI [−2.75, −0.35]) [37,40]. As the average minimum peripheral oxygen saturation exceeded 90% for both drugs, it was difficult to determine which drug was superior in preventing hypoxemia.

One of the six selected studies evaluated the frequency of hypotension during sedation. The meta-analysis results showed no significant difference in the incidence of hypotension (systolic blood pressure ≤ 90 mmHg) between the propofol and midazolam monotherapy groups (RR: 0.75, 95% CI [0.14, 4.13]) [39].

Four of the included studies evaluated the time required to recover consciousness after the completion of the procedure. The
recovery time was significantly shorter after propofol than after midazolam administration (MD: −8.88 min, 95% CI [−10.45, −7.32]) [38,39,41,42]. Three of the included studies targeted patients with liver cirrhosis [38,39,42], and one included general patients [41]. The duration of the effect of propofol was shorter than that of midazolam due to the large distribution volume and short distribution half-life of propofol [43,44]. Both propofol and midazolam are metabolized by the liver. Although the pharmacokinetics of propofol are not significantly affected by cirrhosis [45], the pharmacokinetics of midazolam are dependent on liver function, resulting in a prolonged elimination half-life and a potentially longer duration of action in patients with liver cirrhosis [46]. Thus, compared to propofol, the recovery time for midazolam may be relatively delayed in patients with liver cirrhosis [38,39,42]. However, even in general patients, the recovery time with midazolam was significantly longer than that with propofol [41]. Patient satisfaction was similar for propofol and midazolam (RR: 0.38, 95% CI [−0.59, 1.36]) [38,42].

In our meta-analysis of studies on adult patients undergoing moderate sedation, the average recovery time was 8.88 min shorter when propofol was used than when midazolam was used. However, the incidence of hypoxemia, hypotension, and patient satisfaction were not significantly different between the groups. Propofol and midazolam are widely used for sedation in primary, secondary, and tertiary care institutions, and the views and preferences of sedation providers vary. However, the recovery time is longer with midazolam than with propofol. Therefore, patients should be provided with sufficient recovery time and caution should be exercised when administering midazolam.

In addition to midazolam and propofol, various sedatives and narcotics, including ketamine and dexmedetomidine, are currently used for sedation. Sedatives should be selected and used in appropriate combinations based on factors such as the time required for the examination or procedure, level of stimulation, experience of the provider, and the healthcare environment. A drug can be used alone or in combination with other drugs. When sedatives and narcotic analgesics are administered concurrently, the synergistic effects of sedation and analgesia require careful dose adjustments.

In the external expert survey regarding this clinical practice guideline, no significant differences or additional opinions were noted (strongly agree: 20%, agree: 80%). In the user opinion survey, 98.3% of respondents agreed with the final version of this clinical practice guideline.

Key Question 7. Is oral chloral hydrate safer than oral midazolam for sedation of pediatric patients?

Recommendation: As no significant differences have been reported on the safety and efficacy of oral chloral hydrate versus midazolam for sedation in pediatric patients, oral chloral hydrate can be used based on the patient’s condition and availability of the medication.

 Recommendation level: Elective use (Do, conditional).

Level of Evidence: Very low

Background: Oral sedation is widely used as an easy, safe, and inexpensive method of drug-assisted sedation in pediatric patients. Chloral hydrate, which is mainly used for oral sedation and is classified as a sedative-hypnotic, induces sleep in pediatric patients. When chloral hydrate is administered orally, its medicinal effect begins within 15–30 min and the maximum effect occurs after an hour and lasts > 5 h. In the United States, chloral hydrate production was discontinued in 2012, which limited its use. In addition, no antagonist is available for chloral hydrate. In pediatric patients, midazolam is rapidly cleared and oral midazolam is promptly absorbed from the gastrointestinal tract, reaching peak plasma concentrations within one hour. Midazolam can produce a paradoxical reaction, including agitation, irritability, hyperactivity, rage, and hostility toward caregivers. Impaired memory, primarily anterograde amnesia, in which an individual is unable to recall events experienced during the period of drug action, is a potential side effect of midazolam. Flumazenil, an antagonist, can be administered to reverse the effects of midazolam. The key question for this recommendation was the safety and efficacy of oral chloral hydrate versus oral midazolam for sedation in pediatric patients.

Evidence summary: Among the seven selected prospective randomized controlled trials, six included benefits that could be analyzed. Our meta-analysis results showed a success rate of sedation at 93.46% (357/382) among patients administered chloral hydrate and 74.94% (302/403) among patients administered midazolam (RR: 1.26, 95% CI [0.72, 2.19], P = 0.41). Although the difference was not significant, the success rate of sedation was higher in the chloral hydrate group than that in the midazolam group. Oral chloral hydrate is used to achieve sedation in pediatric patients who have difficulty cooperating during diagnostic examinations and invasive procedures, allowing for the success of these examinations and procedures. Systematic reviews and meta-analyses evaluating the safety of chloral hydrate and midazolam for pediatric sedation have been conducted [47–53]. No major neurologic or respiratory adverse effects were reported when chloral hydrate or midazolam was used for pediatric sedation. The fre-
frequency of minor adverse effects was 21.36% (91/426) among patients administered midazolam and 12.35% (50/405) among those administered chloral hydrate. Although minor adverse effects were less frequent with chloral hydrate, the difference was not significant (RR: 0.90, 95% CI [0.34, 2.41], \(P = 0.84\)).

The most frequent adverse reactions were prolonged sedation, paradoxical agitation, and gastrointestinal side effects. Oxygen saturation decreased by > 10% in one patient who received chloral hydrate, and respiratory support was required in three patients who received chloral hydrate and in one patient who received midazolam.

Chloral hydrate may be used as an oral sedative in pediatric patients. Although the success rate of sedation is higher and fewer adverse drug reactions are reported with chloral hydrate than with oral midazolam, the incidence of respiratory side effects is higher with oral chloral hydrate. Therefore, chloral hydrate should be used with caution in patients with respiratory problems.

At the first internal committee meeting, 52.9% of the members agreed with the direction of the recommendation. The contents of this clinical practice guideline were revised, resulting in a 100% agreement at the second internal committee meeting. A total of 80% of the external experts agreed with the level of recommendation of this clinical practice guideline for sedation, and 90% of the respondents to the user opinion survey agreed with the recommendations.

Key Question 8. Is ketamine safer than midazolam for sedation in pediatric patients?

Recommendation: (1) Although no significant differences in the safety or efficacy of ketamine and midazolam for sedation in pediatric patients were found, the use of oral ketamine should be limited given its lower success rate of sedation.

Recommendation level: Limited use (Do not, conditional)

Level of evidence: Very low

Conditions: When additional dosing or titration is challenging.

(2) Intravenous administration of ketamine in pediatric patients has a relatively faster time of onset but an equivalent success rate of sedation and a similar safety profile to that of midazolam; therefore, ketamine can be administered to some pediatric patients depending on the type of sedation needed, the patient's condition, and the preference of the sedation provider.

Recommendation level: Elective use (Do, conditional)

Level of evidence: Very low

Conditions: When rapid sedation is necessary, such as in cases of primary sedation failure.

Background: The use of benzodiazepines is preferred as they allow for a desirable sedation effect and can be reversed using flumazenil. At appropriate doses, benzodiazepines do not induce respiratory depression; however, when used in conjunction with opioid analgesics or multiple types of sedatives, they can lead to dangerous complications such as apnea and hypoxemia.

In contrast, ketamine is a phencyclidine derivative classified as a dissociative anesthetic. Ketamine exhibits analgesic, amnesic, and sedative properties without the loss of protective reflexes, making it an ideal sedative. Patients who receive ketamine may appear awake in a tonic state, as they are unable to communicate, but can perform involuntary movements.

In addition, the “emergence” phenomenon, wherein patients may experience nightmares or frightening hallucinations upon awakening from anesthesia, is a specific adverse reaction associated with ketamine. Administration of midazolam immediately before awakening helps prevent the emergence phenomenon. Ketamine should be administered slowly to avoid the malignant arrhythmias associated with rapid bolus administration. Intramuscular ketamine has a similar safety profile to intravenous ketamine.

The key question addressed by these recommendations is whether the safety and efficacy of ketamine for sedation in pediatric patients is superior to those of midazolam.

Evidence summary: Through a literature search and selection process, three randomized controlled trials [54–56] with a total of 167 patients were included in the analysis. Overall, 80 and 87 patients received ketamine and midazolam, respectively. In all three studies, the commonly reported outcomes were the success rate of sedation; time to loss of consciousness; adverse drug reactions; and frequency of hypoxemia, agitation, and postoperative nausea and vomiting.

The study conducted by Rubinstein et al. [54] reported a serious risk of bias with the randomization process. The remaining studies also reported a risk of bias, although not as severe. Therefore, the overall risk of bias was high. The level of evidence for the success rate of sedation, which was the key outcome, was rated very low, as inconsistency and imprecision each reduced the level of evidence by one. The level of evidence for the time to loss of consciousness was rated low, as imprecision reduced the score by one level [5]. The level of evidence for other adverse reactions was rated very low, as inconsistency and imprecision each reduced the level of evidence by one.

The number of individual studies and total patients included in the meta-analysis was also small. Detecting significant differences in the incidence of the outcomes of interest was difficult as patients were divided into oral and intravenous administration groups and few patients were included.

https://doi.org/10.4097/kja.23745
Considering these factors, the strength of the evidence was determined to be low and the evidence did not fully reflect all pediatric patients undergoing sedation.

In the case of oral administration, the success rate of sedation was significantly higher with oral midazolam than with oral ketamine. In the study by Rubinstein et al. [54], sedation was administered to 68 pediatric patients (aged 1–10 years) who underwent wound closure in the emergency room, and the effects of oral ketamine (5 mg/kg) and oral midazolam (0.7 mg/kg) were compared. The success rate of sedation was significantly lower with ketamine than with midazolam (RR: 0.72, 95% CI [0.57, 0.92], I² = 0%, P = 0.008). However, no significant differences in pain scores according to the visual analog scale were noted between the groups. Considering the small patient population and the lack of statistical significance, the clinical significance remains unclear. Conversely, a previous meta-analysis [57] reported a higher success rate of sedation with oral midazolam than with oral ketamine (RR: 1.32, 95% CI [1.07, 1.62], I² = 0%, P < 0.01).

Oral formulations of midazolam and ketamine are currently unavailable in South Korea. Although intravenous drugs have been mixed with syrups or glucose solutions in some cases, no oral formulations have been officially approved for use. Therefore, ketamine is typically administered parenterally (via a non-oral route) in South Korea.

No significant differences were noted in the success rates of sedation between intravenous ketamine and midazolam. In the study by Thevaraja et al. [55], sedation was administered to 34 pediatric outpatients with an ASA status of I who were undergoing a urodynamic study. Patients in the ketamine group received 0.25 mg/kg of intravenous ketamine followed by a continuous infusion at 10–20 μg/kg/min. Patients in the midazolam group received 0.02 mg/kg of intravenous midazolam followed by a continuous infusion at 1–2 μg/kg/min. Although the time to loss of consciousness was shorter in the ketamine group than in the midazolam group, the success rate of sedation was 100% in both groups. Both intravenous midazolam and low-dose intravenous ketamine provided satisfactory sedation, without affecting the urodynamic test values in pediatric patients (RR: 1.00, 95% CI [0.94, 1.07]). No studies comparing oral and intravenous ketamine were included in the meta-analysis. A systematic meta-analysis by Cheng et al. [57] reported no significant differences in the success rate of sedation and hypnosis or in the duration of sedation between oral and intravenous midazolam (P > 0.05).

Data from all three prospective randomized controlled studies were included in the comparative analysis of drug reactions between ketamine and midazolam. Intravenous administration was used in one study, whereas oral administration was used in the other two. Among the 167 patients (Younge and Kendall [56], 2001; Thevaraja et al. [55], 2012; Rubinstein et al. [54], 2016), adverse effects were observed in 23 (13.8%). When calculated per 1,000 individuals, the incidence of adverse reactions was lower in patients who received ketamine (126 per 1,000) than in those who received midazolam (156 per 1,000). However, the difference between the two groups was not statistically significant (RR: 0.81, 95% CI [0.39, 1.69], I² = 0%, P = 0.58). Thevaraja et al. [55], in their study involving 34 participants, reported no adverse reactions in either the intravenous ketamine or midazolam groups. Due to the rare incidence of severe complications, the total number of patients in this study was determined to be insufficient to draw accurate conclusions.

Ketamine can increase salivary secretion, leading to coughing and laryngospasms in severe cases. Therefore, ketamine should either be avoided or used with caution in cases of airway procedures and upper respiratory tract infections or when dealing with uncontrolled asthma or hypertension. These effects can be mitigated by the complementary use of atropine or glycopyrrolate [58]. Although ketamine is generally recognized as a safe sedative that does not cause significant respiratory depression, apnea can occur when it is administered rapidly or in conjunction with opioids or other sedatives. In addition, ketamine can inhibit the reuptake of catecholamines, thereby increasing sympathetic nervous system stimulation and potentially causing tachycardia. Although it is safe for pediatric patients who are hemodynamically compromised or at risk of bradycardia, it should not be used in pediatric patients with increased intracranial pressure because it can increase cerebral blood flow.

Systematic meta-analyses of adverse reactions to ketamine sedation in pediatric patients have not been reported. In a systematic meta-analysis of adverse reactions to sedation with oral midazolam in pediatric patients reported by Cheng et al. [57], the incidence of adverse drug reactions was 19.57% (189/966). Bellolio et al. [58] conducted a meta-analysis of adverse reactions reported for all pediatric sedation drugs used in an emergency room and found that mild complications such as vomiting (55.5 episodes per 1,000 patients, 95% CI [45.2, 65.8]) and agitation (17.9 episodes per 1,000 patients, 95% CI [12.2, 23.7]) were the most common, whereas dangerous complications such as hypoxia (14.8 episodes per 1,000 patients, 95% CI [10.2, 19.3]) and apnea (11.0 episodes per 1,000 patients, 95% CI [3.2, 0.11]) were less common. The need for intervention with a bag-valve mask, oral airway, or positive pressure ventilation was rare (5.0 episodes per 1,000 patients, 95% CI [2.3, 7.6]). The incidence of laryngospasm was 2.9 episodes per 1,000 patients (95% CI [1.1, 4.7]) and intubation was required in 34 of the 9,136 patients.
No aspiration was reported among the 3,326 patients. Therefore, serious adverse reactions are rare during pediatric sedation with various sedatives, and mild complications such as nausea, vomiting, or nervousness are common. The incidence of hypoxemia among all pediatric sedation cases was approximately 1.5%. In a previous meta-analysis of the adverse reactions to sedation in adult patients, the most common complication was hypoxemia [59]. Although drug selection and co-administration of narcotics differ between adult and pediatric patients, the incidence of severe complications such as hypoxemia is significantly lower in pediatric patients than in adult patients. Most patients who experienced laryngospasms had received ketamine (33/34). Although ketamine is reported to be relatively safe in adult patients, pediatric patients are at risk of severe adverse reactions such as rapidly progressing hypoxemia under sedation. Therefore, sedatives should be administered at an appropriate initial dose, with additional lower doses administered under continuous monitoring. The American Society of Anesthesiology practice guidelines [1] also recommend that the effects of sedatives should be judged by allowing sufficient time for maximum effect when administering sedatives. Even when administered via a non-intravenous route (such as the oral or nasal mucosa), sufficient time should be provided for the absorption of the previous dose and observation of the maximum effect before additional doses are administered. For patients receiving intravenous drugs, the intravenous route should be maintained until the patient is no longer at risk of cardiorespiratory dysfunction. In addition, patients should be carefully monitored for complications.

However, as this meta-analysis focused only on studies of pediatric patients who received with a single sedative agent for a procedure, few studies and patients were included. The included patients were divided into oral and intravenous administration groups owing to inconsistencies in usage and low or very low levels of evidence due to inaccuracy and imprecision. Furthermore, the incidence of events corresponding to harm was low given the low number of patients, making it difficult to detect significant differences. Due to these limitations, classifying one drug as superior was not possible.

As the direction of the recommendation differed between oral and intravenous administration, less than 70% of the attending committee members agreed with the original initial proposal, which provided recommendations solely for intravenous medications. However, oral formulations of these drugs are not commercially available in South Korea. However, as they may become available in the future, recommendations for both oral and intravenous administrations were suggested in the first round of voting, and this clinical practice guideline was revised such that oral and intravenous administrations were classified separately. During the second round of voting, no disagreements regarding the content of this clinical practice guideline were reported, with 100% approval of the direction and level of recommendation. The user opinion survey results indicated an approval rate of 80.8% for the recommended direction, and the external expert review showed an approval rating of 80%. The current clinical practice guideline and level of recommendation were finalized without any additional adjustments.

Key Question 9. Is dexmedetomidine safer than midazolam for sedation in pediatric patients?

Recommendation: In pediatric sedation, dexmedetomidine is not considered as safe as midazolam, given its potential to cause hypotension and bradycardia. However, it is considered effective for deep sedation. Therefore, depending on the type of procedure and the sedative provider’s preference, dexmedetomidine can be used as an alternative to midazolam.

Recommendation level: Elective use (Do, conditional)

Level of evidence: Moderate

Conditions: Close monitoring and management of hypotension and bradycardia in appropriate settings.

Background: Dexmedetomidine has a slightly longer time to loss of consciousness, slightly delayed onset of action, and a longer half-life than other sedatives. As a strong Alpha-2 agonist, dexmedetomidine does not cause respiratory depression, and exerts analgesic effects. Indeed, dexmedetomidine use has increased in various fields as hemodynamic stability and appropriate sedation depth is maintained. Furthermore, it reduces post-procedural agitation and decreases the occurrence of emergence delirium, leading to increased satisfaction for both the operator and examiner, and has thus been gradually replacing midazolam.

Evidence summary: The use of dexmedetomidine over midazolam has increased because provider satisfaction is higher with dexmedetomidine. After a literature search and selection process, two randomized controlled trials were included in the analysis. One study compared the sedative effects of oral midazolam versus intranasal dexmedetomidine during CT examination, and another compared the results of continuous intravenous infusions of dexmedetomidine versus midazolam during EEG [60,61].

A total of 119 patients were included in the meta-analysis, 60 of whom received dexmedetomidine and 59 received midazolam. The sedation score was evaluated in both studies, while blood pressure and heart rate were evaluated in only one study [61]. The risk of bias was low for all assessments.

The level of evidence for maintenance of appropriate sedation...
scores (a key outcome), the incidence of side effects related to blood pressure and heart rate, and the incidence of other adverse effects were determined. The level of evidence was moderately reliable for the maintenance of appropriate sedation scores, and low for side effects related to heart rate and blood pressure as inconsistency and imprecision each lowered the level by one.

According to the meta-analysis results based on the two selected prospective randomized controlled trials, appropriate sedation scores for performing the tests, as measured by the Ramsay Sedation Scale (RSS), were higher for dexmedetomidine than for midazolam (0.13 higher, 95% CI [−0.22, 0.47]). This finding indicates a moderate level of evidence that maintaining appropriate sedation scores with dexmedetomidine can reduce the need for additional medications, minimize the incidence of side effects related to overdosing, and effectively achieve stable sedation.

However, a systematic review comparing dexmedetomidine administration methods for pediatric sedation has not yet been conducted. Indeed, established literature on dexmedetomidine administration methods in pediatric patients is lacking, making it difficult to draw accurate conclusions. Furthermore, owing to the relatively delayed onset of action and unpredictable half-life of dexmedetomidine, its potential as a standalone sedative for maintaining sedation is limited. In addition, as the hemodynamic stability results of this meta-analysis show, dexmedetomidine may induce similar side effects to midazolam, such as hypotension and bradycardia. However, although the decrease in heart rate was concerning (6.00 lower, 95% CI [−9.85, −2.15]), the decrease in systolic blood pressure was not as concerning (16 lower, 95% CI [−0.22, −0.47]). However, a 16 mmHg decrease in systolic blood pressure may be clinically significant, and thus should be considered in decision making.

Because the meta-analysis results did not provide clear evidence that dexmedetomidine is superior to midazolam in terms of safety, fewer than 70% of the participating members supported this recommendation in the first round of voting. However, considering the increased use of dexmedetomidine in clinical practice and evidence showing that dexmedetomidine is more effective at maintaining sedation depth than intravenous midazolam, the recommendation was revised to include careful monitoring to ensure patient safety as a condition. Therefore, dexmedetomidine can be used as an alternative to midazolam, depending on the type of procedure and the preference of the sedation provider. In the second round of voting, more than 70% of the participating members approved the direction and level of the recommendation that dexmedetomidine be used in a setting where careful monitoring and treatment of hypotension and bradycardia are possible. This recommendation was approved by 74.2% of respondents in the internal user opinion survey and 100% of respondents in the external expert review. After discussions with the committee and individual members, the modified recommendations were confirmed without any further changes to the direction or level of recommendation.

Key Question 10. Is it necessary to monitor and record the depth of sedation, respiration, oxygen saturation, and blood pressure and to obtain an electrocardiogram during sedation?

**Recommendation:** Providers are recommended to monitor and record the depth of sedation, respiration, oxygen saturation, and blood pressure during sedation. Additional electrocardiography (ECG) monitoring is recommended for patients with cardiovascular disease.

**Recommendation level:** General use (Do, strong)

**Level of evidence:** Expert consensus/survey

**Background:** Monitoring the patient’s condition during sedation is important for the early detection and management of respiratory and cardiovascular depression or hypoxia. Existing clinical guidelines also recommend that the patient’s level of consciousness, ventilation, oxygenation, and hemodynamics be monitored and recorded during sedation [1,62]. With this key question, evidence-based clinical practice guidelines for depth of sedation, respiration, oxygen saturation, and blood pressure monitoring in patients undergoing moderate sedation in South Korea can be developed. Expert surveys were used as references in cases where evaluation of the evidence level was not possible due to a lack of research.

**Evidence summary:** The selection criteria for this meta-analysis included studies related to basic monitoring and documentation during sedation. Editorials, clinical guidelines, retrospective studies, and studies with specialized monitoring (such as end-tidal carbon dioxide pressure and bispectral index) were excluded. To the best of our knowledge, no study has directly compared the benefits or harms of basic monitoring during sedation in terms of patient outcomes and complications. In addition, no study has found whether monitoring and recording sedation depth improves patient outcomes and reduces complications. As no randomized controlled trials on oxygen saturation monitoring during sedation have been reported, this meta-analysis included four observational studies with oxygen saturation monitoring during sedation using pulse oximetry, and three observational studies of oxygen saturation in two patient groups. Owing to the paucity of studies we were unable to adequately evaluate the level of evidence; thus, sedation provider opinion surveys were collected.
Recommendations were made based on the survey results, and the level of evidence was an expert consensus/survey.

In the expert opinion survey, the majority of respondents agreed (strongly agree: 67.8%, agree: 27.2%) that regular monitoring of sedation depth helps to prevent excessive or shallow sedation. Regular observation of the level of consciousness and sedation depth allows for timely recognition and response when a patient transitions to minimal or deep sedation. Therefore, appropriately managing and recognizing changes in sedation depth can reduce sedation (including minimal sedation) failure, which can cause anxiety and pain and hinder the procedure, and result in respiratory depression due to oversedation.

The majority of respondents to this survey agreed (strongly agree: 79.7%, agree: 16.1%) that continuous oxygen saturation monitoring during sedation helps to reduce the incidence of complications such as respiratory depression, hypoxia, and airway obstruction. In four observational studies that measured oxygen saturation during sedation, desaturation was observed in 49% (60/122) of patients [63–66]. Another previous study reported a decrease in oxygen saturation of 5% or more among 30% of patients aged ≥ 60 years [67]. In addition, oxygen saturation decreased to ≤ 90% in 68% and 58% of healthy pediatric patients and those with cardiovascular disease, respectively. Although no significant difference was found between the two groups, oxygen desaturation was observed in more than half of the patients [68]. Similarly, a study conducted on both adults with cardiovascular disease and healthy adults showed a similar degree of oxygen desaturation in both groups, with a lowest mean oxygen saturation of 89.5% and 90.2%, respectively [69]. Considering the results of these studies, monitoring oxygen saturation during sedation using pulse oximetry in most patients, regardless of age or the presence of cardiovascular disease, can aid in the early diagnosis and management of desaturation and hypoxemia, thereby helping to prevent hypoxemia.

In the survey, the majority of respondents agreed (strongly agree: 79.7%, agree: 16.1%) that monitoring blood pressure regularly during sedation is helpful for the reduction of cardiovascular complications, including hypotension and hypertension. Maintaining an appropriate blood pressure is crucial for ensuring sufficient perfusion of oxygenated arterial blood into tissues, thereby maintaining circulation. Therefore, regular measurement of blood pressure during sedation and prompt recognition and management of changes in blood pressure can prevent cardiovascular complications.

The majority of respondents to the expert opinion survey agreed (strongly agree: 68.2%, agree: 28.4%) that continuous ECG during sedation in patients with cardiovascular disease was useful for reducing the incidence of cardiovascular complications such as bradycardia, arrhythmia, and cardiac arrest. An observational study investigating the incidence of arrhythmias during sedation in patients with cardiopulmonary disease found that 75% (9/12) experienced arrhythmias such as tachycardia and premature ventricular contraction [68]. In patients with clinically significant cardiovascular disease, timely recognition and management of changes in heart rate, arrhythmias, and myocardial ischemia during sedation via ECG monitoring may help prevent cardiovascular complications.

Most respondents agreed (strongly agree: 65.9%, agree: 28.4%) that maintaining a sedation record is helpful for the effective management of sedation and reduction in the occurrence of medical disputes. Documentation of sedation records allows for appropriate management of patients in the future; it can serve as data for education, research, and statistics; and can be used as a legal document to protect physicians and patients in case of medical disputes.

The results of the internal committee vote on this recommendation was 94.4% and 88.2% for the direction and level of the recommendation, respectively. The user opinion survey results indicated an approval rate of 96.7% for the recommendation direction, and the external expert review showed an approval rating of 60%.

Key Question 11. Does capnography (end-tidal carbon dioxide monitoring added to the standard measurement) during sedation in adult patients reduce the occurrence of hypoxemia?

Recommendation: To reduce the occurrence of hypoxemia during sedation in adult patients, capnography (end-tidal carbon dioxide [ETCO₂] monitoring) is recommended.

Recommendation level: Elective use (Do, conditional)

Level of evidence: Moderate

Conditions: If a monitor with ETCO₂ monitoring capabilities is available and sensor placement is possible, capnography is recommended during sedation.

Background: Respiratory depression caused by sedation is a relatively common adverse reaction and one of the most critical concerns during sedation. Failure to promptly detect and address inadequate ventilation due to respiratory depression can lead to hypoxemia, resulting in hypoxic tissue damage and potentially progressing to severe outcomes, such as respiratory arrest and cardiac decompensation. Although serious complications are rare, they are irreversible and can be fatal. Therefore, appropriate respiratory status monitoring during sedation is crucial for patient
safety. Respiratory monitoring during sedation can be categorized into oxygenation and ventilation. Pulse oximetry, the standard device for monitoring oxygenation, does not directly reflect the ventilation status. If only oxygenation is monitored, ventilation failure may not be promptly detected.

Capnography (i.e., ETCO₂ monitoring) provides continuous monitoring of ventilation status and allows for a more direct assessment of ventilation during sedation. The Practice Guidelines for Moderate Procedural Sedation and Analgesia 2018 also recommends capnography during sedation. However, the process used to reach this conclusion is not described in the practice guidelines. Additionally, clinical practice guidelines that reflect the current healthcare situation in South Korea are needed. For this recommendation, the key question was whether capnography (ETCO₂ monitoring) contributes to enhanced patient safety during sedation and whether the addition of capnography is associated with a reduction in hypoxemia.

Evidence summary: The selection criteria for the literature search were prospective studies on capnography during sedation, with hypoxemia as an outcome. Twelve randomized studies with groups based on capnography use that compared the incidence of hypoxemia were selected [70–81]. Studies with fewer than 100 patients and those that included pediatric patients were excluded. The criteria for hypoxemia were similar among the selected studies and the incidence data were clearly specified. A total of 4,932 patients were included in the meta-analysis.

The meta-analysis results demonstrated that the use of capnography significantly reduced the risk of hypoxemia (RR: 0.67, 95% CI [0.57, 0.80]); however, the heterogeneity of the results was high (I² = 65%). The nine randomized studies with an average patient age ≥ 50 years were then analyzed separately. For this analysis, the heterogeneity was not significant (I² = 19%), and the results showed a significant reduction in the risk of hypoxemia (RR: 0.61, 95% CI [0.55, 0.68]).

When hypoxemia was defined as an oxygen saturation (SpO₂) < 90%–95%, capnography led to a significant reduction in hypoxemia in 8 of the 12 included studies. According to the random-effects model, the incidence of hypoxemia was lower (RR: 0.67, 95% CI [0.57, 0.80]). In two studies, hypoxemia occurred more frequently in the group that received capnography monitoring, although no significant difference was observed [73,76]. Among the nine studies that reported the incidence of severe hypoxemia, defined as arterial oxygen saturation (SpO₂) < 85%–90%, the risk of severe hypoxemia was lower when capnography was used (RR: 0.62, 95% CI [0.51, 0.75]).

Therefore, capnography is effective at reducing the incidence of severe hypoxemia. The need for increased oxygen supplementation (RR: 0.88, 95% CI [0.75, 1.03]) and assisted ventilation (RR: 0.67, 95% CI [0.30, 1.46]) were reduced, although not significantly.

Although patients may experience discomfort as the sampling line for collecting exhaled gases is placed on the face, it is noninvasive, and there is no risk of clinical harm to the patient. However, capnography may increase healthcare costs [82,83]. The side-stream sampling line is a disposable item, the price of which varies depending on the equipment and product used (generally KRW 10,000–15,000). However, the cost is only reimbursable for general anesthesia under supervision. Water traps, which are recycled consumable products, cost KRW 30,000–50,000 and are generally replaced once or twice a year. However, no disposable equipment is used in the mainstream method, and the sensor costs more than KRW 2,000,000. The cost of the capnography module varies depending on the type of equipment but is approximately KRW 3,700,000, with an average usage period of over 10 years.

However, the value of promptly detecting respiratory depression, which is the most concerning issue in sedation, and mitigating the risk of hypoxemia cannot be solely judged based on costs and should be taken into consideration.

During the first round of voting, 100% of the participating members approved the direction of the recommendation and 93.8% approved the recommendation level. However, while 86.7% of the internal user group familiar with capnography approved the clinical practice guideline, only 60% of the external experts agreed with the guideline, which prompted the committee to present specific indications, as capnography is not required for all sedation procedures (such as endoscopy). After discussions between the committee and individual members, the final recommendation was confirmed under the condition that capnography should be recommended during sedation if a monitor with capnography capabilities is available and sensor placement is possible.

Key Question 12. Does capnography (end-tidal carbon dioxide monitoring added to the standard measurement) reduce the occurrence of hypoxemia during sedation in pediatric patients?

Recommendation: Adding capnography to standard monitoring during sedation of pediatric patients may be considered. Recommendation level: Elective use (Do, conditional) Level of evidence: Low Conditions: Capnography should be used electively when prolonged sedation is expected (e.g., an average expected time > 30 min).

Background: Effective methods of monitoring ventilation vary
depending on the age and development of the pediatric patient. Auscultatory and interactive monitoring may be sufficient for most procedures requiring shallow or moderate pediatric sedation. However, early detection of insufficient ventilation during procedures in which the respiratory status of pediatric patients cannot be closely observed (e.g., magnetic resonance imaging) is limited with these traditional methods. In addition, a pulse oximeter cannot be used to monitor a patient’s ventilation state as it will not detect hypoxemia until a few minutes after ventilation failure when supplemental oxygen is administered.

Capnography continuously monitors the state of ventilation and is essential for patients undergoing general anesthesia. However, capnography is used selectively when sedation is performed outside the operating room, depending on the guideline being followed, depth of sedation, and duration of the procedure [1,84,85]. In 2019, the American Academy of Pediatrics and the American Academy of Pediatric Dentistry jointly published a revised edition of their guidelines for pediatric sedation [14]. Currently, continuous capnography is strongly recommended for monitoring ventilation during procedures that require moderate sedation. However, the process used to develop this guideline was not clearly described. The key question for this recommendation is whether capnography during sedation in pediatric patients improves patient safety.

Evidence summary: A literature search and selection process for the main research question resulted in the identification of two randomized controlled trials [86,87]. A total of 254 pediatric patients were included in the meta-analysis: 127 who were monitored using capnography (capnography monitoring group) and 127 who were not (control group). In both studies, the incidences of hypoxemia, c, and interventions to improve ventilation (verbal or physical stimulation, head tilt or chin lift, under-shoulder support, and supplemental oxygen) during sedation were noted.

The benefits were analyzed using data from the two prospective randomized controlled trials. However, no significant difference was noted in the incidence of hypoxemia between the capnography and control (non-capnography) groups in this meta-analysis (RR: 0.52, 95% CI [0.10, 2.56]). Langhan et al. [86] conducted a randomized controlled study that included 154 pediatric patients who underwent various procedures under sedation in the emergency room and found 23 episodes of hypoxemia (oxygen saturation < 95%) among the patients receiving continuous ECG, impedance plethysmography, and pulse oximetry monitoring, and 23 among those additionally receiving capnography, indicating no significant difference between the groups. In contrast, among the 100 patients who underwent upper gastrointestinal endoscopy under sedation who were included in the study conducted by Kılıç and Gerenli [87], two patients in the capnography group and 10 in the control group experienced hypoxemia (oxygen saturation < 90%) (P = 0.0014).

In this meta-analysis, no significant difference was noted in the incidence of hypoventilation between the two groups (RR: 0.94, 95% CI [0.68, 1.29]). In the study by Langhan et al. [86], the proportion of patients who reported hypoventilation increased with increasing sedation time. The change in the ratio of patients who reported hypoventilation per minute increased more significantly in the control group than in the capnography group (change in the rate of hypoventilation per minute: 7.1% vs. 1.0%, P = 0.008, OR: 1.06, 95% CI [1.02, 1.11]). Although a longer sedation time seemed to increase the frequency of hypoventilation, the total incidence of hypoventilation was not dependent on the sedation time, indicating that the use of capnography did not significantly reduce the incidence of hypoventilation.

Regarding airway management interventions performed when oxygenation or ventilation impairment was suspected, the meta-analysis results showed a significant reduction in the frequency of head-tilt or jaw-thrust maneuvers in pediatric patients monitored via capnography (RR: 0.23, 95% CI [0.07, 0.71]). The use of capnography appeared to be beneficial for reducing the frequency of simple airway management interventions (head-tilt and jaw-thrust maneuvers). In the study by Langhan et al. [86], interventions were more likely to result from hypoventilation in the capnography group (OR: 2.26, 95% CI [1.34, 3.81]). Interventions that were not temporally consistent with hypoventilation were associated with a high incidence of hypoxemia (OR: 5.31, 95% CI [2.76, 10.22]). These results suggest that sedation providers reduced the frequency of hypoxemia by performing appropriate airway management interventions once hypoventilation occurred, detected via capnography.

However, as only two studies were included in the analysis and the level of evidence was low resulting from high inconsistency and imprecision, the potential benefit that capnography reduces the frequency of hypoxemia cannot be ruled out. One study reported that capnography reduced the frequency of hypoxemia and increased the frequency of airway management interventions for hypoventilation as sedation time increased, reducing the incidence of hypoxemia [86].

In pediatric patients undergoing moderate sedation, capnography alone cannot reduce the incidence of hypoxemia. With appropriate monitoring of ventilation (observation of chest movements and auscultation of breath sounds) during sedation, most patients can undergo moderate sedation without capnography. However, for patients requiring continuous monitoring of ventilation status (e.g., prolonged procedure time or inability to close-
ly observe the patient), additional monitoring with capnography and timely airway interventions are expected to improve patient safety (Table 7).

In the first round of voting, 100% of the participating members approved the level and direction of the recommendations, with no disagreement regarding the content of this clinical practice guideline. In a user opinion survey of the draft of the clinical practice guideline, 83.3% agreed with the guideline. In the external review, 20% of the respondents strongly agreed, 40% agreed, 0% did not agree or disagree, and 40% disagreed with this clinical practice guideline, indicating that it was generally agreed that capnography should be used.

**Key Question 13. Does the assessment of the depth of sedation improve patient safety during pediatric sedation?**

**Recommendation:** The use of a sedation depth assessment tool is recommended for pediatric patients.

**Recommendation level:** Elective use (Do, conditional)

**Level of evidence:** Expert consensus/survey

**Conditions:** If observation and evaluation are not possible during the procedure or examination or if evaluation is difficult because of the patient’s age or developmental status, providers are recommended to monitor the ventilation status and vital signs more closely.

**Background:** The patient’s level of consciousness should be monitored continuously during sedation to detect any unintentional loss of consciousness or transition to deep sedation. Children have varying abilities to control their behavior during procedures and tests depending on their age and cognitive and emotional development, and infants and children with developmental delays may require deeper sedation. In particular, pediatric patients can show a rapid transition from minimal to deep sedation. In deep sedation, serious adverse effects such as airway obstruction, apnea, and lung aspiration may occur [88,89]. The clinical scales used to assess the depth of sedation include the RSS, the Modified Observer’s Assessment of Alertness/Sedation Scale, and the Pediatric Sedation State Scale. These scales are subjective, and their clinical application may be difficult because the stimuli used for evaluation may interfere with the sedation state. The American Academy of Pediatrics and the American Academy of Pediatric Dentistry have published a series of guidelines regarding pediatric sedation, the 2019 amendments of which recommend ventilation monitoring rather than the use of a specific sedation depth evaluation scale [14]. The 2018 moderate sedation guidelines published in collaboration with the American Society of Anesthesiologists and clinical societies related to sedation recommend the level of consciousness be monitored by measuring the patient’s response to communication during moderate sedation, with no additional descriptions for specific pediatric populations, although insufficient evidence that assessing the patient’s level of consciousness improves patient safety is currently available [1].

Monitoring devices using EEG have been developed as an objective method for assessing sedation depth in adult patients. Although correlations with clinical scales have been suggested for pediatric sedation, these monitoring devices do not provide a reliable distinction between moderate and deep sedation [90–92]. Currently, processed EEG is not recommended for routine clinical practice.

**Evidence summary:** A literature search was conducted to determine whether the assessment of sedation depth improves patient safety in the pediatric population. However, no suitable studies were identified for the meta-analysis. Recommendations were therefore made based on a review of papers and expert surveys on pediatric sedation, and the level of evidence was thus classified as very low.

A total of 261 user experts responded to the user opinion survey on pediatric sedation. The majority of respondents agreed (strongly agree: 57.1%, agree: 34.9%) that assessing the depth of sedation in pediatric patients is helpful for effective sedation and pain management and reducing complications. To assess sedation depth during pediatric sedation, respondents reported using MOASS (25.3%), EEG-based monitoring (19.9%), and RSS (11.9%). However, the most common response was that only the adequacy of ventilation was monitored (40%).

Both the level and direction of the clinical practice guideline for the selective use of a sedation level assessment tool when performing sedation in pediatric patients were approved by 100% of the participating members. In the user opinion survey, 85% of the respondents agreed with the recommendations, although only 60% agreed with the selective use of a sedation level assessment tool for pediatric sedation in the external expert review of the draft clinical practice guideline.

**Key Question 14. Does the recommended standard procedure for airway management (intubation, laryngeal mask airway, etc.) increase patient safety in pediatric patients with dyspnea during sedation?**

**Recommendation:** If respiratory complications, such as dyspnea, occur during sedation in pediatric patients, providers are recommended to follow the appropriate recommendations for
airway management.

Recommendation level: Elective use (Do, conditional)
Level of evidence: Expert consensus/survey

Conditions: Elective use in cases where intervention is required for respiratory complications during sedation. Background: The possibility of patients entering deep sedation or general anesthesia, in which respiratory function is unexpectedly suppressed, is present even during moderate sedation, and appropriate measures can have a considerable impact on patient safety. However, in most sedation practice settings, individual treatment approaches are often adopted according to the clinical experience and judgment of the sedation provider rather than based on specific recommendations on the management of respiratory complications during sedation. Ultimately, the methods of managing complications differ depending on the level of education and training of individual sedation providers, which could significantly affect patient safety. Therefore, this clinical practice guideline was established as a reference for managing respiratory complications in pediatric patients undergoing sedation.

Evidence summary: A literature search of studies on the management of pediatric patients with complications during sedation was conducted. Review articles, treatment guidelines, and studies that included adult patients were excluded. As studies have directly compared the benefits and potential harm associated with management methods in patients with complications during sedation were insufficient, no study was eligible for inclusion in this meta-analysis. This may be attributable to the low incidence rate of respiratory complications during sedation, ethical concerns of intentionally not implementing the recommended management, and challenges in conducting the research. Because no studies were identified that could be used to evaluate the level of evidence for this key question, an expert opinion survey of sedation providers was conducted to develop recommendations for this clinical practice guideline.

Although it was excluded from the meta-analysis during the study selection process, one retrospective observational study was identified that indirectly estimated the effect of differences in managing respiratory complications during pediatric sedation [93]. The study reported that the incidence of respiratory complications during sedation was not significantly correlated with the location of sedation; however, secondary cardiac complications were more likely to occur in primary care settings than in secondary or higher care-based settings. Furthermore, serious harm, such as death and neurological damage, was more common in primary care settings than in secondary or higher care-based settings [93]. Although the specific conditions of each setting were not identified in the study, these results indirectly indicate that differences in the management of respiratory complications during sedation in pediatric patients can significantly affect the development of more serious complications, such as bradycardia and cardiac arrest, as well as patient outcome. Therefore, the majority of respondents to the expert survey reported that guidelines regarding airway management in pediatric patients with dyspnea during sedation would be helpful in ensuring patient safety (strongly agree: 70.5%, agree: 25.3%).

As respiratory complications are a common complication of sedatives, sedation providers should continuously monitor changes in respiratory patterns during the stages of sedation. They should also be familiar with the appropriate treatments and general approaches used in cases of respiratory failure (Table 7). Additionally, they should receive sufficient education and training regarding treatment methods (including head tilt, jaw thrust, under-shoulder support, oral [nasal] airway, and bag-mask ventilation) that can be used during the early stages of respiratory complications. In addition, sedation providers should understand that it is possible to insert a supraglottic airway and perform tracheal intubation if respiratory failure progresses further, and appropriate devices should be prepared prior to sedation. According to the expert survey, the most important methods used to treat dyspnea during sedation in pediatric patients are as follows: head tilt or jaw thrust (86.2%), bag-mask ventilation (76.6%), oral (nasal) airway (71.6%), under-shoulder support (20.7%), and supraglottic airway device (18.4%).

For this clinical practice guideline on the management of respiratory complications during sedation in pediatric patients according to appropriate standards, 94.4% of the clinical practice guideline committee agreed on the direction and level of recom-

Table 7. Treatment of Respiratory Failure During Sedation (General Approach)

Management of respiratory failure: general approach
Open the airway and keep it patent using:
- Adequate head and body alignment
- Head tilt-chin lift or jaw thrust
- Careful suctioning of secretions
Consider oropharyngeal airway in the unconscious child, in whom there is no gag reflex
Consider nasopharyngeal airway in the semi-conscious child
To support ventilation:
- Bag-mask ventilation (recommended, first-line method)
- Tracheal intubation
- Supraglottic airways

mended. After consultation and review by external experts, 100% agreement with the recommendations was obtained, and the user opinion survey showed 99.2% agreement. Therefore, this clinical practice guideline was finalized by reflecting on the results of voting by the clinical practice guideline committee, external expert consultation, and user consultation and voting.

Key Question 15. Are well-defined discharge criteria essential for safely discharging patients after sedation?

**Recommendation:** Providers are recommended to apply appropriate discharge criteria when discharging adult patients who have undergone sedation after recovery.

*Recommendation level:* General use (Do, strong)

*Level of evidence:* Expert consensus/survey

**Background:** It is important to decrease the risk of sedation-related complications and ensure patient safety not only during but also after the sedation procedure. To reduce complications related to sedation and maintain patient safety after sedation, patients should be assessed using well-established discharge criteria [94].

**Evidence summary:** A literature search was conducted for studies assessing discharge criteria after sedation in adult patients. Review articles, treatment guidelines, retrospective studies, and studies with fewer than 100 participants or pediatric patients were excluded. As there were insufficient studies that directly compared the benefits and harms of patient evaluation based on discharge criteria and the reduction in complications, expert opinion surveys of sedation providers were collected. The recommendations were based on the results of the survey; hence, the level of evidence was considered very low.

Patient assessment using appropriate discharge criteria is believed to improve patient safety after sedation and reduce sedation-related complications. Most respondents to the expert survey reported that the Modified Aldrete Score was a suitable scoring system and assessment tool for determining a patient’s preparedness for discharge after sedation. Most respondents also agreed that assessing patients in a recovery area for 30 min after sedation while recording their level of consciousness and vital signs at regular intervals reduces the occurrence of complications after sedation. Furthermore, providing education on water and food intake, emergency contact information, driving restriction instructions, and discharge with a caregiver can help reduce the occurrence of complications after sedation.

Discharge criteria focused on enhancing patient stability and reducing potential complications following sedation, such as postoperative nausea and pain, should be selected and presented in a simple manner (Table 8).

All participating members expressed 100% agreement with this recommendation, and no objections were expressed. However, due to the variety of possible procedures and sedation methods, several members expressed that using a single set of discharge criteria is inadequate and the sedation provider’s judgment is important. External experts agreed with the recommendations (strongly agree: 20%, agree: 60%, disagree: 20%). Nevertheless, in the user-opinion survey, a majority vote of 98.3% was obtained. After discussions with the committee and individual members, a consensus was reached that the benefits outweighed the potential harm, and the original draft of the clinical practice guideline was finalized.

**Conclusion**

The present work, the Korean clinical practice guidelines for di-

<table>
<thead>
<tr>
<th>Table 8. Post-sedation Discharge Criteria</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Discharge criteria</strong></td>
<td></td>
</tr>
<tr>
<td>Level of consciousness</td>
<td></td>
</tr>
<tr>
<td>Awake and oriented</td>
<td>2</td>
</tr>
<tr>
<td>Arousable with minimal stimulation</td>
<td>1</td>
</tr>
<tr>
<td>Responsive only to tactile stimulation</td>
<td>0</td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
</tr>
<tr>
<td>Able to move all extremities on command</td>
<td>2</td>
</tr>
<tr>
<td>Some weakness in movement of extremities</td>
<td>1</td>
</tr>
<tr>
<td>Unable to voluntarily move extremities</td>
<td>0</td>
</tr>
<tr>
<td>Hemodynamic stability</td>
<td></td>
</tr>
<tr>
<td>Blood pressure ± 15% of baseline MAP value</td>
<td>2</td>
</tr>
<tr>
<td>Blood pressure ± 15%–30% of baseline MAP value</td>
<td>1</td>
</tr>
<tr>
<td>Blood pressure ± 30% below baseline MAP value</td>
<td>0</td>
</tr>
<tr>
<td>Respiration</td>
<td></td>
</tr>
<tr>
<td>Able to breathe deeply</td>
<td>2</td>
</tr>
<tr>
<td>Tachypnea with good cough</td>
<td>1</td>
</tr>
<tr>
<td>Dyspneic with weak cough</td>
<td>0</td>
</tr>
<tr>
<td>Oxygen saturation</td>
<td></td>
</tr>
<tr>
<td>Maintains value &gt; 90% on room air</td>
<td>2</td>
</tr>
<tr>
<td>Requires supplemental oxygen (nasal prongs)</td>
<td>1</td>
</tr>
<tr>
<td>Saturation &lt; 90% with supplemental oxygen</td>
<td>0</td>
</tr>
<tr>
<td>Postoperative pain</td>
<td></td>
</tr>
<tr>
<td>None or tolerable</td>
<td>2</td>
</tr>
<tr>
<td>Moderate to severe pain controlled with intravenous analgesics</td>
<td>1</td>
</tr>
<tr>
<td>Persistent severe pain</td>
<td>0</td>
</tr>
<tr>
<td>Postoperative nausea and vomiting</td>
<td></td>
</tr>
<tr>
<td>Tolerable nausea without vomiting</td>
<td>2</td>
</tr>
<tr>
<td>Temporary vomiting</td>
<td>1</td>
</tr>
<tr>
<td>Persistent severe nausea and vomiting</td>
<td>0</td>
</tr>
<tr>
<td>Total score</td>
<td>14</td>
</tr>
</tbody>
</table>

MAP: mean arterial pressure.
agnostic and procedural sedation, is developed as a clinical practice guideline in accordance with the clinical situation related to sedation in Korea. The development method was "de novo", and 15 key-questions were selected based on the opinions of various experts, and 15 recommendations were made. The purpose of these evidence-based multidisciplinary clinical practice guidelines is to ensure the safety and efficacy of sedation, thereby contributing to patient safety and ultimately improving public health. Although proposed guidelines are not mandatory, we hope to assist sedation providers and patients in sedation-related decision making for diagnostic and therapeutic examinations or procedures.

**Funding**

This work was supported by the Korean Society of Anesthesiologists.

**Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

**Data Availability**

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Author Contributions**

Sang-Hyun Kim (Conceptualization; Data curation; Project administration; Resources; Supervision; Validation; Writing – original draft; Writing – review & editing)
Young-Jin Moon (Data curation; Investigation; Methodology; Writing – original draft)
Min Suk Chae (Investigation; Methodology; Writing – original draft)
Yea-Ji Lee (Investigation; Methodology; Writing – original draft)
Myong-Hwan Karm (Investigation; Methodology; Writing – original draft)
Eun-Young Joo (Investigation; Methodology; Writing – original draft)
Jeong-Jun Min (Formal analysis; Investigation; Writing – original draft)
Bon-Nyeo Koo (Investigation; Methodology; Project administration; Supervision; Writing – original draft)
Choi Jeong-Hyun (Data curation; Investigation; Methodology; Writing – original draft; Writing – review & editing)
Jin-Young Hwang (Data curation; Investigation; Writing – original draft)
Yeonmi Yang (Formal analysis; Investigation; Writing – original draft)
Min A Kwon (Data curation; Investigation; Methodology; Writing – original draft)
Hyun Jung Koh (Investigation; Methodology; Writing – original draft)
Jong Yeop Kim (Formal analysis; Investigation; Writing – original draft)
Sun Young Park (Data curation; Formal analysis; Writing – original draft)
Hyunjee Kim (Investigation; Methodology; Writing – original draft)
Yang-Hoon Chung (Formal analysis; Investigation; Writing – original draft)
Na Young Kim (Investigation; Methodology; Writing – original draft)

**ORCID**

Sang-Hyun Kim, https://orcid.org/0000-0001-6267-7365
Young-Jin Moon, https://orcid.org/0000-0003-3719-1691
Min Suk Chae, https://orcid.org/0000-0002-1426-4651
Yea-Ji Lee, https://orcid.org/0000-0002-6460-5442
Myong-Hwan Karm, https://orcid.org/0000-0002-7494-4747
Eun-Young Joo, https://orcid.org/0000-0003-3359-2850
Jeong-Jun Min, https://orcid.org/0000-0002-7584-2670
Bon-Nyeo Koo, https://orcid.org/0000-0002-3189-1673
Jeong-Hyun Choi, https://orcid.org/0000-0003-1995-1220
Jin-Young Hwang, https://orcid.org/0000-0003-1719-4350
Yeonmi Yang, https://orcid.org/0000-0003-3359-9278
Min A Kwon, https://orcid.org/0000-0002-7253-3768
Hyun Jung Koh, https://orcid.org/0000-0002-9634-5120
Jong Yeop Kim, https://orcid.org/0000-0003-3402-365X
Sun Young Park, https://orcid.org/0000-0003-2588-3324
Hyunjee Kim, https://orcid.org/0000-0002-6336-7622
Yang-Hoon Chung, https://orcid.org/0000-0002-9823-9030
Na Young Kim, https://orcid.org/0000-0003-3685-2005
Sung Uk Choi, https://orcid.org/0000-0003-3609-2253

**References**

1. Practice Guidelines for Moderate Procedural Sedation and An-


Introduction

As surgical procedures lead to actual or potential tissue damage, 20%–80% of patients complain of moderate to severe acute postoperative pain [1]. Therefore, it is important to accurately evaluate intraoperative nociception in patients undergoing surgery under general anesthesia and provide appropriate analgesia to reduce postoperative pain.

Various methods and modalities have been developed for quantitative and objective monitoring of nociception during surgery under general anesthesia [2], among which the most widely used and studied device is the surgical pleth index (SPI; GE Healthcare).

The SPI is a monitoring tool that uses the photoplethysmographic signals of finger arterioles to detect the balance between nociceptor activation and analgesia during general anesthesia [3]. The SPI values are calculated using the following equation: SPI = 100 – (0.33 × HBI + 0.67 × PPGA), where HBI is the heartbeat interval and PPGA is the photoplethysmographic arterial pressure gauge reading. The SPI values are used to guide the administration of opioids, including remifentanil, fentanyl, and sufentanil. Indeed, SPI-guided analgesia is associated with lower intraoperative opioid consumption, faster patient recovery, and comparable or lower levels of postoperative pain and rates of adverse events compared with conventional analgesia. In addition, SPI monitoring allows for the degree of postoperative pain and analgesic requirements to be predicted through the SPI values immediately before patient arousal. However, because patient age, effective circulating volume, position, concomitant medication and anesthetic regimen and level of consciousness may be confounding factors in SPI monitoring, clinicians must be careful when interpreting SPI values. In addition, as SPI values can differ depending on anesthetic and analgesic regimens and the underlying disease, an awareness of the effects of these variables with an understanding of the advantages and disadvantages of SPI monitoring compared to other nociception monitoring devices is essential. Therefore, this review aimed to help clinicians perform optimal SPI-guided analgesia and to assist with the establishment of future research designs through clarifying current usefulness and limitations of SPI monitoring in perioperative pain management.

Keywords: Analgesia; Autonomic nervous system; General anesthesia; Intraoperative monitoring; Nociception test; Pain measurement; Photoplethysmography.

Surgical pleth index monitoring in perioperative pain management: usefulness and limitations

Seok Kyeong Oh*, Young Ju Won*, Byung Gun Lim

Department of Anesthesiology and Pain Medicine, Korea University Guro Hospital, Korea University College of Medicine, Seoul, Korea

Surgical pleth index (SPI) monitoring is a representative, objective nociception-monitoring device that measures nociception using photoplethysmographic signals. It is easy to apply to patients and the numerical calculation formula is intuitively easy to understand; therefore, its clinical interpretation is simple. Several studies have demonstrated its efficacy and utility. Compared with hemodynamic parameters, the SPI can detect the degree of nociception during surgery under general anesthesia with greater accuracy, and therefore can provide better guidance for the administration of various opioids, including remifentanil, fentanyl, and sufentanil. Indeed, SPI-guided analgesia is associated with lower intraoperative opioid consumption, faster patient recovery, and comparable or lower levels of postoperative pain and rates of adverse events compared with conventional analgesia. In addition, SPI monitoring allows for the degree of postoperative pain and analgesic requirements to be predicted through the SPI values immediately before patient arousal. However, because patient age, effective circulating volume, position, concomitant medication and anesthetic regimen and level of consciousness may be confounding factors in SPI monitoring, clinicians must be careful when interpreting SPI values. In addition, as SPI values can differ depending on anesthetic and analgesic regimens and the underlying disease, an awareness of the effects of these variables with an understanding of the advantages and disadvantages of SPI monitoring compared to other nociception monitoring devices is essential. Therefore, this review aimed to help clinicians perform optimal SPI-guided analgesia and to assist with the establishment of future research designs through clarifying current usefulness and limitations of SPI monitoring in perioperative pain management.

Keywords: Analgesia; Autonomic nervous system; General anesthesia; Intraoperative monitoring; Nociception test; Pain measurement; Photoplethysmography.
toplethysmographic waveform amplitude [4]. Using this tool only requires that a pulse oximeter be attached to the finger; no additional consumable medical devices are required for continuous, noninvasive monitoring [5,6].

SPI values range from 0 to 100, with higher values indicating a greater nociceptive (stress) response. The target range for adequate intraoperative analgesia during general anesthesia is usually 20–50 [4]; thus, SPI values should be maintained < 50, and a rapid increase in SPI > 10 should be avoided [7]. Fig. 1 shows the determinants of the SPI value and the mechanism underlying the increase in SPI values due to surgical stimuli.

The first SPI-associated studies published were designed to investigate the correlation between the SPI and the nociception–antinociception balance and changes in stress hormones during the perioperative period [3,8]. Following these studies, randomized controlled trials (RCTs) comparing SPI-guided and conventional analgesia (hemodynamic parameter-guided analgesia) have mainly been conducted [9–12]. Various opioids (e.g., remifentanil, fentanyl, sufentanil, and oxycodone) were used in these studies, and several reported lower intraoperative opioid consumption, faster recovery, and similar postoperative pain scores with SPI-guided analgesia. Subsequently, the results were verified by meta-analyses [6,13]. However, some conflicting results have been reported, as one study found that SPI-guided analgesia alone was not associated with a reduction in intraoperative opioid consumption [14] and another reported that SPI-guided analgesia provides appropriate analgesia with more sufficient intraoperative remifentanil consumption compared to the controls [15]. Moreover, several studies have discussed the various limitations of the two parameters that are used to calculate the SPI (the HBI and PPGA), as they can be influenced not only by surgical stress but also by other confounding factors such as vasoactive drugs, population age, and cardiac arrhythmia [16–20].

Based on the findings of the SPI-related literature to date, this review aimed to provide a summary of the usefulness and limitations of SPI monitoring in perioperative pain management to help clinicians perform more appropriate perioperative analgesia in clinical practice and to assist with the establishment of future research to compare SPI monitoring with other objective tools for measuring nociception.

**Fig. 1.** Determinants of the SPI and mechanism of increased SPI values by surgical stimulus. A surgical stimulus increases the heart rate and vascular tone by increasing sympathetic tone; consequently, both the HBI and PPGA decrease, which inversely increases the SPI value. SPI: surgical pleth index, HBI: heartbeat interval, PPGA: photoplethysmographic waveform amplitude, LED: light-emitting diode.
Usefulness of intraoperative SPI–guided analgesia during general anesthesia

The effectiveness of SPI monitoring at quantifying nociception has been demonstrated in several clinical settings (Table 1) [5,9–12,21,22]. Although different types of surgery and opioids were assessed in these studies, most compared a group receiving opioids based on conventional hemodynamic parameters (e.g., heart rate and blood pressure) with a group receiving opioids based on SPI-quantified nociception. Most studies reported a significant reduction in intraoperative opioid consumption with SPI-guided analgesia. Accordingly, extubation time was shorter and postoperative pain and adverse events, including postoperative nausea or vomiting, were comparable or lower in the SPI group than in the conventional analgesia group.

During general anesthesia, the SPI can provide reliable quantitative information reflecting nociceptive stimulation and autonomic nervous system activation and can thus be used to guide analgesic administration [22–25]. Several RCTs have suggested that SPI-guided analgesia results in better detection of nociceptive stimuli and more timely administration of analgesics than conventional analgesia during general anesthesia [9,10,12,21]. Hence, SPI-guided analgesia is associated with fewer hemodynamic changes secondary to noxious stimulus [26] and less opioid consumption. Chen et al. [8] reported that the SPI was moderately correlated with stress hormone levels (ACTH, cortisol, epinephrine, and norepinephrine). Funcke et al. [27] also found that, compared to controls, SPI-guided analgesia was associated with lower cortisol and ACTH levels.

In several studies performed in adult patients without severe underlying diseases, including cardiovascular and neurological diseases, opioid titration based on the nociception-antinociception balance using the SPI with a cutoff value of 50 (target range of 20–50 and avoidance of rapid increases > 10 for noxious stimuli) showed a significant reduction in opioid consumption during surgery and a shorter extubation time. Moreover, SPI-guided analgesia using these criteria can help reduce the incidence of intraoperative adverse events such as hypertension, hypotension, tachycardia, and unwanted somatic movement compared to controls using hemodynamic parameter-guided analgesia [5,12,13] and can lead to better or comparable outcomes with regard to postoperative pain and complications as well as intraoperative outcomes in adult patients [12,13,15,28,29]. SPI monitoring has also been found to reduce the dose of anesthetics required during surgery and shorten the length of stay in the recovery room [9,30].

In elderly patients, SPI-guided analgesia is associated with a lower incidence of delirium in the post-anesthesia care unit (PACU) than conventional analgesia [15]. SPI monitoring can also be effective at detecting nociceptor stimulation that is masked by hypotension in the elderly due to decreased myocardial contractility, vascular elasticity, and β-adrenergic response, providing appropriate analgesia with sufficient intraoperative analgesic consumption [15].

However, several studies evaluating SPI-guided intraoperative analgesic administration in children have yielded conflicting results, suggesting that the SPI cannot be used to provide adequate analgesia within the target SPI value range of 20–50 in this population [10,18,31]. As children usually have higher blood vessel distensibility and baseline heart rates than adults [10], and as autonomic control of cardiac chronotropic function is strongly influenced by age [32,33], SPI values may be less valid in children than in adults [18]. This finding suggests that clinicians should be cautious when considering the use of the SPI in pediatric practice. A detailed explanation of the considerations for SPI monitoring according to different age groups is provided below (see Age).

SPI monitoring for the prediction of postoperative pain and analgesic requirements

Another advantage of intraoperative SPI monitoring is that it can be used to predict postoperative pain severity. The SPI values measured before arousal or in response to nociceptive stimuli during surgery are closely related to the degree of postoperative pain and opioid requirements.

Higher SPI values before arousal at the end of surgery were closely associated with moderate-to-severe pain in the PACU [29,34–37]. However, some differences in the results of these studies must be mentioned. Park et al. [36] reported that higher SPI values before arousal from anesthesia were significantly associated with higher pain scores in the PACU, and an SPI value of 60 was defined as the cut-off for moderate-to-severe pain with a numerical rating scale (NRS) ≥ 5. These authors also reported that patients with an SPI value > 60 before arousal from anesthesia required a higher amount of fentanyl during the postoperative 48 h than patients with an SPI < 60. Meanwhile, Ledowski et al. [37] validated that a cut-off point of approximately 30 showed the best sensitivity/specificity to predict moderate-to-severe pain in the PACU; however, these authors suggested that the overall predictive accuracy was poor. These differences appear to be due to variations in the level of consciousness at the end of surgery. Generally, the SPI can be significantly affected by the patient’s arousal status [35,37,38] such that the SPI values obtained during the pre-awareness period (anesthesia status) are reliable for predicting postoperative pain and analgesic requirements in the acute post-

https://doi.org/10.4097/kja.23158
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study design</th>
<th>Experimental group (n)</th>
<th>Comparator group (n)</th>
<th>Age range at inclusion (mean or median)*</th>
<th>Type of surgery</th>
<th>Anesthetic/ intraoperative opioid</th>
<th>Processed EEG (target)</th>
<th>Primary outcome/main secondary outcomes</th>
<th>Main results and conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahonen et al. 2007 [51]</td>
<td>RCT</td>
<td>Esmolol (15)</td>
<td>Remifentanil (15)</td>
<td>20-65 (32/34)</td>
<td>Gynecological laparoscopic day-care surgery</td>
<td>Desflurane and nitrous oxide/fentanyl</td>
<td>SE (50)</td>
<td>SPI value</td>
<td>While keeping SE at a predetermined level, SPI was higher in patients receiving esmolol than in those receiving remifentanil during laparoscopy.</td>
</tr>
<tr>
<td>Chen et al. 2010 [5]</td>
<td>Pilot study, RCT</td>
<td>SPI (40)</td>
<td>Conv. (40)</td>
<td>18-70 (47/46)</td>
<td>ENT surgery expected to last 1 h</td>
<td>Propofol/ remifentanil</td>
<td>BIS (40-60)</td>
<td>Opioid consumption/ unwanted events, recovery times</td>
<td>SPI resulted in lower remifentanil consumption, more stable hemodynamics, and a lower incidence of unwanted events.</td>
</tr>
<tr>
<td>Bergmann et al. 2013 [9]</td>
<td>RCT</td>
<td>SPI (76)</td>
<td>Conv. (75)</td>
<td>18-75 (48/44)</td>
<td>Outpatient orthopedic surgery</td>
<td>Propofol/ remifentanil</td>
<td>SE (40-60)</td>
<td>Recovery time, consumption of anesthetics/ complications</td>
<td>SPI reduced the consumption of both remifentanil and propofol and resulted in faster recovery.</td>
</tr>
<tr>
<td>Gruenewald et al. 2014 [21]</td>
<td>RCT</td>
<td>SPI (42)</td>
<td>Conv. (40)</td>
<td>18-65 (37/41)</td>
<td>Gynecological and orthopedic procedures</td>
<td>Sevoflurane / sufentanil</td>
<td>BIS (40-60)</td>
<td>Unwanted somatic events/hemodynamics, opioid consumption, recovery times</td>
<td>SPI showed no significant differences from standard care in terms of unwanted somatic events, sufentanil consumption, and recovery times.</td>
</tr>
<tr>
<td>Gruenewald et al. 2015 [58]</td>
<td>Comparative study</td>
<td>SPI (24)</td>
<td>ANI (24: same patients)</td>
<td>18-65 (40)</td>
<td>Elective surgery</td>
<td>Sevoflurane/ remifentanil</td>
<td>BIS (30-60)</td>
<td>Prediction probabilities using receiver operating characteristic for change (Δ) in ANI and SPI values</td>
<td>ΔANI and ASPI significantly indicated the patient’s movement after tetanic stimulation with a prediction probability of 0.74 and 0.84. Both reflected nociceptive stimulation.</td>
</tr>
<tr>
<td>Colombo et al. 2015 [22]</td>
<td>RCT</td>
<td>SPI (30)</td>
<td>Conv. (30)</td>
<td>18-50 (46.6/49.9)</td>
<td>Laparoscopic cholecystectomy</td>
<td>Propofol/ remifentanil</td>
<td>SE (40-60)</td>
<td>Sympathetic modulation/hemodynamic variables, opioid consumption, recovery time</td>
<td>SPI led to a more stable sympathetic modulation but did not offer clinically relevant advantages in terms of remifentanil consumption and recovery time.</td>
</tr>
<tr>
<td>Park et al. 2015 [10]</td>
<td>RCT</td>
<td>SPI (21)</td>
<td>Conv. (24)</td>
<td>3-10 (7/7)</td>
<td>Adenotonsillectomy</td>
<td>Sevoflurane and nitrous oxide/fentanyl</td>
<td>SE (40-60)</td>
<td>Opioid consumption/ sevoflurane consumption, postoperative emergence agitation</td>
<td>SPI does not appear to be valid in children due to differences in blood vessel distensibility and increased baseline heart rates.</td>
</tr>
<tr>
<td>Won et al. 2016 [12]</td>
<td>RCT</td>
<td>SPI (23)</td>
<td>Conv. (22)</td>
<td>20-65 (54/42)</td>
<td>Thyroidectomy</td>
<td>Sevoflurane/ oxycodone</td>
<td>BIS (40-60)</td>
<td>Opioid consumption/ extubation time, NRS</td>
<td>SPI reduced intravenous oxycodone consumption and extubation time compared with conventional analgesia.</td>
</tr>
<tr>
<td>Won et al. 2017 [19]</td>
<td>RCT</td>
<td>Nicardipine (15)</td>
<td>Remifentanil (15)</td>
<td>20-65 (46/46)</td>
<td>Thyroidectomy</td>
<td>Desflurane and nitrous oxide</td>
<td>BIS (50)</td>
<td>SPI value</td>
<td>No difference in SPI values between nicardipine and remifentanil. Calcium channel-blocking vasodilators may confound interpretation of the SPI.</td>
</tr>
</tbody>
</table>

(Continued to the next page)
Jain et al. 2019 RCT  SPI (68)  Conv. (65)  18-65 (38.4/40.3)  Laparoscopic cholecystectomy  Sevoflurane/ fentanyl  BIS (40-60)  Opioid consumption/ hemodynamic changes, recovery time, VAS, PACU analgesia  Intraoperative fentanyl consumption was higher in the SPI group than in controls. Recovery time and hemodynamic changes were comparable. Postoperative VAS and adjuvant fentanyl were higher in controls.

Choi et al. 2019 RCT  Pectoral nerve block type II (20)  Control (19)  20-65 (52.7/51.4)  Breast surgery  Propofol/ remifentanil  BIS (40-60)  Opioid consumption/ VAS, PACU analgesia  Pectoral nerve block reduced intraoperative remifentanil consumption by approximately 30% and improved postoperative pain in PACU.

Wang et al. 2020 RCT  Dexmedetomidine (46)  Normal saline (44)  18-75 (56.8/60.5)  Video-assisted thoracoscopic lung lobectomy  Isoflurane  N/A  SPI and hemodynamic changes/NRS  Dexmedetomidine decreased the intraoperative SPI and NRS scores. Dexmedetomidine attenuated noxious stimuli.

Sriganesh et al. 2020 RCT  Dexmedetomidine (12)  Fentanyl (12)  18-60 (42.9/42.3)  Craniotomy  Isoflurane  SE (40-60)  SPI changes/biomarkers of surgical stress  No differences were shown in the SPI values or biomarkers, such as cortisol, glucose, and pH, between dexmedetomidine and fentanyl.

Kim et al. 2020 RCT  SPI (43)  Pupillometry (43)  20-65 (49.4/49.1)  Laparoscopic cholecystectomy  Propofol/ remifentanil  SE (40-60)  Peak NRS/opioid consumption  Pupillometry may reduce intraoperative opioid analgesics, recovery room opioid requirements, and pain scores.

Funcke et al. 2020 Pilot study, RCT  SPI (12)  Conv. (12), PPI (12), NOL (12)  ≥ 18 (64/61/64/62)  Radical retropubic prostatectomy  Sevoflurane/ sufentanil  N/A  Opioid consumption/adrenocorticotropic hormone and cortisol  Lower sufentanil in the PPI was associated with an increased endocrine stress response. Titration using the SPI resulted in no reduction in opioid consumption compared to the control but was associated with a reduced endocrine stress response.

Funcke et al. 2021 RCT  SPI (23)  Conv. (24), PPI (24), NOL (24)  ≥ 18 (62/61/64/62)  Radical retropubic prostatectomy  Propofol/ remifentanil  BIS (40-50)  Opioid consumption/adrenocorticotropic hormone and cortisol  Opioid consumption was different for each device (SPI > NOL > PPI). The devices do not seem to be sufficiently validated yet.

Gruenewald et al. 2021 Multicenter, RCT  SPI (246)  Conv. (248)  ≥ 18 (48/48)  Gynecological, ENT and maxillofacial, orthopedic, trauma  Propofol/ remifentanil  SE (40-60)  Unwanted event/eye-open time, PONV, VAS  Entropy and SPI did not reduce adverse events compared with standard monitoring alone. However, there was a reduction in propofol use and shorter emergence time and PACU stay.

Guo et al. 2021 RCT  SPI (31)  Conv. (31)  18-65 (47.1/48.8)  Laparoscopic cholecystectomy  Propofol/ fentanyl  BIS (40-60)  Opioid consumption/extubation time, VAS  SPI lowered intraoperative fentanyl consumption with a shorter extubation time.
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study design</th>
<th>Experimental group (n)</th>
<th>Comparator group (n)</th>
<th>Age range at inclusion (mean or median)*</th>
<th>Type of surgery</th>
<th>Anesthetic/ intraoperative opioid</th>
<th>Processed EEG (target)</th>
<th>Primary outcome/main secondary outcomes</th>
<th>Main results and conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stasiowski et al. 2021 [63]</td>
<td>RCT</td>
<td>SPI (31)</td>
<td>Conv. (30), PDR (28)</td>
<td>18-65 (47.7/49/50.2)</td>
<td>Endoscopic sinus surgery</td>
<td>Propofol/ Remifentanil</td>
<td>SE (40-60)</td>
<td>Boezaart bleeding scale</td>
<td>SPI can optimize the condition of the surgical field and reduce blood loss, whereas monitoring based on PDR reduced the use of anesthetic drugs.</td>
</tr>
<tr>
<td>Muthukalai et al. 2022 [59]</td>
<td>Observation study, plot study</td>
<td>SPI (50)</td>
<td>ANI (50); same patients</td>
<td>18-60 (40)</td>
<td>Craniotomy</td>
<td>Sevoflurane/ fentanyl</td>
<td>SE (40-50)</td>
<td>Bleeding and noradrenaline infusion – correlation with the SPI and ANI</td>
<td>The SPI was not affected by bleeding or noradrenaline infusion, contrary to the ANI.</td>
</tr>
<tr>
<td>Yi et al. 2022 [70]</td>
<td>RCT</td>
<td>Deep NMB (64)</td>
<td>Moderate NMB (64)</td>
<td>19-85 (63/65)</td>
<td>Laparoscopic herniorrhaphy</td>
<td>Sevoflurane/ remifentanil</td>
<td>PSI (25-50)</td>
<td>Opioid consumption/ PACU stay</td>
<td>Deep NMB reduced the remifentanil requirement compared with moderate NMB in SPI-guided remifentanil administration for laparoscopic herniorrhaphy.</td>
</tr>
<tr>
<td>Park et al. 2022 [73]</td>
<td>Observation study</td>
<td>High MELD (≥ 16) (20)</td>
<td>Low MELD (&lt; 16) (20)</td>
<td>20-70 (58.6/52.1)</td>
<td>Liver transplantation</td>
<td>Isoflurane/ remifentanil</td>
<td>BIS (40-60)</td>
<td>Opioid consumption/ rescue analgesia</td>
<td>Patients with a higher MELD showed lower remifentanil requirement during surgery but no significant difference during the neo-hepatic phase.</td>
</tr>
<tr>
<td>Kim et al. 2022 [69]</td>
<td>RCT</td>
<td>Abdominal wall nerve block (24)</td>
<td>Control (28)</td>
<td>18-70 (57/51)</td>
<td>Inguinal hernia repair</td>
<td>Propofol/ remifentanil</td>
<td>SE (40-60)</td>
<td>Opioid consumption/ VAS and rescue analgesia</td>
<td>Remifentanil dose during surgery was lower in the nerve block group than the control group when using SPI.</td>
</tr>
<tr>
<td>Koschmieder et al. 2023 [65]</td>
<td>Observation study</td>
<td>SPI (60)</td>
<td>Conv., PPI, NOL (60; same patients)</td>
<td>≥ 18 (42)</td>
<td>Lower extremities surgery</td>
<td>Sevoflurane/ sufentanil</td>
<td>BIS (&lt; 60)</td>
<td>AUC analyses to predict immediate moderate-to-severe postoperative pain</td>
<td>None of these monitors alone had sufficient diagnostic accuracy to predict early postoperative pain.</td>
</tr>
</tbody>
</table>

EEG: electroencephalography, RCT: randomized controlled trial, SE: state entropy, ENT: ear nose throat, Conv: conventional analgesia or standard practice, BIS: bispectral index, ANI: analgesia nociception index, NRS: numerical rating scale for pain, VAS: visual analog scale for pain, PONV: postoperative nausea and vomiting, PACU: post-anesthesia care unit, N/A: data not available, NOL: nociception level, PPI: pupillary pain index, PDR: pupillary dilatation reflex, NMB: neuromuscular blockade, MELD: model for end-stage liver disease, AUC: area under the receiver operating characteristic curve, PSI: patient state index. *Age range at inclusion indicates the range indicated in the inclusion criteria, and the values in parentheses are the ages of the included participants.
operative period. From this point of view, variations in the patients’ level of consciousness before arousal may be linked to differences in the results of these studies.

A recent meta-analysis [39] identified studies investigating the association between the SPI at the end of surgery and immediate moderate-to-severe pain in the PACU and revealed that SPI values were higher in patients with moderate-to-severe pain and a higher SPI at the end of surgery could predict moderate-to-severe pain with a sensitivity of 0.71 and a specificity of 0.58. Additionally, according to the summary receiver operating characteristic curve, the overall accuracy was 0.72, suggesting that the SPI may be a useful predictor of postoperative pain in adult patients undergoing general anesthesia. However, given the limited number of studies included in this meta-analysis and high heterogeneity of some of the results, further studies are required to verify these findings.

Jung et al. [40] evaluated whether the highest SPI value during surgical incision was associated with postoperative pain and opioid consumption. These authors recorded the highest SPI value during surgical incision and compared the postoperative NRS scores for pain and opioid consumption during the first 24 h postoperatively between patients with an SPI > 50 or 20–50. Patients with an SPI > 50 showed higher NRS scores for pain in the PACU and 24 h postoperatively and higher fentanyl consumption during the 24 h postoperatively, suggesting that changes in the SPI in response to nociceptive stimuli during the initial surgical incision is closely related to the degree of postoperative pain and opioid consumption.

Limitations: factors that can affect the reliability of the SPI in various clinical settings

Age

The SPI is determined by two factors (HBI and PPGA) that are inseparably related age [41]. The reference value for heart rate variability differs for individuals aged < 20 and > 60 years [42]. Vascular properties such as arterial stiffness and elasticity are associated with age [43], and the PPGA depends on vascular wall distensibility and intravascular pulse pressure [44]. Therefore, age is a major confounder of SPI monitoring. Additionally, as pediatric patients exhibit lower vascular wall stress and higher distensibility, they are less likely to show prominent decreases in the PPGA from sympathetic stimulation and have increased baseline heart rates compared with adults, resulting in an underestimation of the SPI value [10,45]. For these reasons, an SPI < 40 is the target range for adequate intraoperative analgesia in pediatric patients rather than an SPI < 50, which is the reference range for adults (Fig. 2B) [10,18,32]. In contrast, in older adults, the delivery of pressure waves is accelerated and the intensity is increased owing to increased stiffness in the small and large arteries. Therefore, changes in the PPGA due to sympathetic stimulation increase with age, whereas changes in the heart rate due to sympathetic stimulation decreases with age because of autonomic functional degeneration [46]. These two factors are offset each other; thus, the SPI is maintained at a range of 20–50, which is similar to that of normal healthy adults (Fig. 2C) [15]. However, as the study assessing the effectiveness and characteristics of SPI monitoring in the elderly had a small sample size, it is difficult to generalize the results; thus, further validation is required.

Anesthetics

Most previous RCTs assessing SPI monitoring have included patients receiving total intravenous anesthesia (TIVA) for general anesthesia and found that SPI-guided analgesia reduces opioid consumption [47]. In contrast, in the first study conducted by Gruenewald et al. [21] using an inhalation agent (sevoflurane), SPI-guided analgesia did not reduce intraoperative opioid (sufentanil) consumption. The authors thus concluded that the anesthesia regimen may affect the efficacy of SPI guidance. In another study conducted by Jain et al. [29] using sevoflurane, intraoperative fentanyl consumption was higher in the SPI-guided analgesia group than in the control group. However, another study using sevoflurane showed significantly lower intraoperative oxycodone consumption in the SPI guidance group than in the conventional analgesia group [12]. Therefore, the efficacy and feasibility of inhalational anesthesia rather than TIVA for SPI-guided analgesia requires further exploration.

The concentration of propofol in TIVA has also been found to affect the SPI. Hans et al. [48] reported that high propofol effect-site concentrations tended to increase the SPI due to a decrease in pulse wave amplitude; however, the authors did not provide a clear explanation for this finding. Propofol-induced vasoplegia can occur because high propofol concentrations decrease the peripheral vascular resistance [49,50], which may reduce vascular wall distensibility. Consequently, the magnitude of the change in the PPGA in response to sympathetic stimulation could increase, which has similarly been found in the elderly [15].

Cardiovascular drugs and diseases

The concomitant use of cardiovascular drugs may affect SPI monitoring. Vasodepressor agents (epinephrine, phenylephrine, and nicardipine) in particular may affect SPI values by altering the PPGA and HBI, which may interfere with accurate interpretation
of SPI monitoring [19]. Additionally, chronic treatment (regardless of drug type) for hypertension lowers the SPI response [3]. Nicardipine, a calcium channel-blocking vasodilator, increases PPGA levels, thereby lowering the SPI. Therefore, the SPI does not appropriately reflect the level of nociception and may be ineffective as a guide for opioid administration when nicardipine is administered during general anesthesia [19]. In contrast, the magnitude of change in the PPGA resulting from sympathetic stimulation is higher due to increased stiffness in the small and large arteries. In the elderly, the change in heart rate in response to stimuli decreases with age because of autonomic functional degeneration. These two factors have the effect of offsetting each other; thus, the SPI is maintained at a reference range of 20–50, similar to that in normal healthy adults (C). Δ: change, SPI: surgical pleth index, HR: heart rate, HBI: heartbeat interval, PPGA: photoplethysmographic waveform amplitude.

**Position**

In urological surgery, the SPI was found to increase after a 30° head-up tilt and decrease after a head-down tilt, lasting for at least 45 min [53]. The effect of prone positioning on the SPI during spinal surgery under general anesthesia was also investigated in a previous study [54]. Prone positioning induced a significant increase in the SPI, probably owing to increased sympathetic tone, followed by a gradual reduction over the subsequent 20 min. After moving the patient from supine to prone positioning, the SPI values tended to increase in the absence of noxious stimulation. Therefore, the interpretation of the SPI can be confounded by positioning.

**Consciousness**

The sympathovagal balance is influenced by arousal and emotions. Therefore, during consciousness, the SPI shows no correlation with endocrine stress hormones, including ACTH, cortisol, epinephrine, and norepinephrine, but shows a moderate correlation in anesthetized patients [5].

**Fluid status**

The SPI can be affected by fluid status during steady-state conditions with propofol-remifentanil anesthesia. The SPI is more likely to decrease with worsening hypovolemia [3,48]. However, SPI values are not affected by fluid challenges in normovolemic patients.
However, a correlation between the SPI and opioid consumption has been reported in patients with reduced awareness who were conscious but not fully awake in the PACU [34,55,56]. Moreover, in a study performed in healthy volunteers and parturients by Choi et al. [57], an algometer was used to induce bone pain in volunteers until they rated their pain as an NRS score of 5. This procedure was repeated during the administration of remifentanil or normal saline. The parturients’ SPI data were collected for 2 min when they rated their pain levels at the NRS score of 0, 5, or 7. The SPI was effective at distinguishing pain intensity, irrespective of remifentanil administration. Therefore, further research on the relationship between the SPI and consciousness is needed.

Comparison of SPI monitoring with other nociception monitoring devices on perioperative opioid consumption and quantification of nociception during general anesthesia

Analgesia nociception index

The analgesia nociception index (ANI; MetroDoloris Medical Systems) measures cardiac parasympathetic tone through heart rate variability and shows parasympathetic activity on a scale, ranging from 0 (minimum parasympathetic tone and a high nociceptive level) to 100 (maximum parasympathetic tone and a low nociceptive level). Gruenewald et al. [58] assessed nociceptive balance in terms of the ANI and SPI and the prediction probabilities using the receiver operating characteristic for change in the ANI and SPI values during sevoflurane-remifentanil anesthesia. The ANI and SPI were both significant for indicating patient movement after tetanic stimulation, with a prediction probability of 0.74 and 0.84, respectively. Both the ANI and SPI reflected nociceptive stimulation, although a higher probability was observed for the SPI.

Acute episodes of blood loss are confounding factors in nociception monitoring. The ANI significantly increases during acute intraoperative blood loss and with coadministration of noradrenaline; however, the SPI is not affected [59]. Therefore, the SPI appears to be more reliable during intraoperative bleeding than the ANI.

In addition, the SPI and ANI were compared in a study of conscious patients conducted by Choi et al. [57]. An algometer was used to induce bone pain in the volunteers until they rated their pain as an NRS score of 5 during the administration of remifentanil or normal saline. At an NRS score of 5, the SPI showed similar values irrespective of the solution administered (remifentanil or normal saline), whereas the ANI showed significantly lower values with remifentanil administration. Thus, although both the SPI and ANI were effective indices for detecting pain in healthy volunteers, the SPI showed better performance in terms of the perception of pain intensity, suggesting that the SPI may be useful for pain evaluation even in conscious patients.

Pupillometry

For pupillometry and its variants, such as the pupillary pain index (PPI) and pupillary dilatation reflex (PDR), an infrared camera is used to measure the dynamic pupillary diameter as the width increases in response to nociceptive stimulation. Several studies have shown that pupillometry can be used to accurately measure nociception during anesthesia [60]. SPI monitoring and pupillometry were compared for perioperative opioid consumption during propofol-remifentanil anesthesia [61], and the pupillometry group was associated with better responsiveness to fentanyl and lower analgesic consumption than the SPI group.

Funcke et al. [27] compared the SPI with the PPI and nociception level (NOL) in a pilot study of patients undergoing radical retropubic prostatectomy. Although PPI monitoring reduced sufentanil consumption compared with SPI monitoring and other methods, it consequently increased the endocrine stress response. Additionally, although analgesic titration with the SPI did not result in a reduction in opioid consumption compared with conventional analgesia, it was associated with a reduction in the endocrine stress response. Another full study with a similar design but a larger number of patients was conducted by Funcke et al. [62]. As in previous studies, the opioid consumption was lower with PPI-guided analgesia but the cortisol levels were higher than with SPI-guided analgesia. In this context, although PPI-guided analgesia has been associated with lower opioid consumption, SPI-guided analgesia may reduce the endocrine stress response.

Stasiowski et al. [63] investigated the volume of intraoperative blood loss and a condition (visibility) of the surgical field using the Boezaart bleeding scale in the SPI, PDR, and control groups. By providing better analgesic guidance, the SPI was found to optimize the condition (visibility) of the surgical field, thereby reducing the amount of bleeding compared with other methods. Similar to the results of previous studies [27,62], PDR monitoring was associated with a reduction in the use of opioids and anesthetics.

Nociception level

The NOL (Medasense, Ramat Gan) is a multiparameter index for which photoplethysmography, galvanic skin response, temperature, and accelerometry for finger motion are measured using...
a finger probe. Similar to the SPI, the NOL values range from 0 (no nociception) to 100 (maximum nociception); however, an NOL range of 10–25 is considered appropriate under general anesthesia [64]. According to the studies conducted by Funcke et al. [27,62], although SPI monitoring resulted in higher opioid consumption than NOL monitoring, the endocrine stress response was lower. PPI monitoring resulted in the lowest opioid consumption but the highest endocrine stress response among the three devices. Therefore, further studies comparing these nociception monitoring devices in terms of intraoperative opioid dosing are needed.

In addition, the predictive capacity of these three devices (SPI, PPI, and NOL) for immediate postoperative pain after arousal from general anesthesia was investigated. The study concluded that none of these monitors alone had sufficient diagnostic accuracy for predicting postoperative pain [65], suggesting that a combination of these nociceptive indices and clinical factors may increase the accuracy of postoperative pain prediction.

**Effect of the anesthetic and analgesic regimen or the underlying disease on the intraoperative SPI or perioperative opioid consumption under SPI-guided analgesia**

**Dexmedetomidine**

Although opioids are the mainstay analgesics for moderate-to-severe perioperative pain, greater efforts toward opioid-sparing or opioid-free anesthesia have been made to minimize opioid abuse and its related side effects. In this regard, dexmedetomidine is one of the most commonly investigated non-opioid analgesics. In lung lobectomy with isoflurane anesthesia, dexmedetomidine decreased the intraoperative SPI and NRS scores compared to normal saline as a control [66]. In a preliminary study, adult patients undergoing elective craniotomy for brain tumor resection randomly received an infusion of either fentanyl 1 μg/kg/h or dexmedetomidine 0.5 μg/kg/h. The SPI was similar for both groups during the study period and no differences in biomarkers such as serum cortisol, glucose, or pH were seen between the groups [67].

**Peripheral nerve block**

The type II pectoral nerve block reduced remifentanil consumption during breast surgery with TIVA under SPI-guided analgesia [68]. Abdominal wall blocks, including the rectus sheath and quadratus lumborum blocks, were compared with controls in terms of remifentanil consumption under SPI-guided analgesia, and the abdominal wall blocks significantly reduced both the remifentanil dose during surgery and pain scores [69]. Therefore, during general anesthesia, the regional analgesic effect may be confirmed using the SPI.

**Depth of neuromuscular blockade**

Yi et al. [70] explored the effects of the depth of neuromuscular blockade (NMB), a triad of anesthesia which consists of narcosis, analgesia and muscle relaxation, on nociception. Deep NMB reduced the remifentanil requirement and length of PACU stay compared to moderate NMB during SPI-guided analgesia. This study is consistent with several other studies that found that deep NMB can reduce postoperative pain [71,72].

**Severe liver dysfunction**

The severity of liver dysfunction may affect the intraoperative nociceptive response. In a study by Park et al. [73], liver transplantation patients were assigned according to their median model for end-stage liver disease (MELD) score and divided into low (<16) and high (≥16) MELD groups. When anesthetic depth was maintained within the bispectral index of 40 to 60 and SPI of 20 to 60, the remifentanil requirement was lower in patients with high MELD scores than in those with low MELD scores during the dissection and anhepatic phases; however, no significant differences were observed during the neohepatic phase. The effect of SPI-guided analgesia on patients with liver dysfunction is not clear; thus, further research is needed to clarify this effect.

**Discussion and directions for future research**

Numerous studies of SPI-guided analgesia have been conducted over the past decade, most of which compare SPI-guided analgesia to conventional analgesia. Previous studies have focused on perioperative opioid consumption and postoperative recovery, pain, and adverse events. Although conflicting results have been reported, SPI monitoring has repeatedly been associated with a reduction in intraoperative opioid consumption and the endocrine stress response, faster recovery, and comparable or reduced levels of postoperative pain and rates of adverse events in many studies, including meta-analyses. However, most of these studies were performed in healthy adult populations without underlying diseases. Therefore, further studies involving patients with specific diseases or conditions and of different age groups are warranted. Although some studies have been conducted on children,
the evidence is insufficient, and SPI studies of elderly patients are limited. Considering the growing elderly population worldwide, further research on SPI-guided analgesia in this population is urgently needed. In addition, studies on concomitant medications (e.g., various anesthetics, including remimazolam or other vasoactive agents) and pain assessment (e.g., postoperative pain in the PACU) in conscious patients would improve our understanding of the proper application of SPI-guided analgesia.

Objective measures of nociception during surgery are important in the management of acute perioperative pain. SPI monitoring has been shown to be useful as a surrogate index for predicting the degree of postoperative pain and for intraoperative analgesia guidance. Although SPI values before patient arousal may be useful for predicting the degree of postoperative pain (though diagnostic accuracy is not sufficient), the range for predicting moderate-to-severe postoperative pain, estimated between approximately 30 and 60, has not yet been fully clarified. Further studies are thus needed to clarify this characteristic.

Other nociception monitoring devices such as the ANI, PPI, and NOL have been developed and are currently available. Although these devices are all based on sympathetic-vagal balance, they operate using different underlying mechanisms and autonomic nervous system marker parameters. Each device may thus evaluate nociception differently according to changes in the patient's physiological condition. Therefore, future studies comparing the strengths and weaknesses of all three devices for more detailed purposes, populations, and clinical situations should be conducted. Considering that none of these monitors alone have sufficient diagnostic accuracy for measuring intraoperative nociception or predicting postoperative pain, future studies investigating the accuracy and efficacy of various combinations of nociception-monitoring devices to measure intraoperative nociception or predict postoperative pain should be conducted.

Conclusions

This review summarizes the usefulness and limitations of SPI monitoring for perioperative pain management. SPI-guided analgesia generally allows for the administration of appropriate doses of intraoperative analgesia with fewer adverse hemodynamic events, thereby improving patient recovery and resulting in comparable or reduced levels of postoperative pain and rates of adverse events in patients undergoing surgery under general anesthesia. In addition, the SPI values recorded before patient arousal can help clinicians predict the degree of postoperative pain and analgesic requirements. However, the efficacy of SPI monitoring may be limited by various confounding factors, and various anesthetic and analgesic management strategies or underlying conditions may affect SPI values. As reported thus far, SPI-guided analgesia may allow for adequate analgesia through a reduction in the endocrine stress response and optimization of the surgical conditions by providing superior analgesic guidance and reducing bleeding compared with other nociception monitoring devices.

Through an understanding of the characteristics of SPI monitoring provided by this review, anesthesiologists can provide more appropriate perioperative analgesia in clinical practice, and through recognizing the limitations of our current knowledge on SPI monitoring, future research can be designed comparing SPI and other nociception monitoring devices.

Acknowledgements

We would like to thank Andante, a registered nurse.

Funding

None.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Seok Kyeong Oh (Conceptualization; Validation; Visualization; Writing – original draft; Writing – review & editing)
Young Ju Won (Validation; Visualization; Writing – original draft; Writing – review & editing)
Byung Gun Lim (Conceptualization; Supervision; Visualization; Writing – original draft; Writing – review & editing)

ORCID

Seok Kyeong Oh, https://orcid.org/0000-0002-2939-1848
Young Ju Won, https://orcid.org/0000-0003-4046-0020
Byung Gun Lim, https://orcid.org/0000-0002-3302-1831

https://doi.org/10.4097/kja.23158
References


43. Thijssen DH, Carter SE, Green DJ. Arterial structure and function in vascular ageing: are you as old as your arteries? J Physiol 2016; 594: 2275-84.
72. Oh SK, Kwon WK, Park S, Ji SG, Kim JH, Park YK, et al. Comparison of operating conditions, postoperative pain and recovery; and overall satisfaction of surgeons with deep vs. no neuromuscular blockade for spinal surgery under general anesthesia:

European anesthesiologists’ experiences with gender-based mistreatment in the workplace: a secondary multilevel regression analysis

Joana Berger-Estilita\textsuperscript{1,2,3}, Luana Fritsche\textsuperscript{4}, Kariem El-Boghdady\textsuperscript{5}, Claudia Camila Dias\textsuperscript{3,6}, Marko Zdravkovic\textsuperscript{7,8}

\textsuperscript{1}Institute of Anesthesiology and Intensive Care, Salemspital, Hirslanden Medical Group, Bern, Switzerland, \textsuperscript{2}Institute for Medical Education, University of Bern, Bern, Switzerland, \textsuperscript{3}CINTESIS@RISE, Center for Health Technology and Services Research, Faculty of Medicine, University of Porto, Porto, Portugal, \textsuperscript{4}Medical Faculty, University of Bern, Bern, Switzerland, \textsuperscript{5}Department of Anesthesia, Guy’s and St Thomas’ NHS Foundation Trust, London, UK, \textsuperscript{6}Knowledge Management Unit and Department of Community Medicine, Information and Health Decision Sciences (MEDCIDS), Faculty of Medicine of the University of Porto (FMUP), Alameda Prof. Hernâni Monteiro, Porto, Portugal, \textsuperscript{7}Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia, \textsuperscript{8}Department of Anesthesiology, Intensive Care and Pain Management, University Medical Center Maribor, Maribor, Slovenia

Background: Workplace gender-based mistreatment (GBM) refers to negative or harmful behaviors directed towards employees. In healthcare settings, this can lead to job dissatisfaction and underperformance and potentially compromise patient outcomes. The aim of this study was to examine workplace GBM among European anesthesiologists and produce the first European GBM Rank in Anesthesiology.

Methods: We conducted a secondary analysis from a worldwide cross-sectional survey database consisting of a 46-item questionnaire exploring, among other outcomes, gender bias attributable to workplace attitudes. The survey completion rate was 80.8%. All respondents were selected from European countries. Associations between mistreatment and the remaining variables were analyzed using univariate and multivariable logistic regression analyses. A generalized linear mixed model was then used to quantify the impact of mistreatment in each European country. Statistical significance was set at \( P < 0.05 \).

Results: This study included 5,795 respondents from 43 European countries. The independent predictors of GBM were as follows: female gender, younger age, perceiving gender as a disadvantage for leadership, and perceiving gender as a disadvantage for research. The full model was statistically significant, indicating an ability to distinguish between those who experienced GBM and those who did not (\( P < 0.001 \)). Thus, 26 European countries were ranked based on the prevalence of mistreatment, with Italy showing the best performance (lowest prevalence).

Conclusions: The aim of our study was to provide preliminary insight into GBM in anesthesiology in Europe, function as a key benchmark for gender equity, and chart the evolution of disparities over time.

Keywords: Anesthesiology; Gender bias; Gender equity; Occupational stress; Perceived discrimination; Sexism; Working conditions; Workplace violence.
Introduction

The values espoused by an institution and the social support it provides are key determinants of employees' level of engagement [1]. Workplace gender-based mistreatment (GBM) refers to any negative or harmful behavior directed towards an employee in a workplace setting [2]. GBM can take many different forms, including discrimination, abuse, and harassment. The presence of GBM in a healthcare setting can create a hostile work environment that may lead to job dissatisfaction and underperformance, potentially compromising patient outcomes and leading to burnout, depression, and other poor psychological outcomes, such as suicidality [3–7].

Rates of GBM vary among physicians, with studies reporting rates of harassment ranging from 18% to 50% [3,8], depending on the source within the healthcare setting. Current literature indicates that GBM is particularly common among surgical specialties, specifically among female surgeons and surgical residents [3,8–10]. Given that anesthesia is recognized as a high-stress medical specialty mainly due to a lack of control over the working schedule; poor interpersonal professional relationships; and poor recognition by surgical colleagues, the general public, and the media [11], it would be reasonable to assume that these issues also exist in the anesthesia community.

Indeed, prior research has established that GBM occurs in the workplace for anesthesiologists [12–14]. Sources of GBM among anesthesiologists include colleagues, surgeons, patients, visitors, and supervising physicians [3,14]. A recent survey demonstrated that female anesthesiologists perceived the attitudes of coworkers (including surgeons, patients, nurses, and other anesthesiology colleagues) towards them to be worse than those perceived by male anesthesiologists [14]. The odds being mistreated in the workplace was 10.6 times greater for female anesthesiologists than for male anesthesiologists, and women chose to report GBM in only 24% of cases. This may be due to the limited number of countries with gender policy statements in the field of anesthesia and unclear country-specific legal dispositions for workplace GBM offenders [15].

The aspects of the work environment that are associated with perceptions of workplace GBM among anesthesiologists in Europe and the differences among European countries are currently not clear. The aim of this study is to address this knowledge gap and explore the variables associated with workplace GBM among anesthesiologists in Europe and the specific countries that are more at risk of being subjected to these forms of work-related environmental stress. We expect this ranking to provide a basis for comparing different European countries and, more importantly, serve as a benchmarking tool for monitoring progress over time. In this study, the term “gender” refers to an individual’s gender identity, which is distinct from the sex assigned at birth. Gender identity refers to a person’s deeply felt sense of gender, regardless of whether it aligns with the sex they were assigned at birth. It encompasses one's internal sense of being male, female, neither, or any other gender identity. It is important to differentiate between gender and sex assigned at birth, as the latter is based on biological attributes such as genitalia, while gender identity is a deeply personal and subjective experience.

Materials and Methods

Ethics

We conducted a secondary analysis of an existing database that assessed anesthesiologists’ careers, including leadership and research opportunities, clinical work attitudes, and considerations for gender equality. The project underwent a rigorous ethical review process, provided by the Ethics Committee at the University Medical Center Maribor, Maribor, Slovenia (Chairperson, Associate Professor Milan Reljic, M.D., Ph.D.) and collected under Ref. UKC-MB-KME-75/19 on September 11, 2019. The data were maintained in accordance with the highest ethical standards, including measures to protect the participants’ confidentiality and privacy. A separate ethical approval was not required for the publication of the secondary analysis, as the Institutional Review Board review of the initial survey was considered adequate. Moreover, as part of the survey, the respondents explicitly granted permission for an analysis to be published. At the end of the survey, participants were presented with a comprehensive set of questions and informed about the research objectives. They provided informed consent for the use of their responses in the subsequent analyses. As this type of consent ensures that participants have a full understanding of how their data will be used, it is particularly robust and enhances the ethical foundation of our secondary analysis. This study complies with the CROSS EQUATOR reporting guidelines.

Participants

We conducted an international, internet-based, cross-sectional survey of anesthesia physicians. Briefly, we used a 46-item questionnaire to assess anesthesiologists’ perceptions of leadership, research opportunities, and clinical work attitudes (Questionnaire – Supplementary Material 1). After a pilot was conducted and validated, the questionnaire was hosted online on
SurveyMonkey®. It was then distributed through social media using the ‘snowballing’ sampling technique [16,17]. The survey was available from September 14, 2019 to October 26, 2019, and included 15,714 respondents from 148 countries. The survey completion rate was 80.8% [14]. We aimed to reduce selection bias by collecting at least 10% of the members of the national anesthesiology society for each country or at least five responses per million people [17]. An in-depth description of the survey development and distribution methodology has been published elsewhere [14].

In this secondary analysis, we examined the factors associated with workplace GBM among European anesthesiologists. The survey questionnaire consisted of several items assessing various aspects of gender bias and workplace mistreatment. We focused on the associations and potential predictors of GBM based on the survey responses to question 22: ‘Have you ever been mistreated at your workplace because of your gender?’ (Questionnaire – Supplementary Material 1). Importantly, the questions used as explanatory variables in our regression analyses are independent of the dependent variable (i.e., the presence of GBM). These questions primarily focus on demographic information and perceptions of gender-related disadvantages in leadership and research. As these questions were independent from the outcome variable, we were able to independently analyze their individual contributions to GBM. To ensure the validity of our regression models, we assessed the assumption of independence among the independent variables. This assessment was carried out both before and during the modeling phase. Before initiating regression modeling, we evaluated the potential correlations among the independent variables by computing the correlation matrices and creating scatterplots to visualize any relationships or associations among the independent variables. This pre-modeling assessment allowed us to identify any significant correlations that could affect the independence assumption. Throughout the modeling process, we employed variance inflation factor (VIF) analyses as an additional measure to quantify the degree of multicollinearity among the independent variables. High VIF values indicate problematic levels of multicollinearity that can affect the independence assumption of the regression models. We closely monitored the VIF values to ensure that our models met the independence criterion. Regardless, this assumption of independence would not have affected the validity of the regression analyses. We also recognize that additional factors or interactions not captured by these questions may also contribute to GBM, and further research should explore these factors in more detail.

We selected all respondents from European countries, as defined by the European Society of Anesthesiology and Intensive Care and the World Health Organization [18]. Demographic characteristics were assessed, including self-reported gender (woman, man, non-binary), age, and level of training.

**Statistical analysis**

A descriptive statistical analysis was conducted to determine the characteristics of the respondents. Proportions are reported for categorical variables. Parametric data are reported as mean ± SD and were analyzed using the Student’s t-test. Associations between GBM and the remaining variables were analyzed using univariate and multivariable logistic regression, with the goal of identifying independent predictors. Model fit was examined using the Cox & Snell R² and Nagelkerke R² of the variance in checklist completion. Statistical significance was set at P < 0.05. Receiver operating characteristic curves of the multivariate observations were plotted to assess the predictive performance of the logistic regression model. All the statistical analyses were performed using SPSS version 27 (IBM Corp.).

Generalized linear mixed models (GLMMs) were then developed to quantify the impact of GBM in each European country. We used GLMMs because they estimate fixed and random effects and are useful when the dependent variable is binary, ordinal, count, or quantitative but not normally distributed [19]. We developed several models using the fixed variables that were statistically significant in the prior logistic regression. Among all possible models, we chose the one with the lowest Akaike information criterion (AIC) because this would represent a better model fit. The AIC is an estimator of the prediction error and thereby the relative quality of a statistical model for a given dataset and is used to determine how well a dataset fits the data from which it was generated [20]. We assumed a binomial distribution for the GLMM estimation as this was the most appropriate for modeling the variability in our data, considering the nature of our response variable and the design of the study. We used the logit link function in the GLMM as the response variable was categorical.

Among the models with lower AICs, we chose the one with the fewest variables. The fixed-effect factor covariates in our chosen model were gender, ratio of women to men in the workplace, gender of the department head, and perception of gender as a disadvantage for leadership. The random variable was the country of practice. Fixed-effect factor covariates were estimated using an extended likelihood or first-order Laplace approximation of marginal probability [21]. This approach is suitable for non-Gaussian response distributions, and effectively handles random effects, ensuring accurate parameter estimations and precise GBM score predictions for European countries.

Using the “1 variable per 10 events” criterion, we excluded
countries with fewer than 50 total responses. A total of 26 countries were thus included in the GLMM analyses. A random intercept for each country accounted for the intra-country correlations. The statistical significance of the analysis point covariate was tested using the drop in the deviation compared with the null model. The GBM value was analyzed in a manner consistent with its bounded range, acknowledging that the range of possible values associated with this variable was limited. For zero values, a marginal value of 0.001 was added to comply with the beta distribution range. All the analyses were based on the input dataset. For the GLMM, statistical significance was set at $P < 0.05$. Statistical analyses were performed using R and R Studio (R version 4.2.1., The R Foundation for Statistical Computing). The following R packages were used in our analysis: ggplot2 (version 3.3.3) [22], lme4 (version 1.1-27) [23], dplyr (version 1.0.6) [24], caret (version 6.0-88) [25], and foreign (version 0.8-82) [26].

Treatment of missing data and response consistency

Our approach to missing data involved the use of multiple imputation techniques to estimate the missing values. This method involves creating several datasets with imputed values for missing data points. The imputed datasets were generated based on the observed information and relationships within the dataset. We then analyzed these datasets and combined the results to consider the variability introduced by the imputation process. To maintain response consistency and ensure data quality, we implemented data validation checks and quality control procedures throughout survey administration and the data collection process. These measures included data validation checks, peer debriefing, and interim analyses. Automated data validation checks were integrated into the online survey platform to ensure that the respondents provided complete and internally consistent responses. For example, we used logic checks to confirm that responses to certain questions were consistent with previous answers or fell within a valid range. Our research team regularly engaged in peer debriefing sessions to collectively review and discuss the survey responses. This iterative process allowed us to identify and rectify any inconsistencies or discrepancies in the data. Finally, we conducted interim analyses in clusters of 1,500 responses for open-ended questions. This approach assessed data saturation and identified common themes and emerging patterns. These interim analyses helped us to refine our understanding of the data and maintain response consistency. We used complete case analysis, commonly referred to as listwise deletion, as our method for handling missing data during data analysis. To implement this approach, we first identified missing data for each variable of interest in our dataset. Cases or observations with any missing values for these variables were systematically excluded from the analysis, resulting in a dataset comprising only complete cases.

Results

In our analysis, we included responses from 43 European countries ($n = 5,795$) to investigate the factors associated with GBM in the workplace (Table 1). Univariate and multivariable logistic regression analyses were conducted to understand the impact of various factors on the likelihood of experiencing GBM.

The multivariable logistic regression model included four independent variables: age, gender, perception of gender as a disadvantage for leadership, and perception of gender as a disadvantage for research. We also considered interactions such as the ratio of women to men, number of female anesthesiologists per department, and their respective interactions (Supplementary Material 2). The full model, which contained all these predictors, was statistically significant ($P < 0.001$), demonstrating that it could distinguish between individuals who had and those who had not experienced GBM (for detailed logistic regression results, see Supplementary Material 2). Notably, female gender, younger age, and perceiving gender as a disadvantage for leadership or research were identified as independent predictors of GBM.

We employed GLMMs to further explore variations in GBM across European countries. The GLMMs were constructed using a binomial distribution and logit link function suitable for the binary nature of the response variable (presence or absence of GBM). Our chosen GLMM incorporated four fixed-effect predictor variables: gender, ratio of women to men in the workplace, gender of the department head, and perception of gender as a disadvantage for leadership. The random effect was the country of practice. This analysis allowed us to rank European countries based on GLMMs and generate the 2020 European GBM Rank in Anesthesiology (Fig. 1, Table 2). Fig. 2 shows the observed rates of Workplace GBM across various European countries. These rates visually represent the state of GBM in each country, with lower rates indicating a more favorable workplace environment in terms of mistreatment.

In addition to our primary results, we conducted model validation analyses to assess the predictive performance and reliability of the GLMMs used to predict the GBM scores for each European country. For detailed results and information on model selection, see the Supplemental Digital Contents (Supplementary Tables 1 and 2). These supplementary analyses ensure transparency and provide a comprehensive explanation of the performance of the statistical model.
<table>
<thead>
<tr>
<th>Country</th>
<th>Respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albania</td>
<td>7 (43)</td>
</tr>
<tr>
<td>Armenia</td>
<td>16 (50)</td>
</tr>
<tr>
<td>Austria</td>
<td>287 (53)</td>
</tr>
<tr>
<td>Belgium</td>
<td>133 (47)</td>
</tr>
<tr>
<td>Bosnia &amp; Herzegovina</td>
<td>55 (30)</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>42 (50)</td>
</tr>
<tr>
<td>Croatia</td>
<td>115 (70)</td>
</tr>
<tr>
<td>Cyprus</td>
<td>13 (77)</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>59 (36)</td>
</tr>
<tr>
<td>Denmark</td>
<td>91 (48)</td>
</tr>
<tr>
<td>Estonia</td>
<td>49 (59)</td>
</tr>
<tr>
<td>Finland</td>
<td>101 (53)</td>
</tr>
<tr>
<td>France</td>
<td>301 (41)</td>
</tr>
<tr>
<td>Georgia</td>
<td>7 (43)</td>
</tr>
<tr>
<td>Germany</td>
<td>420 (72)</td>
</tr>
<tr>
<td>Greece</td>
<td>105 (65)</td>
</tr>
<tr>
<td>Hungary</td>
<td>63 (60)</td>
</tr>
<tr>
<td>Iceland</td>
<td>15 (74)</td>
</tr>
<tr>
<td>Ireland</td>
<td>60 (29)</td>
</tr>
<tr>
<td>Israel</td>
<td>47 (40)</td>
</tr>
<tr>
<td>Italy</td>
<td>869 (63)</td>
</tr>
<tr>
<td>Kosovo</td>
<td>6 (50)</td>
</tr>
<tr>
<td>Latvia</td>
<td>36 (29)</td>
</tr>
<tr>
<td>Lithuania</td>
<td>27 (70)</td>
</tr>
<tr>
<td>Malta</td>
<td>27 (43)</td>
</tr>
<tr>
<td>Montenegro</td>
<td>4 (50)</td>
</tr>
<tr>
<td>Netherlands</td>
<td>124 (48)</td>
</tr>
<tr>
<td>Norway</td>
<td>37 (46)</td>
</tr>
<tr>
<td>Poland</td>
<td>170 (12)</td>
</tr>
<tr>
<td>Portugal</td>
<td>192 (66)</td>
</tr>
<tr>
<td>Republic of Moldova</td>
<td>31 (48)</td>
</tr>
<tr>
<td>Republic of North Macedonia</td>
<td>31 (47)</td>
</tr>
<tr>
<td>Romania</td>
<td>216 (67)</td>
</tr>
<tr>
<td>Russia</td>
<td>130 (59)</td>
</tr>
<tr>
<td>Serbia</td>
<td>89 (76)</td>
</tr>
<tr>
<td>Slovakia</td>
<td>42 (48)</td>
</tr>
<tr>
<td>Slovenia</td>
<td>80 (69)</td>
</tr>
<tr>
<td>Spain</td>
<td>631 (63)</td>
</tr>
<tr>
<td>Sweden</td>
<td>110 (17)</td>
</tr>
<tr>
<td>Switzerland</td>
<td>112 (51)</td>
</tr>
<tr>
<td>Turkey</td>
<td>256 (68)</td>
</tr>
<tr>
<td>Ukraine</td>
<td>247 (33)</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>342 (47)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender as disadvantage for research (of agree/unsure)</th>
<th>Gender as disadvantage for leadership (of agree/unsure)</th>
<th>Woman as current HOD</th>
<th>Woman as past HOD</th>
<th>Ever been mistreated at workplace</th>
<th>Reported the incident</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.34 ± 0.19 45 ± 7</td>
<td>1 (25)</td>
<td>2 (29)</td>
<td>2 (29)</td>
<td>3 (43)</td>
<td>1 (33)</td>
</tr>
<tr>
<td>0.35 ± 0.22 42 ± 13</td>
<td>3 (30)</td>
<td>3 (30)</td>
<td>2 (13)</td>
<td>5 (31)</td>
<td>1 (6)</td>
</tr>
<tr>
<td>0.49 ± 0.16 44 ± 11</td>
<td>33 (22)</td>
<td>122 (48)</td>
<td>25 (9)</td>
<td>45 (16)</td>
<td>68 (24)</td>
</tr>
<tr>
<td>0.66 ± 0.23 42 ± 12</td>
<td>72 (38)</td>
<td>21 (12)</td>
<td>69 (15)</td>
<td>14 (18)</td>
<td>13 (17)</td>
</tr>
<tr>
<td>0.56 ± 0.23 40 ± 8</td>
<td>13 (43)</td>
<td>28 (64)</td>
<td>19 (35)</td>
<td>15 (29)</td>
<td>20 (36)</td>
</tr>
<tr>
<td>0.68 ± 0.14 42 ± 9</td>
<td>17 (35)</td>
<td>49 (47)</td>
<td>54 (47)</td>
<td>38 (33)</td>
<td>52 (45)</td>
</tr>
<tr>
<td>0.71 ± 0.23 43 ± 10</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>9 (69)</td>
<td>5 (56)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>0.56 ± 0.12 37 ± 9</td>
<td>8 (25)</td>
<td>25 (46)</td>
<td>4 (7)</td>
<td>3 (5)</td>
<td>14 (24)</td>
</tr>
<tr>
<td>0.45 ± 0.14 44 ± 9</td>
<td>6 (43)</td>
<td>27 (33)</td>
<td>13 (14)</td>
<td>18 (21)</td>
<td>21 (23)</td>
</tr>
<tr>
<td>0.58 ± 0.14 42 ± 11</td>
<td>2 (10)</td>
<td>16 (35)</td>
<td>7 (14)</td>
<td>10 (21)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>0.54 ± 0.15 47 ± 11</td>
<td>22 (51)</td>
<td>19 (23)</td>
<td>46 (46)</td>
<td>30 (31)</td>
<td>22 (22)</td>
</tr>
<tr>
<td>0.45 ± 0.17 42 ± 12</td>
<td>42 (38)</td>
<td>78 (31)</td>
<td>70 (25)</td>
<td>64 (23)</td>
<td>51 (17)</td>
</tr>
<tr>
<td>0.61 ± 0.09 40 ± 8</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>3 (43)</td>
<td>2 (29)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>0.47 ± 0.15 41 ± 10</td>
<td>60 (36)</td>
<td>149 (41)</td>
<td>18 (4)</td>
<td>24 (6)</td>
<td>96 (23)</td>
</tr>
<tr>
<td>0.65 ± 0.17 43 ± 9</td>
<td>13 (39)</td>
<td>29 (31)</td>
<td>77 (74)</td>
<td>55 (53)</td>
<td>46 (44)</td>
</tr>
<tr>
<td>0.58 ± 0.13 43 ± 12</td>
<td>9 (31)</td>
<td>27 (52)</td>
<td>12 (19)</td>
<td>19 (30)</td>
<td>26 (41)</td>
</tr>
<tr>
<td>0.43 ± 0.09 50 ± 10</td>
<td>0 (0)</td>
<td>1 (8)</td>
<td>5 (33)</td>
<td>1 (7)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>0.34 ± 0.11 41 ± 9</td>
<td>10 (53)</td>
<td>18 (35)</td>
<td>36 (60)</td>
<td>3 (5)</td>
<td>16 (27)</td>
</tr>
<tr>
<td>0.30 ± 0.10 47 ± 13</td>
<td>5 (36)</td>
<td>8 (23)</td>
<td>3 (6)</td>
<td>0 (0)</td>
<td>8 (17)</td>
</tr>
<tr>
<td>0.57 ± 0.15 42 ± 11</td>
<td>120 (47)</td>
<td>451 (58)</td>
<td>203 (24)</td>
<td>108 (13)</td>
<td>203 (23)</td>
</tr>
<tr>
<td>0.49 ± 0.07 49 ± 13</td>
<td>0 (0)</td>
<td>3 (75)</td>
<td>0 (0)</td>
<td>1 (17)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>0.60 ± 0.15 35 ± 10</td>
<td>4 (33)</td>
<td>12 (40)</td>
<td>26 (74)</td>
<td>10 (29)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>0.65 ± 0.13 33 ± 9</td>
<td>3 (27)</td>
<td>7 (33)</td>
<td>14 (52)</td>
<td>13 (48)</td>
<td>13 (48)</td>
</tr>
<tr>
<td>0.46 ± 0.04 38 ± 10</td>
<td>4 (29)</td>
<td>11 (41)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5 (19)</td>
</tr>
<tr>
<td>0.45 ± 0.37 41 ± 3</td>
<td>0 (0)</td>
<td>2 (67)</td>
<td>2 (50)</td>
<td>3 (75)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>0.46 ± 0.14 43 ± 10</td>
<td>9 (24)</td>
<td>31 (28)</td>
<td>14 (12)</td>
<td>8 (7)</td>
<td>24 (19)</td>
</tr>
<tr>
<td>0.30 ± 0.10 47 ± 13</td>
<td>3 (19)</td>
<td>8 (29)</td>
<td>13 (35)</td>
<td>9 (26)</td>
<td>10 (27)</td>
</tr>
<tr>
<td>0.57 ± 0.16 41 ± 10</td>
<td>18 (21)</td>
<td>55 (39)</td>
<td>30 (18)</td>
<td>43 (26)</td>
<td>41 (24)</td>
</tr>
<tr>
<td>0.67 ± 0.17 40 ± 10</td>
<td>15 (18)</td>
<td>50 (29)</td>
<td>87 (46)</td>
<td>111 (59)</td>
<td>28 (15)</td>
</tr>
<tr>
<td>0.52 ± 0.18 34 ± 7</td>
<td>2 (18)</td>
<td>10 (44)</td>
<td>4 (13)</td>
<td>6 (20)</td>
<td>11 (36)</td>
</tr>
<tr>
<td>0.68 ± 0.15 35 ± 7</td>
<td>11 (52)</td>
<td>8 (29)</td>
<td>21 (68)</td>
<td>68 (21)</td>
<td>12 (39)</td>
</tr>
</tbody>
</table>

Values are presented as number, number (%) or mean ± SD. HOD: head of department.
Fig. 1. Workplace gender-based mistreatment ranking for anesthesiology in European countries: the 2020 European Gender-Based Mistreatment Rank in Anesthesiology. Lower regression coefficients (green) indicate better performance.

Fig. 2. Observed rates of workplace gender-based mistreatment (GBM). This figure illustrates the observed rates of workplace-GBM among various European countries. The rates visually represent the state of mistreatment in each country. Lower rates indicate better performance (lower rates of gender-based mistreatment in the workplace). The figure is meant as a complementary visual representation of the mistreatment data to be used alongside our modeling results.

https://doi.org/10.4097/kja.23392
Table 2. Workplace Gender-based Mistreatment Ranking - the 2020 European Gender-based Mistreatment Rank in Anesthesiology: Results for the Generalized Linear Mixed Model with a Binary Dependent Variable

<table>
<thead>
<tr>
<th>Country</th>
<th>n = 5,358</th>
<th>Betas</th>
</tr>
</thead>
<tbody>
<tr>
<td>Italy</td>
<td>869</td>
<td>1.537</td>
</tr>
<tr>
<td>Portugal</td>
<td>192</td>
<td>1.611</td>
</tr>
<tr>
<td>Russia</td>
<td>130</td>
<td>1.623</td>
</tr>
<tr>
<td>Belgium</td>
<td>133</td>
<td>1.721</td>
</tr>
<tr>
<td>Serbia</td>
<td>89</td>
<td>1.799</td>
</tr>
<tr>
<td>Austria</td>
<td>287</td>
<td>1.825</td>
</tr>
<tr>
<td>Poland</td>
<td>170</td>
<td>1.910</td>
</tr>
<tr>
<td>France</td>
<td>301</td>
<td>1.923</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>59</td>
<td>1.938</td>
</tr>
<tr>
<td>Sweden</td>
<td>110</td>
<td>1.945</td>
</tr>
<tr>
<td>Denmark</td>
<td>91</td>
<td>1.953</td>
</tr>
<tr>
<td>Switzerland</td>
<td>112</td>
<td>1.956</td>
</tr>
<tr>
<td>Finland</td>
<td>101</td>
<td>1.960</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>124</td>
<td>2.001</td>
</tr>
<tr>
<td>Turkey</td>
<td>256</td>
<td>2.008</td>
</tr>
<tr>
<td>Romania</td>
<td>216</td>
<td>2.011</td>
</tr>
<tr>
<td>Ukraine</td>
<td>247</td>
<td>2.056</td>
</tr>
<tr>
<td>Ireland</td>
<td>60</td>
<td>2.060</td>
</tr>
<tr>
<td>Germany</td>
<td>420</td>
<td>2.095</td>
</tr>
<tr>
<td>Bosnia and Herzegovina</td>
<td>55</td>
<td>2.199</td>
</tr>
<tr>
<td>Slovenia</td>
<td>80</td>
<td>2.216</td>
</tr>
<tr>
<td>UK</td>
<td>342</td>
<td>2.232</td>
</tr>
<tr>
<td>Spain</td>
<td>631</td>
<td>2.326</td>
</tr>
<tr>
<td>Hungary</td>
<td>63</td>
<td>2.434</td>
</tr>
<tr>
<td>Croatia</td>
<td>115</td>
<td>2.521</td>
</tr>
<tr>
<td>Greece</td>
<td>105</td>
<td>2.916</td>
</tr>
</tbody>
</table>

The fixed effects in the model with their regression coefficients are as follows: intercept (−3.124), female gender (2.078), ratio of women to men in the department (−0.108), gender of the department head (woman) (0.119), gender as a disadvantage for leadership (1.305), and AIC (3.614). Lower regression coefficients indicate better performance. AIC: Akaike information criterion, n: number of respondents.

Discussion

To the best of our knowledge, this is the first study to analyze GBM data among anesthesiology workplaces in Europe. The most significant predictors of GBM in the workplace were female gender, younger age, perceiving gender as a disadvantage for leadership, and perceiving gender as a disadvantage for research. The 2020 EGMRA, which ranks European countries based on GBM, shows a different ranking from well-known gender equity indices for European countries [27–29], where central and northern European countries are usually placed in the top positions.

Given that gender equity is fundamental for developing more collaborative environments, increasing teamwork efficacy [30], and improving patient outcomes [31–34], effective monitoring of gender equity in the field of anesthesiology is essential. We compared the countries' overall performance in achieving gender equity in anesthesia using a single measure that combines multiple indicators and dimensions into a single standardized value. The GBM score generated from this study may offer insights into overall gender inequality and inequity in the field of anesthesiology at the national level. It can function as a crucial benchmark for gender equity and could be used to chart the evolution of gender equity over time.

The fact that our predictors for GBM were female gender and younger age was not surprising. Female residents are at risk of several forms of GBM [3,7,35] and are more likely than male residents to report experiences of gender-based discrimination and harassment [4,14,36]. Our GBM ranking shows that mistreatment in anesthesiology does not follow general patterns of gender equity, as seen in the Gender Equality Index [27] or the Global Gender Gap Index [37]. These indices consistently show better performance for Scandinavian countries compared to other European countries, and Mediterranean countries frequently perform below the European average. Thus, applying these general indices to the medical workforce may be inappropriate. These indices primarily measure human development while accounting for gender inequity [29] rather than directly addressing specific factors and considerations pertinent to GBM in the context of the workforce in the medical sector.

Additionally, the degree to which women in anesthesiology face inequity today may differ among countries without necessarily implying a cultural or geographical relationship. However, our ranking trend loosely resembles Eurofound's index of adverse social behaviors for healthcare workers, where Central, Western European, and Scandinavian countries show the highest percentages of workers reporting violence or harassment in the workplace. Eurofound, short for the European Foundation for the Improvement of Living and Working Conditions, is an EU agency that primarily aims to provide research and information on social and work-related issues to support policy development in Europe. In contrast, a smaller proportion of workers reported GBM in half of the Eastern and Southern European countries [36].

In our analysis, Italy was found to have the lowest gender mistreatment among the countries studied. While pinpointing the precise reasons for this distinction requires careful examination, several pertinent factors may have contributed to Italy's relatively lower index value. First, Italy's legislative framework and policies regarding GBM and workplace harassment within the medical sector, including anesthesiology, may be more robust and diligent.
ly enforced than those in other countries [38]. Robust legal safeguards and effective reporting mechanisms can reduce the incidence of gender mistreatment. Cultural and societal norms also play pivotal roles in shaping workplace dynamics. Italy may have made significant advancements in promoting gender equality and cultivating respectful environments within anesthesiology [39,40]. Furthermore, Italy’s leadership within anesthesiology societies, such as the Società Italiana di Anestesia Analgesia Rianimazione e Terapia Intensiva (SIAARTI), may have significantly influenced the lower gender mistreatment index among anesthesiologists. The presence of women in influential roles, including as board chairs, can also foster an inclusive and respectful workplace culture [38]. Therefore, effective reporting mechanisms require further consideration. Italy may have established accessible and efficient systems for reporting gender mistreatment incidents within the field of anesthesiology, which can encourage victims to come forward.

Nevertheless, even within specific medical specialties such as anesthesiology, international comparisons of gender mistreatment indices can be complex because of variations in reporting practices and data collection methods. Italy’s lower index may reflect recent improvements in addressing gender mistreatment within anesthesiology, while other countries may still be implementing comprehensive measures, like, for example, the implementation of clear policies, training programs, reporting mechanisms, diversity initiatives, leadership commitment, and research to tackle GBM and discrimination. Although our analysis suggests that Italy exhibits a lower gender mistreatment index within the specialized context of anesthesiology, further in-depth research into the interplay of these factors and a meticulous examination of workplace practices, policies, and cultural attitudes specific to anesthesiology are needed to gain a more nuanced understanding of this phenomenon.

Some evidence suggests that having more women in leadership roles may be associated with less GBM in the workplace, including sexual harassment and discrimination [41–44]. However, this correlation does not necessarily imply causation. Other factors, such as organizational culture and policies, may also play a role in reducing GBM in the workplace.

Overall, many factors contribute to higher levels of gender harassment among healthcare workers in some European countries. These factors include the absence of legal protections, workplace culture and policies, education and training, and societal norms and values [36]. It is difficult to directly compare the GBM of anesthesiologists in Greece, our worst-ranked country, and other European countries, as GBM is influenced by many factors. However, anesthesiologists in Greece may encounter higher GBM levels partly due to the severe economic crisis that occurred the decade before data collection, leading to cuts in healthcare spending and hospital understaffing [45]. The Greek healthcare system has been underfunded for many years, leading to a shortage of resources, such as medical supplies, equipment, and hospital beds [46]. Despite recent legislation by the Greek government [47] creating policies against violence and harassment in the workplace, enforcement mechanisms may still be lacking, making it easier for GBM to occur.

**Limitations**

Although our secondary analysis provided valuable insights into the rankings of GBM among European countries based on the collected data, the study had some limitations. This study represents a secondary analysis of a pre-existing dataset. Although the primary survey was global in scale, exploring the European subset provides a valuable opportunity to gain region-specific insights. Our logistic regression analysis identified factors linked to GBM within the European context. It is important to note that this focus on Europe entailed a reduction in sample size, which is acknowledged as a tradeoff. We also acknowledge that gender inequity is multifaceted and thus is often measured using multiple indicators. While gender equity in anesthesia must be effectively monitored, specific dimensions of GBM may also require qualitative assessments. This recognition acknowledges the multifaceted nature of gender equity and the need for subjective experiences and qualitative aspects to be captured that cannot be easily measured numerically. Therefore, combining quantitative and qualitative assessments would provide a more holistic understanding of gender equity in anesthesia and help in addressing the diverse factors that contribute to gender disparities. Additionally, we only examined gender, thus other protected characteristics (e.g., ethnicity, sexual orientation, disability) that should be considered for a more comprehensive understanding of GBM were not assessed. For instance, the observation that women from Low- and Middle-Income Countries appear more ‘content’ than those from Upper Income Countries, as mentioned in our recent paper [14], warrants further investigation to identify the specific factors that contribute to these sentiments.

Efforts to reduce GBM within healthcare, particularly in fields such as anesthesiology, can benefit significantly from data-supported actions. These actions involve harnessing data to inform and implement strategies. Robust data collection and analyses help clarify the prevalence and patterns of GBM and identify areas that require attention [14]. Grounded in data-guided insights, educational programs and awareness campaigns can promote respectful behavior among healthcare professionals and raise aware-
ness about GBM. Data-guided policymaking ensures the development and enforcement of effective anti-GBM measures. In addition, training programs, diverse leadership initiatives, and support for victims can be tailored to data-derived needs [12]. Conducting observations, evaluations, and ongoing research has further enhanced these efforts. International collaboration in sharing data and best practices widens the impact and creates safer and more equitable healthcare environments [48].

Although our study provides valuable insights into the prevalence of GBM among anesthesiologists across Europe, certain limitations must be acknowledged. We recognize that the number of respondents varied according to country, which could have introduced bias into our findings. However, we took steps to address this issue. First, we restricted our analysis to countries meeting specific criteria, including a minimum number of responses (either five per million population or 10% of the members of the national anesthesiologists' associations). Second, for robust statistical analysis, we required a minimum of 50 respondents per country. Another limitation was the lack of essential demographic and sociodemographic factors in our study such as race, sexual orientation, and disability, all of which could influence how individuals perceive and experience GBM. However, collecting more detailed demographic information may have raised ethical concerns and affected respondents’ willingness to participate. Furthermore, the GBM scores obtained in this study represent only a snapshot assessment of the second half of 2019. Nevertheless, the key aspects of the GBM explored in our analysis can serve as a foundation for future research to track trends in this area over time. In addition, the survey responses could have been affected by subjective judgments. The limitations of our previous study [14] regarding the potential for bias and subjectivity in respondents’ answers also apply to this dataset. We also recognize that the reported rates of GBM may not accurately reflect the true prevalence in each country. Some healthcare workers may choose not to report GBM because of fear of retaliation or job loss. Additionally, some hospitals or healthcare settings may have a culture of tolerance towards GBM or the expectation that healthcare workers should endure mistreatment as part of their job. Such analyses usually benefit from external validation, which was not possible in this study; the data are only from Europe and may not be generalizable to other parts of the world. It is also important to clarify that our intention was not to make broad generalizations based on a single example. Although collecting additional direct information or conducting further surveys involving Italian respondents could have resulted in a more comprehensive understanding, such extensive investigations were beyond the scope of this study. Moreover, providing explanations of our findings may be challenging because data on GBM in anesthesia and other fields are limited in most European countries. Finally, although the original survey included a non-binary gender option, only a small proportion of participants identified as non-binary; therefore, further statistical analyses were precluded. These limitations underscore the need for ongoing research efforts to offer a more holistic understanding of GBM in the context of anesthesiology across Europe. Incorporating nuanced analyses that consider contextual factors, such as national policies, institutional dynamics, and healthcare system structures, is essential for understanding the complexities of GBM across different countries. Further examinations of cases in Italy, where potential preferential treatment policies exist, could provide valuable insights into how these factors intersect with the anesthesiologists’ experiences of GBM.

Scientific and institutional interest in workplace inequity is rapidly increasing. Therefore, our methodologically-validated ranking could be used as a monitoring tool. However, specific intrapersonal, interpersonal, or socio-environmental factors are often used as an inaccurate explanation for the cause of GBM. Our ranking aims not only to provide initial insight into GBM among anesthesiologists in Europe, but also to function as a key benchmark for gender equity and to chart the evolution of disparities over time.

Acknowledgements

We would like to thank Dr. Natalie Urwyler for her valuable input and assistance with this article.

Funding

None.

Conflicts of Interest

MZ is an ESAIC Gender Equity Committee member. JBE is a member of the ESAIC eLearning, Scientific and Examinations Committee and has received support from Medtronic® for implementation of the Safe Brain Initiative. The remaining authors declare no conflicts of interest.

Data Availability

The datasets generated during and/or analyzed during the current study are not publicly available due to the sensitive nature of some questions but are available from the corresponding author on reasonable request.
Author Contributions

Joana Berger-Estilita (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing)
Luana Fritsche (Writing – original draft; Writing – review & editing)
Kariem El-Boghdadly (Conceptualization; Formal analysis; Project administration; Supervision; Writing – review & editing)
Claudia Camila Dias (Formal analysis; Methodology; Software; Writing – original draft; Writing – review & editing)
Marko Zdravkovic (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing)

Supplementary Materials

Supplementary Material 1. Questionnaire.
Supplementary Material 2. Detailed statistical results of the logistic regression.
Supplementary Table 1. Workplace gender-based mistreatment ranking - the 2020 European Gender-Based Mistreatment Rank in Anesthesiology: results for the generalized linear mixed model with a binary dependent variable and five independent variables.
Supplementary Table 2. Workplace gender-based mistreatment ranking - the 2020 European Gender-Based Mistreatment Rank in Anesthesiology: results for the generalized linear mixed model with a binary dependent variable and nine independent variables.

ORCID

Joana Berger-Estilita, https://orcid.org/0000-0002-8695-4264
Kariem El-Boghdadly, https://orcid.org/0000-0002-9912-717X
Claudia Camila Dias, https://orcid.org/0000-0001-9356-3272
Marko Zdravkovic, https://orcid.org/0000-0002-0033-7071

References

international survey about rapid sequence intubation of 10,003 anaesthetists and 16 airway experts. Anaesthesia 2020; 75: 313-22.
26. Team RC. _foreign: Read Data Stored by 'Minitab', 'S', 'SAS', 'SPSS'.
38. ILO ILO. Italy ratifies the ILO Convention (No. 190) on the elimination of violence and harassment in the world of work. International Labor Organization. 2021.
39. SIAARTI ISoARAIC. Gender Equity in Anaesthesia and Intensive Care: Italy's portrait [Internet]. 2021 [2022 Feb 8]
40. SIAARTI ISoARAIC. SIAARTI policy on diversity and inclusion [Internet]. Italy: 2021 [2022 Feb 8]. Available from https://d1c2g5q2tikk0.cloudfront.net/assets/uploads/3152270/asset/Poli_cy_diversità_e_inclusione_SIAARTI.pdf?1629362437

Background: To enhance perioperative outcomes, a perioperative registry that integrates high-quality real-world data throughout the perioperative period is essential. Singapore General Hospital established the Perioperative and Anesthesia Subject Area Registry (PASAR) to unify data from the preoperative, intraoperative, and postoperative stages. This study presents the methodology employed to create this database.

Methods: Since 2016, data from surgical patients have been collected from the hospital electronic medical record systems, de-identified, and stored securely in compliance with privacy and data protection laws. As a representative sample, data from initiation in 2016 to December 2022 were collected.

Results: As of December 2022, PASAR data comprise 26 tables, encompassing 153,312 patient admissions and 168,977 operation sessions. For this period, the median age of the patients was 60.0 years, sex distribution was balanced, and the majority were Chinese. Hypertension and cardiovascular comorbidities were also prevalent. Information including operation type and time, intensive care unit (ICU) length of stay, and 30-day and 1-year mortality rates were collected. Emergency surgeries resulted in longer ICU stays, but shorter operation times than elective surgeries.

Conclusions: The PASAR provides a comprehensive and automated approach to gathering high-quality perioperative patient data.

Keywords: Anesthesia; Big data; Data science; Intraoperative care; Perioperative care; Postoperative care; Preoperative care; Statistical data interpretation.

Introduction

According to the Lancet Commission on Global Surgery, 4.2 million people worldwide die within 30 days of surgery per year. This major mortality risk exceeds that of human immunodeficiency virus, malaria, and tuberculosis combined [1,2]. Many of these deaths are potentially preventable [3–5]. This is in addition to other nonfatal perioperative complications, which can cause negative long-term health outcomes [6,7] and contribute to high healthcare costs [8,9]. Hence, improving perioperative outcomes is essential, as not only individual patients but also health systems as a whole benefit.

Both research and quality improvement in healthcare require an accurate understand-
ing of patient profiles and care trajectories. To enable such efforts, a curated registry comprising high-quality real-world data for the entire perioperative period, including the preoperative, intraoperative, and postoperative periods of hospitalization, is paramount. Such a registry would provide the essential data for retrospective studies of factors influencing patient outcomes and prospective evaluations of clinical interventions. By consolidating and organizing perioperative data in an integrated database, researchers could easily access and analyze a large amount of collected data, which could lead to more accurate predictive models, an improvement in patient outcomes, and ultimately, improvements in clinical decision-making. In addition, an integrated perioperative registry would ensure access to data that is standardized and high quality, through the use of quality assessment methods. This is critical for accurate data analysis and the development of machine-learning models. By enforcing data standards and quality checks, researchers can minimize the risk of bias and errors in statistical analysis and develop machine-learning models. Furthermore, the use of a registry could address the data sharing and privacy concerns associated with the use of large institutional datasets. A secure and centralized location for data storage ensures that patient data are properly de-identified and protected and can only be accessed by authorized personnel.

Currently available high-resolution datasets include those derived from intensive care unit (ICU) stays, such as the frequently cited Medical Information Mart for Intensive Care (MIMIC) III and IV datasets and the eICU, Amsterdam UMCdb, and HiRID databases [10–12]. Other datasets, such as the Multicenter Perioperative Outcomes Group (MPOG) dataset, have focused on perioperative information in the western populations [13,14]. These datasets have enabled important research such as predictive analytics using machine learning and waveform processing [15]. However, no large high-resolution databases integrating all patient-care areas throughout the perioperative period are currently available. To address this gap, we established an integrated, standardized, and curated perioperative registry database at our institution.

Singapore General Hospital (SGH) is a quaternary care and academic medical center. It is the largest hospital in Singapore, with approximately 28,000–30,000 surgeries conducted each year. A comprehensive electronic medical record (EMR) has been implemented at SGH along with a fully digital anesthesia information and monitoring system (AIMS) for the operating room. Every patient’s surgical journey generates a digital footprint that encompasses the medical doctors, nursing, and allied health consultation notes; laboratory and imaging results; physiological patient monitoring; medication or blood product prescriptions; operation time; and length of hospital stay. These data exist in the following formats: structured data (e.g., patient demographics and comorbidities), unstructured data (e.g., patient communication notes), high-resolution physiological time-series data (e.g., intraoperative heart rate and blood pressure), and imaging data (e.g., radiology images).

This study aims to describe the methodology used to set up the perioperative data mart used at SGH, the Perioperative and Anesthesia Subject Area Registry (PASAR), which combines data from the preoperative, intraoperative, and postoperative periods, allowing for a seamless investigation of a patient’s entire journey from the operating room to the ICU. An overview of the case mix and available data within this registry is also presented.

Materials and Methods

The PASAR covers all patients who undergo surgery at SGH. It was initiated in 2016 and continues to be populated with data to the present day.

Approval for the database was granted by the SingHealth Centralised Institutional Review Board (Singhealth CIRB 2014/651/D, 2020/2915, and 2021/2547). The requirement for individual patient consent was waived as the data are collected during routine clinical care and de-identified. The PASAR operates in compliance with Singapore’s Personal Data Protection Act and the Human Biomedical Research Act as well as other ethical guidelines based on the Declaration of Helsinki, 2013 [16–18]. The pipeline from routine clinical data and de-identification protocols are described below.

The main data source for the registry is the EMR (Sunrise Clinical Manager, Allscripts), AIMS (WinChart®, WinChart Health Informatics), and administrative billing (SAP ISH, SAP SE) systems at SGH. All data from internal sources are acquired during routine patient care (i.e., no specific data are collected for research). The Singapore National Registration Identification number is a national identifier unique to each individual and is the common identifier for data contained in various systems throughout Singapore.

All hospital data are stored in raw format in our enterprise data warehouse system (SingHealth-IHIS Electronic Health Intelligence System — eHINTS). This structured query language (SQL) database allows for data staging before it is uploaded to the registry. Manual data entries are unavailable. All data are stored securely within an approved access-controlled facility at SGH in a manner compliant with local privacy and data protection laws. The database is synchronized with the National Registry of Births and Deaths to ensure that all out-of-hospital deaths are captured.

All patients undergoing surgery at SGH require a preoperative
anesthesia assessment. A standardized electronic clinical document has been used since 2016 to identify individuals who qualify for inclusion in the database. All patients aged ≥ 18 years who undergo surgery under anesthesia care at SGH are included.

De-identification processes are performed by a trusted third party within SGH that is not involved in research-related activities using PASAR data. This trusted third party acts in accordance with Singapore's Personal Data Protection Act and Human Biomedical Research Act [16,17].

Our institution mandates the de-identification of 15 direct identifiers, which include case and visit numbers, death dates, postal codes, and names in structured fields and free-text data. De-identification of case and visit numbers is performed by pseudonymization using a hashing algorithm (SHA-256) that returns substitute values. Before hashing, the identifiers are salted with project-specific values at the beginning and end. This process of salting and hashing the case and visit numbers is used consistently to ensure that the study team is able to link cases across all tables using substitute values. Death dates are de-identified by generalization to months and years (i.e., the exact day is censored).

In addition to fields that explicitly contain these 15 direct identifiers, other high-risk data fields, such as unstructured text (which can contain names and other identifiers) are completely concealed.

For each individual, data are collected during the preoperative, intraoperative, and postoperative periods.

The clinical variables included in the data registry have expanded over time. At the time the PASAR was initiated in 2016, data on preoperative medical history and laboratory results as well as important clinical outcomes such as length of hospital stay, ICU admissions, and death were included [19,20]. Currently, additional data routinely captured during preoperative anesthesia assessment visits are included, such as patient demographics, comorbidities, preoperative laboratory test results, and surgery details; intraoperative AIMS data including all administered medications, procedures performed, and high-velocity vital signs time series data; and postoperative data including post-anesthesia care unit, ICU, 30-day vital signs, and fluid balance data. Furthermore, discharge summaries in both free-text entries and structured ICD-10 codes are included for all case entries. A full data dictionary is available for accredited users.

Establishing clear data ownership ensures that the data are properly collected, stored, and maintained, and that all stakeholders are aware of their roles and responsibilities regarding the data. Ownership of the PASAR lies with the first author (HRA), who is responsible for ensuring proper delegation to authorized nominees and users. Only authorized users with a legitimate need to access the data are granted access, and access is monitored and audited regularly to ensure that the data is not being accessed inappropriately. The Data Science and Artificial Intelligence Laboratory at SGH is a data management team that is responsible for establishing data quality checks and ensuring that the data are stored securely.

Data sharing is essential to facilitate research collaboration and advance perioperative research. However, data sharing must be performed in a manner that protects patient privacy and confidentiality. This includes establishing data-sharing agreements that specify how data can be used and who can access it. All data are anonymized before being released to researchers, and researchers must sign a data-use agreement that prohibits re-identification and unauthorized redistribution of the data. The authors can be contacted for details on the data-sharing agreement and protocols.

Results

As of December 2022, the PASAR consists of a relational database containing 26 tables linked by the patient's case number (a unique identifier for every admission), operation session identifier, and operation identifier (as multiple operations can be performed in a single session). The database is segmented into three schemata based on the perioperative period the data were collected: pre_op (preoperative), intra_op (intraoperative), and post_op (postoperative). The pre_op, intra_op, and post_op schemata consist of 5, 7, and 14 tables, respectively. Detailed entity relationship diagrams of these three schemata and variable descriptions are available in Supplementary Fig. 1 and Supplementary Table 1. A total of 153,312 patients were admitted, among which 168,977 operation sessions containing 183,687 operations were conducted. Fig. 1 shows these data broken down by year.

The profiles of the patients included in the study are listed in Table 1. Discrete variables are reported as counts and percentages and continuous variables are reported as median (Q1, Q3). These measures provide a concise overview of patient characteristics, allowing for other studies or populations to be easily compared. This patient cohort consisted of 153,312 patients, with a median age of 60.0 years (45.0, 69.0) and a balanced sex distribution (females: 50.2%). The majority of patients were Chinese (72.4%), followed by Indian (10.6%) and Malay (9.6%). Almost half of the patients had hypertension (44.9%) and a significant number of cardiovascular comorbidities were reported, such as ischemic heart disease (12.7%), kidney dysfunction (5.8%), diabetes mellitus on insulin (4.8%), and congestive heart failure (3.3%). Operation characteristics are provided in Table 2. Summary statistics were calculated on a per-operation basis. Counts and percentages
Fig. 1. Number of patients, operation sessions, and operations per year.

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient cohort (n = 153,312)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>60.0 (45.0, 69.0)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>72,759 (50.2)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>104,902 (72.4)</td>
</tr>
<tr>
<td>Indian</td>
<td>15,442 (10.6)</td>
</tr>
<tr>
<td>Malay</td>
<td>13,917 (9.6)</td>
</tr>
<tr>
<td>Other races</td>
<td>10,663 (7.4)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>64.7 (55.8, 75.0)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>10,945 (8.0)</td>
</tr>
<tr>
<td>No</td>
<td>96,981 (70.5)</td>
</tr>
<tr>
<td>Not asked</td>
<td>15,473 (11.2)</td>
</tr>
<tr>
<td>Yes</td>
<td>14,242 (10.3)</td>
</tr>
<tr>
<td>Creatinine &gt; 2 mg/dl</td>
<td>8,467 (5.8)</td>
</tr>
<tr>
<td>Diabetes mellitus on insulin</td>
<td>6,786 (4.8)</td>
</tr>
<tr>
<td>History of congestive heart failure</td>
<td>4,634 (3.3)</td>
</tr>
<tr>
<td>History of cerebrovascular accident</td>
<td>5,319 (3.8)</td>
</tr>
<tr>
<td>History of ischemic heart disease</td>
<td>18,002 (12.7)</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>57,213 (44.9)</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3) or number (%). Creatinine > 2 mg/dl indicate patients with kidney dysfunction.

are presented for discrete variables, while median (Q1, Q3) are presented for continuous variables. Most patients had American Society of Anesthesiologists physical status scores of 2 (50.0%) and 3 (35.1%), while 14.6% of the patients underwent emergency surgeries.

Table 3 provides information on surgical outcomes. Summary statistics were calculated on a per-operation basis. Counts and percentages are presented for discrete variables, while median (Q1, Q3) are presented for continuous variables. Clinically relevant outcomes included the operation time, ICU length of stay, and 30 days and 1-year mortality. The median ICU length of stay after emergency surgery was 3 days longer than that after elective operations (5.1 vs 1.9 days); however, the median operation time was shorter (0.9 vs 1.2 h).

Discussion

Significance of the PASAR

The PASAR can be used to obtain high-fidelity data on a patient's perioperative journey at scale via automated retrieval from EMR sources and clinical databases. This ensures complete coverage of all relevant cases without requiring human data entry, thus
reducing human labor, ensuring data accuracy, and minimizing the risk of privacy and security breaches. We believe that the link between high-frequency intraoperative data and long-term postoperative outcomes will further facilitate quality improvements and research in perioperative medicine. Moreover, a large-scale perioperative registry provides a centralized location for perioperative data, ensures data quality and standardization, and addresses the privacy concerns associated with the use of large institutional datasets. The availability of such data repositories can drive innovation in perioperative medicine and improve patient outcomes. To the best of our knowledge, this is the first large database in Asia to achieve this.

Our cases follow national gender and ethnic distributions [21]. Patients in our cohort were older adults, with a median age of 60 years. This is similar to the MPOG database, where older adults aged > 65 years comprised a significant proportion of patients. However, patient distribution may be atypical or skewed owing to the reduction in elective surgeries performed due to COVID pandemic measures. Only semi-urgent elective procedures, such as malignancy operations, were permitted [22] in our institution from February 2020 [23], and normal operations resumed slowly over the course of 2021–2022. This may have affected the summary statistics for the median age, length of stay, and mortality rates. However, with elective operations resuming in the post-pandemic period, the case distributions are expected to normalize.

We recognize that an EMR-based approach to data collection has limitations [24] and may not fully capture every aspect of a patient’s perioperative status. For example, events recorded in the EMR (e.g., administration of a drug) may deviate slightly from the actual administration time, as documentation may be retrospective in emergencies. Important qualitative observations such as patient discomfort are also challenging to capture. Records external to electronic data sources, such as laboratory results and prescriptions from different healthcare hospitals, cannot be directly accessed. Although free-text records may provide useful information, they are censored in the current database because of the lack of standardized de-identification protocols for free text. These factors can cause unmeasured data loss and bias within the PASAR, similar to other EMR-based registries. Data users must be aware of these limitations.

We envision the PASAR as the cornerstone for Singaporean researchers interested in leading and participating in international perioperative studies. Although this registry is currently not avail-

### Table 2. Operation Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Operation sessions (n = 168,977)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASA class</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>12,398 (11.1)</td>
</tr>
<tr>
<td>II</td>
<td>55,864 (50.0)</td>
</tr>
<tr>
<td>III</td>
<td>39,205 (35.0)</td>
</tr>
<tr>
<td>IV</td>
<td>4,250 (3.8)</td>
</tr>
<tr>
<td>V</td>
<td>110 (0.1)</td>
</tr>
<tr>
<td>VI</td>
<td>7 (0.0)</td>
</tr>
<tr>
<td><strong>Urgency</strong></td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>144,358 (85.4)</td>
</tr>
<tr>
<td>Emergency</td>
<td>24,619 (14.6)</td>
</tr>
<tr>
<td>Transplant</td>
<td>119 (0.1)</td>
</tr>
<tr>
<td>ENT</td>
<td>5,690 (4.6)</td>
</tr>
<tr>
<td><strong>Discipline</strong></td>
<td></td>
</tr>
<tr>
<td>Gynecology</td>
<td>7,311 (5.9)</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>2,475 (2.0)</td>
</tr>
<tr>
<td>Orthopedics</td>
<td>33,656 (27.2)</td>
</tr>
<tr>
<td>Plastics</td>
<td>3,565 (2.9)</td>
</tr>
<tr>
<td>Urology</td>
<td>11,660 (9.4)</td>
</tr>
<tr>
<td>Vascular</td>
<td>5,292 (4.3)</td>
</tr>
<tr>
<td>Burns</td>
<td>1,237 (1.0)</td>
</tr>
<tr>
<td>Cardiothoracic surgery</td>
<td>7,786 (6.3)</td>
</tr>
<tr>
<td>Neonatology</td>
<td>47 (0.0)</td>
</tr>
<tr>
<td>Obstetrics</td>
<td>2,521 (2.0)</td>
</tr>
<tr>
<td>Others</td>
<td>11,771 (9.5)</td>
</tr>
</tbody>
</table>

Values are presented as number (%). ASA: American Society of Anaesthesiologists physical status, ENT: ear, nose and throat.

### Table 3. Surgical Outcomes

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Overall</th>
<th>Urgency</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>168,977</td>
<td>144,358</td>
<td>24,619</td>
<td></td>
</tr>
<tr>
<td>Operation time (h)</td>
<td>1.2 (0.6, 2.1)</td>
<td>1.2 (0.6, 2.2)</td>
<td>0.9 (0.5, 1.7)</td>
<td></td>
</tr>
<tr>
<td>ICU stay &gt; 24 h</td>
<td>9719 (78.3)</td>
<td>7,087 (74.9)</td>
<td>2,632 (89.3)</td>
<td></td>
</tr>
<tr>
<td>ICU stay (day)</td>
<td>2.2 (1.0, 6.8)</td>
<td>1.9 (1.0, 4.8)</td>
<td>5.1 (2.0, 13.4)</td>
<td></td>
</tr>
<tr>
<td>30-day mortality</td>
<td>2,268 (1.3)</td>
<td>1,382 (1.0)</td>
<td>886 (3.6)</td>
<td></td>
</tr>
<tr>
<td>1-year mortality</td>
<td>8,008 (4.7)</td>
<td>5,815 (4.0)</td>
<td>2,193 (8.9)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number, median (Q1, Q3) or number (%). ICU: intensive care unit.
able as an open-access resource for international researchers owing to prevailing local regulatory limitations, collaborative access with legal and infrastructural safeguards is possible. Further steps to improve data usability would include implementing mappings to a widely accepted data model such as the common data model (CDM) promulgated by the Observational Medical Outcomes Partnership (OMOP) \[25\]. The OMOP CDM is an open community data standard designed to standardize the structure and content of observational data to enable efficient analyses and produce reliable evidence. The use of such a model would allow for pooled analyses using the PASAR and other databases \[26\]. At present, no perioperative databases have been fully mapped using the OMOP CDM. We envision our PASAR dataset to act as a leading case study to form a perioperative research consortium for our region.

**Limitations and future work**

The handling of large relational databases can be challenging for average clinical users. Even after taking steps to manage the “4Vs of big data” (volume, velocity, variety, veracity), EHR data often overwhelms clinical providers with the sheer size and complexity of the database structure. Relational databases can be challenging to navigate, particularly for users unfamiliar with the underlying data model, making complex queries or data analysis tasks difficult to perform. At present, information technology tools such as SQL, which require further technical training, are used to query databases. The lack of user-friendly and convenient access to structured data for clinical providers is frequently a rate-limiting step in clinical research and quality improvements. We hope to implement low-code or no-code interfaces in the future to facilitate clinician interaction with the data.

In conclusion, the PASAR provides a comprehensive and automated approach to collecting high-fidelity data on a patient’s perioperative journey. By linking high-frequency intraoperative data with long-term postoperative outcomes, this database has the potential to facilitate quality improvements and research in perioperative medicine.

**Funding**

This work was supported by the National Research Foundation Singapore under the AI Singapore Programme (Award Number: AISG-100E-2020-055) and the RIE2025 Industry Alignment Fund (I2101E0002 – Cisco-NUS Accelerated Digital Economy Corporate Laboratory).

**Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

**Data Availability**

The data that support the findings of this study are available from Singapore General Hospital but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Singapore General Hospital.

**Author Contributions**

Hairil Rizal Abdullah (Conceptualization; Data curation; Supervision; Writing – original draft)
Daniel Yan Zheng Lim (Investigation; Methodology)
Yuhe Ke (Investigation; Writing – original draft)
Nur Nasyitah Mohamed Salim (Investigation)
Xiang Lan (Methodology; Software)
Yizhi Dong (Formal analysis; Writing – original draft)
Mengling Feng (Conceptualization; Data curation; Formal analysis; Writing – review & editing)

**Supplementary Materials**

Supplementary Fig. 1. Entity relationship diagram (ERD) of the three schematas: pre_op, intra_op, and post_op. This ERD was generated using the web application draw.io (https://www.draw.io.com). Except for table intra_op.nur_vitables which only has a single Anon_Case_No identifier, every table is linked together using three identifiers: Anon_Case_No, session_id, and operation_id. The pre_op.char table stores the fundamental characteristics of each patient, operation session, and operation, collected before the operation. This table forms the core of the database.

Supplementary Table 1. Description of the variables used for each schema (pre_op, intra_op, and post_op).

**ORCID**

Hairil Rizal Abdullah, https://orcid.org/0000-0003-1916-0832
Daniel Yan Zheng Lim, https://orcid.org/0000-0002-9715-6970
Yuhe Ke, https://orcid.org/0000-0001-7193-4749
Nur Nasyitah Mohamed Salim, https://orcid.org/0009-0008-3621-1252

https://doi.org/10.4097/kja.23580
References


23. Ministry of Health. Risk assessment raised to DORSCON Or-


Perioperative adverse cardiac events and mortality after non-cardiac surgery: a multicenter study

Byungjin Choi1,11, Ah Ran Oh2,3,*, Jungchan Park1,2, Jong-Hwan Lee2, Kwangmo Yang1,4, Dong Yun Lee1, Sang Youl Rhee5, Sang-Soo Kang6, Seung Do Lee7, Sun Hack Lee8, Chang Won Jeong8, Bumhee Park1,10, Soobeen Seol1, Rae Woong Park1, Seunghwa Lee11

1Department of Biomedical Sciences, Ajou University Graduate School of Medicine, Suwon, 2Department of Anesthesiology and Pain Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, 3Department of Anesthesiology and Pain Medicine, Kangwon National University Hospital, Chuncheon, 4Center for Health Promotion, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, 5Department of Endocrinology and Metabolism, Kyung Hee University School of Medicine, Seoul, 6Department of Anesthesiology and Pain Medicine, Kangdong Sacred Heart Hospital, Seoul, 7Division of Cardiology, Department of Internal Medicine, Gyeongsang National University Hospital, Jinju, 8Division of Cardiology, Department of Internal Medicine, Pusan National University Hospital, Busan, 9Center Research Center of Biomedical Research Institute, Wonkwang University Hospital, Iksan, 10Office of Biostatistics, Medical Research Collaborating Center, Ajou Research Institute for Innovative Medicine, Ajou University Medical Center, Suwon, 11Department of Cardiology, Wiltse Memorial Hospital, Suwon, Korea

Background: Perioperative adverse cardiac events (PACE), a composite of myocardial infarction, coronary revascularization, congestive heart failure, arrhythmic attack, acute pulmonary embolism, cardiac arrest, and stroke during 30-day postoperative period, is associated with long-term mortality, but with limited clinical evidence. We compared long-term mortality with PACE using data from nationwide multicenter electronic health records.

Methods: Data from 7 hospitals, converted to Observational Medical Outcomes Partnership Common Data Model, were used. We extracted records of 277,787 adult patients over 18 years old undergoing non-cardiac surgery for the first time at the hospital and had medical records for more than 180 days before surgery. We performed propensity score matching and then an aggregated meta-analysis.

Results: After 1:4 propensity score matching, 7,970 patients with PACE and 28,807 patients without PACE were matched. The meta-analysis showed that PACE was associated with higher one-year mortality risk (hazard ratio [HR]: 1.33, 95% CI [1.10, 1.60], P = 0.005) and higher three-year mortality (HR: 1.18, 95% CI [1.01, 1.38], P = 0.038). In subgroup analysis, the risk of one-year mortality by PACE became greater with higher-risk surgical procedures (HR: 1.20, 95% CI [1.04, 1.39], P = 0.020 for low-risk surgery; HR: 1.69, 95% CI [1.45, 1.96], P < 0.001 for intermediate-risk; and HR: 2.38, 95% CI [1.47, 3.86], P = 0.034 for high-risk).

Conclusions: A nationwide multicenter study showed that PACE was significantly associated with increased one-year mortality. This association was stronger for the older age group, emergency surgery group, and high surgical risk group. Further studies to improve mortality associated with PACE are needed.

Keywords: Cardiac arrhythmias; Cardiovascular diseases; Embolism; General surgery; Mortality; Myocardial infarction.
Introduction

Cardiac complications have emerged as major adverse events after non-cardiac surgery [1]. With advances in perioperative medicine, the incidence of major postoperative complication is decreasing [2]. Such advances in perioperative medicine are beneficial in daily clinical practice but a need for relevant studies on new outcome measures has arisen. Unlike major adverse events during perioperative periods, which are well associated with long-term prognosis, the association of some of the adverse events with long-term prognosis still remains unclear. According to some studies, some of the events that were even considered spontaneously reversible could also affect long-term prognosis [3,4]. Previously, we hypothesized that a composite of cardiac events could reflect prognosis adequately and be used as an objective and reliable outcome measure in non-cardiac surgery. By defining perioperative adverse cardiac events (PACE) as a composite of myocardial infarction (MI), coronary revascularization, congestive heart failure, arrhythmic attack, acute pulmonary embolism, cardiac arrest, and stroke during the 30-day postoperative period, we demonstrated an association with one-year mortality after non-cardiac surgery [5]. We used a large-scale cohort dataset of over 200,000 consecutive adult patients undergoing non-cardiac surgery, but it was still limited to a single center, which lacks generalization.

Recently, the concept of a distributed research network has been developed to overcome the privacy issue in generating multicenter patient-level data. This method uses standardized, deidentified, decentralized electronic medical records (EMR), and conducts clinical research only with combined summary statistics [6,7]. In this study, we investigated data from multiple institutions within a distributed research network and aimed to demonstrate the association between PACE and long-term mortality with further nationwide multicenter evidence.

Materials and Methods

We conducted a multicenter retrospective cohort study using a distributed research network without patient-level data sharing. This study was approved by the Institutional Review Board (IRB) of Ajou University Medical Center (AJIRB-MED-MDB-21-662), and the need for individual written informed consent was waived. The other six hospitals are affiliated with the Research Border Free Zone of Korea that accepts approval of the research organizing center in the study using deidentified Common Data Model (CDM) data. This study complied with the principles of the Declaration of Helsinki, 2013 and was compiled using the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

Data sources

This study included 8,280,723 patients from Korea’s electronic medical records database. Patient-level EMR data were standardized and deidentified into the standard vocabulary of the Observational Medical Outcomes Partnership (OMOP) CDM [8] and were stored in each hospital. The hospitals included Ajou University Medical Center (AUMC; 1994.01-2022.02; 2,873,443 patients), Kyung Hee Medical Center (KHMC; 2008.01-2022.02; 1,168,640 patients), Kyung Hee University Hospital at Gangdong (KUIMS; 2006.06-2021.10; 805,332 patients), Kangdong Sacred Heart Hospital (KDH; 2005.01-2021.10; 1,101,850 patients), Pusan National University Hospital (PNUH; 2011.02-2019.08; 1,753,001 patients), Gyeongsang National University Hospital (GNUH; 2009.10-2022.04; 626,663 patients), and Wonkwang University Hospital (WKUH; 1998.03-2018.12; 1,001,794 patients).

Study design

We extracted the records of 277,276 adult patients over 18 years of age who underwent surgery for the first time at the hospital and had medical records for more than 180 days before surgery. Because we planned to stratify patients according to the development of PACE during 30 days after surgery, those with mortality during the first 30 days after surgery were excluded from the study. Adult patients who underwent surgery before August 2018 at each hospital were recruited for a sufficient follow-up period. Fig. 1 shows a flow chart of the study design.

We divided the patients into two groups in each hospital, according to PACE, defined as a composite of heart failure, arrhythmic attack, acute pulmonary embolism, cardiac arrest, MI, coronary revascularization, and stroke within 30 days of surgery. An arrhythmic attack was defined as rapid atrial fibrillation, ventricular tachycardia, and bradycardia that required medical intervention such as electrical shock, temporary cardiac pacing, or two or more consecutive administrations of antiarrhythmic agents. Cardiac arrest was defined as a diagnosis of cardiac arrest or a record of cardiopulmonary resuscitation. Pulmonary embolism was defined as the presence of a diagnostic code and an elevated d-dimer level. Coronary revascularization was confirmed by surgical records of coronary angiography using stent placement or coronary artery bypass graft surgery. MI was defined as the presence of a diagnostic code and a blood troponin level. Data on heart failure and stroke were obtained from the diagnostic codes, but only the
The first recorded diagnosis of each respective condition was included. The primary endpoint was one-year mortality, and the secondary endpoint was three-year mortality. Mortality data were extracted from the death certificates issued by each hospital.

We divided the patients into two groups in each hospital according to the occurrence of PACE and generated a 1:4 matched population with propensity score matching (PSM). We conducted a stratified Cox regression analysis in a matched population to calculate the hazard ratio (HR) of one-year and three-year mortality [9].

After conducting survival analysis in a distributed research network, we aggregated the results of seven databases by meta-analysis. Then we conducted a subgroup analysis on emergency operation status and surgical risk, categorized according to the European Society of Cardiology/European Society of Anesthesiology guidelines on non-cardiac surgery. We also performed a subgroup analysis based on comorbidities such as diabetes, hypertension, and chronic kidney disease, and cancer. Furthermore, we performed subgroup analysis with different demographics, sex, and older age (≥ 65 years). When performing subgroup analysis, variables that divide the subgroup were excluded from the PSM variable.

Further, we categorized the PACE events into six subgroups, including heart failure, MI or revascularization, pulmonary embolism, cardiac arrest, arrhythmic attack, and stroke during the 30-day postoperative period. For each event subgroup, we conducted survival analysis using Cox regression after performing 1:4 propensity matching separately, as done in the main analysis for PACE. We calculated the HRs for each hospital and conducted a meta-analysis to provide the point estimates, 95% CIs, and P values for the risk ratios for each event group.

In our analysis, age covariates were grouped by five years. The disease covariate was binarized as whether a patient was diagnosed with a specific International Classification of Diseases code in the last 365 days. Comorbidity was quantified using Romano’s adaptation of the Charlson Comorbidity Index [10].

Fig. 1. Study flowchart of patients with or without perioperative adverse cardiac events (PACE). We extracted the records of 277,276 adult patients over 18 years of age who underwent surgery for the first time at the hospital and had medical records for more than 180 days before surgery from deidentified data of 8,615,571 patients in South Korea’s standardized electronic medical records (EMR) databases. After 1:4 propensity score matching, 7,970 patients with PACE and 28,807 patients without PACE were matched. AUMC: Ajou University Medical Center, KHMC: Kyung Hee Medical Center, KUIMS: Kyung Hee University Hospital at Gangdong, KDH: Kangdong Sacred Heart Hospital, PNUH: Pusan National University Hospital, GNUH: Gyeongsang National University Hospital, WKUH: Wonkwang University Hospital.
risk of surgical procedure was classified according to European Society of Cardiology/European Society of Anesthesiology guidelines on non-cardiac surgery [11].

**Statistical analysis**

For baseline characteristics, we calculated mean ± standard deviation or median with interquartile range (IQR) and the t-test or the Mann-Whitney U test for continuous variables. For categorical variables, we calculated percentages and used the chi-square or Fisher’s exact test to compare differences between the groups. In PSM, we matched four patients without PACE to one patient with PACE and used 0.1 standardized logits as the caliper width. The PSM covariates were: sex, age, diabetes, chronic kidney disease, stroke, coronary artery disease, heart failure, arrhythmia, peripheral artery disease, aortic disease, valvular heart disease, current alcohol use, and Romano’s Adaptation of the Charlson comorbidity index [10]. In subgroup analysis, variables that divide the subgroup are excluded from the PSM variable. After PSM, we regarded an absolute standard mean deviation (ASD) of 0.1 as balanced and calculated as HRs with 95% CIs using stratified Cox survival analysis.

In a meta-analysis, we conducted statistical tests of heterogeneity by using χ² and I² statistics. When I² < 50%, we mainly reported a fixed-effects model. Otherwise, a random-effects model was used. All analyses were performed using R (version 4.1.0; R Foundation for Statistical Computing®).

To test for differences between subgroups, we adopted single variable meta-regression. Meta-regression is a method that considers confounding covariates while conducting meta-analysis.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before PSM adjustment</th>
<th>After PSM adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With PACE</td>
<td>Without PACE</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20–24</td>
<td>0.3</td>
<td>3.9</td>
</tr>
<tr>
<td>25–29</td>
<td>0.4</td>
<td>6.4</td>
</tr>
<tr>
<td>30–34</td>
<td>0.4</td>
<td>5.7</td>
</tr>
<tr>
<td>35–39</td>
<td>1.6</td>
<td>5.9</td>
</tr>
<tr>
<td>40–44</td>
<td>1.9</td>
<td>7.5</td>
</tr>
<tr>
<td>45–49</td>
<td>5.1</td>
<td>9.7</td>
</tr>
<tr>
<td>50–54</td>
<td>6.9</td>
<td>10.5</td>
</tr>
<tr>
<td>55–59</td>
<td>9.6</td>
<td>10.1</td>
</tr>
<tr>
<td>60–64</td>
<td>13.6</td>
<td>10.1</td>
</tr>
<tr>
<td>65–69</td>
<td>15.4</td>
<td>9.9</td>
</tr>
<tr>
<td>70–74</td>
<td>16.6</td>
<td>9</td>
</tr>
<tr>
<td>75–79</td>
<td>14.7</td>
<td>6.5</td>
</tr>
<tr>
<td>80–84</td>
<td>9.5</td>
<td>3.3</td>
</tr>
<tr>
<td>85–89</td>
<td>3.4</td>
<td>1.2</td>
</tr>
<tr>
<td>90–94</td>
<td>0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Gender (F)</td>
<td>45</td>
<td>56.3</td>
</tr>
<tr>
<td>Heart failure</td>
<td>17.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>12.3</td>
<td>2.9</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>8.8</td>
<td>1.1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>25.5</td>
<td>8.7</td>
</tr>
<tr>
<td>Heart valve disorder</td>
<td>4.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Current drinker</td>
<td>16.3</td>
<td>11.3</td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>2.6</td>
<td>1.3</td>
</tr>
</tbody>
</table>

We calculated mean ± standard deviation or median with interquartile range and the t-test for continuous variables. For categorical variables, we calculated percentages and used the chi-square test to compare differences between the groups for categorical variables. PACE: perioperative adverse cardiac events.
We conducted meta-regression with subgroup characteristics as a single variable. Then, we named the statistical significance of the subgroup variable as the ‘P value for difference’ and used it as a T-test for subgroup difference.

**Results**

In a total of 277,276 patients undergoing non-cardiac surgery, PACE was observed in 7,996 (2.88%) patients. After 1:4 PSM, 7,970 patients with PACE and 28,807 patients without PACE were matched. The baseline characteristics of the matched AUMC cohort are shown in Table 1. The table shows that the PACE group was predominantly male and had a higher incidence of comorbidity. The baseline covariates became well-balanced after PSM (ASD < 0.1). The improvements in the balance between covariates in other cohorts are also shown as changes in ASD in Fig. 2. Propensity score distribution according to the presence or absence of PACE for each hospital is described in Supplementary Fig. 1.

The number of deaths within one year and three years was 480 (6%) and 706 (8.6%) in patients with PACE, and 1,265 (4.4%) and 2,103 (7.3%) in those without PACE. The meta-analysis showed that PACE was associated with a higher risk of one-year mortality (HR: 1.33, 95% CI [1.10, 1.60], P = 0.005) and a higher risk of three-year mortality (HR: 1.18, 95% CI [1.01, 1.38], P = 0.038). The one-year and three-year mortality risks for each cohort are presented in a forest plot in Fig. 3. Survival plots with one-year mortality in each cohort are shown in Fig. 4.

The association between PACE and one-year mortality was analyzed separately according to surgical risk. The association was significant regardless of surgical risk, but the increase of risk for

**Fig. 2.** Covariate balance plot before and after propensity score matching (PSM) across seven hospitals. After PSM, we plotted the absolute standard deviation (ASD) of the covariates to validate the adequacy of matching. After PSM, most of the ASD of the covariates is smaller than 0.1 that shows that matching is balanced and adequate. AUMC: Ajou University Medical Center, GNUH: Gyeongsang National University Hospital, KDH: Kangdong Sacred Heart Hospital, WKUH: Wonkwang University Hospital, KHMC: Kyung Hee Medical Center, KUIMS: Kyung Hee University Hospital at Gangdong, PNUH: Pusan National University Hospital.
Fig. 3. (A) The forest plot represents the meta-analysis results for the risk of one-year mortality in patients with perioperative adverse cardiac events (PACE) across seven hospitals. The hazard ratio (HR) and 95% CIs are indicated by the diamond shape for the combined effect estimate and the squares for each individual study. The size of the square represents the weight of each study. The horizontal line represents the CI, and the diamond shape represents the overall pooled effect estimate. The four numbers within each column represent the number of patients with PACE with outcome (death), without outcome, and patients without PACE with outcome, without outcome, respectively. (B) The forest plot represents the meta-analysis results for the risk of three-year mortality in patients with PACE across seven hospitals. The HRs and 95% CIs are presented in the same way as in (A). AUMC: Ajou University Medical Center, GNUH: Gyeongsang National University Hospital, KDH: Kangdong Sacred Heart Hospital, KHMC: Kyung Hee Medical Center, KUIMS: Kyung Hee University Hospital at Gangdong, PNUH: Pusan National University Hospital, WKUH: Wonkwang University Hospital.
one-year mortality associated with PACE became higher as the risk of surgical risk became higher (HR: 1.20, 95% CI [1.04, 1.39], P = 0.020 for low-risk surgery; HR: 1.69, 95% CI [1.45, 1.96], P < 0.001 for intermediate-risk; and HR: 2.38, 95% CI [1.47, 3.86], P = 0.034 for high-risk). The forest plots for the risk of one-year mortality of each cohort are presented according to surgical risk in Fig. 5. In all groups except for the patients without cancer and young age group, PACE was found to be statistically associated with a higher risk of mortality (HRs ranging from 1.20 to 2.38, 95% CIs ranging from 1.04 to 3.86). In the subgroup analysis, the P value for difference was 0.026 for age, 0.399 for sex, 0.063 for cancer, 0.601 for chronic kidney disease, 0.269 for diabetes, 0.110 for hypertension, 0.011 for emergency operation, and 0.011 for surgical risk. Based on these results, we have shown that there is a
The event-specific analysis showed that except for stroke (HR: 1.22, 95% CI [0.90, 1.64], P = 0.194), all other PACE events were significantly associated with a higher risk of mortality. Specifically, HR for heart failure was (95% CI [1.10, 1.65], P = 0.005), for monary embolism HR was 2.33 (95% CI [1.40, 3.88], P = 0.001), for cardiac arrest HR was 14.42 (95% CI [6.46, 32.17], P < 0.001), for arrhythmic attack HR was 2.07 (95% CI [1.55, 2.76], P < 0.001), and for MI or revascularization HR was 1.51 (95% CI [1.17, 1.95], P = 0.002). The number of patients for each event for each hospital is provided in Supplementary Table 1. We have summarized the results in Supplementary Table 2. The detailed forest plot for each PACE event can be found in Supplementary Fig. 2.

Discussion

This study demonstrates the association between PACE, a composite of MI, coronary revascularization, congestive heart failure, arrhythmic attack, acute pulmonary embolism, cardiac arrest, and stroke during a 30-day postoperative period, and mortality after non-cardiac surgery. We used a multicenter cohort and demonstrated the association between PACE and mortality after non-cardiac surgery, which was consistent with our previous report [5].

Our results may be helpful in future clinical trials because we propose an optimal composite endpoint that is powerfully relevant to prognosis but not too rare. In clinical trials, there is an increased propensity to collate patient outcomes into one composite endpoint, including nonfatal complications, owing to a dramatic improvement in fatal outcomes [12]. An endpoint with extremely low incidence requires a large number of study participants that makes clinical trials difficult to conduct, and is also problematic from an ethical perspective [13]. To enhance the generalizability of the results, we analyzed nationwide multicenter data and further conducted subgroup analyses. In our subgroup analysis, PACE was found to be statistically associated with a higher risk of mortality in all groups except for the patients without cancer and young age group (HRs ranging from 1.20 to 2.38 with corresponding CIs ranging from 1.04 to 3.86). Moreover, the increase in the risk for mortality by PACE tended to be greater in high-risk patients such as the elderly and those who underwent higher-risk
### Table 2. Subgroup Analysis by Demographics and Comorbidity

<table>
<thead>
<tr>
<th>Subgroup analysis</th>
<th>HR</th>
<th>CI</th>
<th>P value</th>
<th>P value for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>1.44</td>
<td>1.26, 1.65</td>
<td>&lt; 0.001</td>
<td>0.399</td>
</tr>
<tr>
<td>F</td>
<td>1.29</td>
<td>1.14, 1.46</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Elder (age &gt; 65)</td>
<td>1.89</td>
<td>1.30, 2.74</td>
<td>0.002</td>
<td>0.026</td>
</tr>
<tr>
<td>Young (age ≤ 65)</td>
<td>1.09</td>
<td>0.79, 1.51</td>
<td>0.590</td>
<td></td>
</tr>
<tr>
<td><strong>Comorbidity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With diabetes</td>
<td>1.20</td>
<td>1.01, 1.53</td>
<td>0.043</td>
<td>0.291</td>
</tr>
<tr>
<td>Without diabetes</td>
<td>1.40</td>
<td>1.04, 1.89</td>
<td>0.026</td>
<td></td>
</tr>
<tr>
<td>With hypertension</td>
<td>1.19</td>
<td>1.00, 1.40</td>
<td>0.005</td>
<td>0.110</td>
</tr>
<tr>
<td>Without hypertension</td>
<td>1.59</td>
<td>1.05, 2.41</td>
<td>0.029</td>
<td></td>
</tr>
<tr>
<td>With chronic kidney disease</td>
<td>1.40</td>
<td>1.09, 1.81</td>
<td>0.002</td>
<td>0.601</td>
</tr>
<tr>
<td>Without chronic kidney disease</td>
<td>1.31</td>
<td>1.06, 1.64</td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>1.66</td>
<td>1.24, 2.20</td>
<td>&lt; 0.001</td>
<td>0.063</td>
</tr>
<tr>
<td>Without cancer</td>
<td>1.16</td>
<td>0.89, 1.51</td>
<td>0.273</td>
<td></td>
</tr>
<tr>
<td><strong>Surgery status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emergency</td>
<td>1.74</td>
<td>1.42, 2.15</td>
<td>&lt; 0.001</td>
<td>0.011</td>
</tr>
<tr>
<td>Not emergency</td>
<td>1.20</td>
<td>1.05, 1.51</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>Low risk surgery</td>
<td>1.20</td>
<td>1.04, 1.39</td>
<td>0.020</td>
<td>0.011</td>
</tr>
<tr>
<td>Intermediate risk surgery</td>
<td>1.69</td>
<td>1.45, 1.96</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>High risk surgery</td>
<td>2.38</td>
<td>1.47, 3.86</td>
<td>0.034</td>
<td></td>
</tr>
</tbody>
</table>

The 'P value' in the table refers to the P value of the hazard ratio (HR) obtained from each individual study. A P value below 0.05 indicates that the occurrence of perioperative adverse cardiac events (PACE) had a significant impact on the mortality rate in that subgroup. The 'P value for difference' refers to the P value of the subgroup covariate obtained from the meta-regression analysis. A P value for difference below 0.05 indicates that the HR of the two subgroups is statistically significantly different due to the criterion for dividing the subgroups, such as differences in sex.

In addition, our data showed that an increase in the risk for mortality by PACE, shown as HR, tended to be greater in high-risk patients such as the elderly, those who underwent higher-risk procedures, or those with comorbidities. Considering that clinical trials generally target patients with certain risk factors, this finding indicates that PACE may be an optimal endpoint. Also, compared to major adverse cardiac events, which already have been used in previous studies, PACE contains arrhythmias that not uncommonly occurs and are associated with poor long-term outcomes after surgery. Therefore, PACE could provide a more accurate reflection of the overall risk of adverse cardiac events following non-cardiac surgery.

When interpreting an association shown in an observational study, the clinical relevance of the result should be carefully discussed. Most of the components in PACE were individually investigated in previous studies. PACE includes the components of major adverse cardiac events, a well-known composite endpoint for the clinical trial [14], and the association with mortality for a major cardiac event is well established. On the other hand, the clinical relevance of some minor components of PACE, such as arrhythmic events, still needs to be clarified. Among arrhythmic events, postoperative atrial fibrillation is prevalent after non-cardiac surgery and is associated with increased morbidity and length of hospital stay [15]. Most postoperative atrial fibrillation spontaneously reverses to a normal rhythm, but it still affects long-term mortality and stroke risk [16,17]. On the other hand, there is still limited data on the individual effects of different types of arrhythmias, and this may need further investigation.

The methodologic strength of this study is that we analyzed the deidentified cohort. Privacy has recently arisen as a major ethical issue in clinical studies, especially when using data from EMR [18]. A privacy protection issue has made it more difficult for investigators to collect and analyze patient-level data for multicenter evidence. The concept of a distributed research network is a recent concept that was developed to overcome privacy issues in a multicenter observational study [8]. In this method, standardized, deidentified, and decentralized EMRs were obtained and analyzed at each center. Instead of centralizing the data for analysis, the results are provided only as combined summary statistics.

The results of this study should be interpreted as descriptive due to the following limitations. As we analyzed a retrospective administrative dataset, unmeasured variables may not have been
balanced even after rigorous statistical adjustments with PSM. Although we used multicenter datasets, they were all in Korea, and most of the study patients were Asian. Therefore, our analysis may not be generalizable in other regions and may show an ethnic difference. This study was conducted as a multi-center, decentralized retrospective study based on OMOP CDM. Due to the nature of the study, some specified information was not feasible that can lead to inconsistencies in the diagnostic criteria of PACE. To address this issue, we combined diagnostic codes with laboratory values, medication prescriptions, and procedural records to increase the reliability. However, inconsistencies in the diagnostic criteria of primary exposures may still exist. In further studies, that include information like imaging reports, transthoracic echocardiography should be included. Due to limited sample size and data availability issues, we could not include variables such as the type of surgery, emergency status, presence of cancer (although we included in the charlson comorbidity index), cancer stage, and functional status in the PSM. To alleviate this limitation, we conducted subgroup analyses based on the type of surgery, emergency status, and presence of cancer. However, due to the current limitations of the CDM, we were unable to include information on cancer stage and functional status. To address these limitations and conduct thorough multi-institutional databases, we need to connect more detailed postoperative information to OMOP CDM-based standardized databases. Lastly, perioperative care was not controlled between centers. Despite the presence of the perioperative guidelines, many clinical decisions may have been made at the clinician's discretion, and over the long study period, some clinical guidelines may have changed. Despite these limitations, we demonstrated an association between PACE 30 days after non-cardiac surgery and one-year mortality in a nationwide multicenter clinical dataset. Our findings show that PACE may be a suitable composite endpoint for future clinical trials.

In non-cardiac surgery patients, an association of PACE with one-year mortality was observed in a nationwide multicenter study. A further prospective study regarding PACE as a composite endpoint that is relevant to prognosis is required.

**Funding**

This research was funded by the Bio Industrial Strategic Technology Development Program (20003883, 20005021) funded by the Ministry of Trade, Industry & Energy (Korea) and a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HR16C0001).

**Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

**Data Availability**

The datasets generated during and/or analyzed during the current study are available in the Common Data Model (CDM) repository.

**Author Contributions**

Byungjin Choi (Formal analysis; Investigation; Methodology; Software; Writing – original draft)
Ah Ran Oh (Formal analysis; Investigation; Methodology; Software; Writing – original draft)
Jungchan Park (Conceptualization; Investigation; Methodology; Supervision; Writing – review & editing)
Jong-Hwan Lee (Supervision; Writing – review & editing)
Kwangmo Yang (Supervision; Writing – review & editing)
Dong Yun Lee (Data curation; Writing – review & editing)
Sang Youl Rhee (Data curation; Writing – review & editing)
Sang-Soo Kang (Data curation; Writing – review & editing)
Seung Do Lee (Data curation; Writing – review & editing)
Sun Hack Lee (Data curation; Writing – review & editing)
Chang Won Jeong (Data curation; Writing – review & editing)
Bumhee Park (Formal analysis)
Soobeen Seol (Formal analysis)
Rae Woong Park (Supervision; Writing – review & editing)
Seunghwa Lee (Conceptualization; Investigation; Methodology; Supervision; Writing – review & editing)

**Supplementary Materials**

Supplementary Fig. 1. Propensity score distribution of patients with and without PACE (Perioperative Adverse Cardiac Events) in each database.
Supplementary Fig. 2. Forest plots of subgroup analysis.
Supplementary Fig. 3. Forest plots of event-specific analysis.
Supplementary Table 1. Number of patients for specific events in PACE.
Supplementary Table 2. Detailed results of event-specific analysis.

**ORCID**

Byungjin Choi, https://orcid.org/0000-0002-1445-5888
Ah Ran Oh, https://orcid.org/0000-0002-8076-5104
Jungchan Park, https://orcid.org/0000-0002-7794-3547
Jong-Hwan Lee, https://orcid.org/0000-0001-8249-5550
Kwangmo Yang, https://orcid.org/0000-0002-7176-4935
Dong Yun Lee, https://orcid.org/0000-0002-3678-9862
Sang Youl Rhee, https://orcid.org/0000-0003-0119-5815
Sang-Soo Kang, https://orcid.org/0000-0002-9347-4883
Seung Do Lee, https://orcid.org/0000-0002-9129-4248
Sun Hack Lee, https://orcid.org/0000-0002-6809-2664
Chang Won Jeong, https://orcid.org/0000-0002-9305-4883
Bumhee Park, https://orcid.org/0000-0002-5271-1571
Soobeen Seol, https://orcid.org/0000-0002-7238-8986
Rae Woong Park, https://orcid.org/0000-0003-4989-3287
Seunghwa Lee, https://orcid.org/0000-0001-5508-7519

References

Reduced side effects and improved pain management by continuous ketorolac infusion with patient-controlled fentanyl injection compared with single fentanyl administration in pelviscopic gynecologic surgery: a randomized, double-blind, controlled study

Insun Park, Seukyoung Hong, Su Yeon Kim, Jung-Won Hwang, Sang-Hwan Do, Hyo-Seok Na

Department of Anesthesiology and Pain Medicine, Seoul National University Bundang Hospital, Seongnam, Korea

Background: A combination of opioids and adjunctive drugs can be used for intravenous patient-controlled analgesia (PCA) to minimize opioid-related side effects. We investigated whether two different analgesics administered separately via a dual-chamber PCA have fewer side effects with adequate analgesia than a single fentanyl PCA in gynecologic pelviscopic surgery.

Methods: This prospective, double-blind, randomized, and controlled study included 68 patients who underwent pelviscopic gynecological surgery. Patients were allocated to either the dual (ketorolac and fentanyl delivered by a dual-chamber PCA) or the single (fentanyl alone) group. Postoperative nausea and vomiting (PONV) and analgesic quality were compared between the two groups at 2, 6, 12, and 24 h postoperatively.

Results: The dual group showed a significantly lower incidence of PONV during postoperative 2–6 h (P = 0.011) and 6–12 h (P = 0.009). Finally, only two patients (5.7%) in the dual group and 18 (54.5%) in the single group experienced PONV during the entire postoperative 24 h and could not maintain intravenous PCA (odds ratio: 0.056, 95% CI [0.007, 0.229], P < 0.001). Despite the administration of less fentanyl via intravenous PCA during the postoperative 24 h in the dual group than in the single group (66.0 ± 77.8 vs. 383.6 ± 70.1 μg, P < 0.001), postoperative pain had no significant intergroup difference.

Conclusions: Two different analgesics, continuous ketorolac and intermittent fentanyl bolus, administered via dual-chamber intravenous PCA, showed fewer side effects with adequate analgesia than conventional intravenous fentanyl PCA in gynecologic patients undergoing pelviscopic surgery.

Keywords: Analgesia; Fentanyl; Ketorolac; Patient-controlled analgesia; Postoperative nausea and vomiting; Postoperative pain.

Introduction

Patient-controlled analgesia (PCA) is a method that allows patients to self-manage pain using a programmable infusion pump. The analgesic drug is placed in a specially de-
signed PCA device in advance, and a portion of it is continuously infused with an additional bolus dose as required. Although opioids are preferentially used for intravenous PCA [1,2], they have various side effects such as nausea, vomiting, dizziness, sedation, and respiratory depression [3,4]. These side effects are major causes for the unexpected early discontinuation of intravenous PCA.

To minimize opioid-related side effects, a combination of opioids with adjunctive medications, such as propacetamol [5], ketorolac [6], nefopam [7], and dexmedetomidine [8], is used. The existing intravenous PCA device is a single-chamber pump. Thus, adjunctive medication should be administered using an additional infusion pump or intermittent bolus injection. Mixing and storing two or more drugs in a single-chamber PCA cannot guarantee their physicochemical and microbiological stability [9]. Meanwhile, a novel dual-chamber PCA device (Bellomic DUO®; Cebi-ka) has been launched that consists of one continuous flow chamber with another chamber having a bolus function.

We hypothesized that two different analgesics, ketorolac and fentanyl, administered separately via a dual-chamber PCA may have fewer side effects with adequate analgesia than those associated with conventional intravenous single-fentanyl PCA. Thus, the accompanying side effects and analgesic quality were evaluated in gynecological patients undergoing pelviscopic surgery.

Materials and Methods

Study design

The study protocol was approved by the Institutional Review Board of Seoul National University Bundang Hospital (No. B-21 10-716-003) and registered at ClinicalTrials.gov (NCT05489796). This was a prospective randomized controlled trial conducted at our hospital in accordance with the principles of the Declaration of Helsinki, 2013. After obtaining written informed consent, patients were recruited for the study.

Study participants

Patients aged 20–65 years who were scheduled for elective laparoscopic gynecologic surgery under general anesthesia were enrolled in this study. According to the analgesic combination, patients were randomly assigned in a 1:1 allocation ratio to two parallel groups: the dual or single group. Block randomization with a block size of six was used to divide the participants into groups. One investigator was aware of the group arrangement and was involved in the preparation of the intravenous PCA. In addition, neither the participants nor the investigators knew to which group each participant was assigned. The exclusion criteria included an American Society of Anesthesiologists physical status classification III-V, pregnancy, side effects of opioids or hypersensitivity to aspirin, ketorolac, or other nonsteroidal anti-inflammatory drugs (NSAIDs), body mass index > 35 kg/m² or < 18 kg/m², alcohol or drug dependency, peptic ulcer or gastrointestinal bleeding, cerebrovascular hemorrhage, increased intracranial pressure, bronchial asthma or bronchospasm, severe respiratory depression, moderate to severe renal impairment or dehydration, nasal polyp, angioedema, a history of convulsive disease, patients for whom the use of neuromuscular blocking agents is contraindicated, or use of monoamine oxidase inhibitors.

General anesthesia

Noninvasive blood pressure, electrocardiography, pulse oximetry, and bispectral index were measured upon arrival at the operating room. With oxygen supplementation via an anesthetic face mask, anesthesia was induced with 1 mg/kg of propofol and target-controlled infusion of remifentanil at 3.0 ng/ml of the effect site concentration. After the loss of consciousness, 0.6 mg/kg of rocuronium was injected and tracheal intubation was performed. Anesthesia was maintained and adjusted using desflurane and remifentanil according to the bispectral index™ (Medtronic) and hemodynamic changes, respectively. At the end of the surgery, intravenous PCA was connected following 0.3 mg of ramosetron. After confirming recovery of consciousness and spontaneous breathing, extubation was performed and patients were transferred to the post-anesthesia care unit (PACU). Patients were discharged from PACU when the post-anesthesia recovery score composed of vital signs, activity, postoperative nausea and vomiting (PONV), pain, and surgical bleeding, became 10.

Intravenous PCA device and analgesic regimen

A dual-chamber PCA device with continuous and selector chambers is commonly used in both groups. The elastomeric pump of the continuous chamber has a drug to be infused at a 2 ml/h of fixed flow rate and the selector chamber has the function of injecting a bolus of 1 ml (10 min of lock-out period) as required without basal infusion.

In the dual group, the continuous chamber of the dual-chamber PCA device contained 180 mg of ketorolac with 94 ml of normal saline for a total volume of 100 ml. The single group received 700 μg of fentanyl with 86 ml of normal saline. The selector chamber in both groups contained 200 μg of fentanyl and 16 ml of normal saline.
saline to a total volume of 20 ml.

Intravenous PCA was discontinued if the patient experienced persistent vomiting or nausea and no longer wished to use it. For rescue analgesia in the PACU, 25 μg of fentanyl was additionally administered if the numerical rating scale (NRS) for postoperative pain was 3 to 5 and 50 μg of fentanyl when the NRS for postoperative pain was 6 or higher. If a patient complained of pain with an NRS score of 4 or higher in the ward, 400 mg of ibuprofen was administered as the first rescue analgesic drug at least 4 h apart. Nevertheless, if the NRS score was still ≥ 4, 100 mg of tramadol was administered additionally.

**Outcome variables**

The primary outcome was the incidence of PONV that was evaluated during the PACU stay, 0–2 h, 2–6 h, 6–12 h, and 12–24 h. PONV severity (nausea, retching, vomiting) and the use of rescue antiemetics were evaluated together. Nausea was defined as a subjectively unpleasant sensation with an awareness of the urge to vomit. Retching was defined as labored, spasmodic contraction of the respiratory muscles without expulsion of the gastric contents. Vomiting was defined as the expulsion of the gastric contents. The secondary outcomes were the NRS score for postoperative pain, use of rescue analgesics, and reason for discontinuation of intravenous PCA.

**Statistical analysis**

We estimated a priori that 32 patients in each group would be sufficient to detect a decrease in PONV incidence from 40% to 10% in the single group versus the dual group (power of 80% and a risk of 0.05 for type I error). Based on the assumption of an overall rate of loss to follow-up of 10%, 36 patients per group were required.

The normal distribution of continuous variables was evaluated using the Shapiro-Wilk test. Normally distributed continuous variables are presented as mean (standard deviation [SD]), and if the distribution is not normal, the median (interquartile range) is presented. Incidence is presented as a number (%) with odds ratio (OR) and 95% confidence interval (CI). Categorical variables were compared using the chi-squared test or Fisher’s exact test, whereas continuous variables were compared using the Student’s t-test or Mann-Whitney U test. Postoperative NRS scores for pain were analyzed using repeated-measures ANOVA. When the postoperative NRS score for pain showed a significant intergroup difference, it was compared using the Mann-Whitney U test at each time frame. The intention-to-treat population included patients who were initially randomized to each group. The full analysis set (FAS) was defined as the remaining population, after excluding patients from the intention-to-treat population who did not receive the designated intravenous PCA. All statistical analyses were performed using the R Statistical Software version 4.2.1 (Foundation for Statistical Computing). Values were considered statistically significant at two-sided P < 0.05.

**Results**

A total of 72 patients were enrolled from June 2022 to August 2022 and four patients were excluded because the intravenous PCA analgesics were configured differently from the protocol (Fig. 1). The characteristics of the patients, surgery, and anesthesia are summarized in Table 1, and they were comparable between the two groups.

The incidence of PONV did not significantly differ between the two groups at the PACU (P = 0.444) and until postoperative 2 h (P = 0.378). However, the dual group showed a significantly lower incidence of PONV during postoperative 2–6 h (P = 0.011) and 6–12 h (P = 0.009; Fig. 2 and Supplementary Table 1) postoperatively. Finally, only two patients (5.7%) in the dual group and 18 (54.5%) in the single group experienced PONV during the entire postoperative 24 h and could not maintain intravenous PCA (OR: 0.056, 95% CI [0.007, 0.229], P < 0.001).

---

https://doi.org/10.4097/kja.23217

---

**Fig. 1.** Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the patients. Dual group: ketorolac and fentanyl delivered by a dual-chamber PCA, Single group: fentanyl alone delivered by a PCA. PCA: patient-controlled analgesia.
### Table 1. The Characteristic of Patients, Surgery, and Anesthesia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dual group (n = 35)</th>
<th>Single group (n = 33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>41.7 ± 10.9</td>
<td>42.2 ± 8.8</td>
<td>0.809</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.7 ± 6.0</td>
<td>161.7 ± 5.1</td>
<td>0.453</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.0 ± 9.5</td>
<td>57.8 ± 6.1</td>
<td>0.103</td>
</tr>
<tr>
<td>ASA PS, I/II (%)</td>
<td>25/10 (71.4/28.6)</td>
<td>25/8 (75.8/24.2)</td>
<td>0.897</td>
</tr>
<tr>
<td>Pelviscopic operation name</td>
<td></td>
<td></td>
<td>0.838</td>
</tr>
<tr>
<td>Myomectomy</td>
<td>17 (48.6)</td>
<td>14 (42.4)</td>
<td></td>
</tr>
<tr>
<td>Total hysterectomy</td>
<td>9 (25.7)</td>
<td>11 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Ovarian cystectomy</td>
<td>6 (17.1)</td>
<td>6 (18.2)</td>
<td></td>
</tr>
<tr>
<td>Salpingo-oophorectomy</td>
<td>3 (8.6)</td>
<td>2 (6.1)</td>
<td></td>
</tr>
<tr>
<td>PONV risk factors</td>
<td></td>
<td></td>
<td>0.532</td>
</tr>
<tr>
<td>Apfel score 2/3/4</td>
<td>1/27/7 (2.9/77.1/20.0)</td>
<td>3/23/7 (9.1/69.7/21.2)</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>0 (0.0)</td>
<td>3 (9.1)</td>
<td>0.217</td>
</tr>
<tr>
<td>History of PONV or motion sickness</td>
<td>7 (20.0)</td>
<td>8 (24.2)</td>
<td>0.958</td>
</tr>
<tr>
<td>Postoperative opioids</td>
<td>34 (97.1)</td>
<td>32 (97.0)</td>
<td>0.999</td>
</tr>
<tr>
<td>Intraoperative vital signs</td>
<td></td>
<td></td>
<td>0.961</td>
</tr>
<tr>
<td>Mean SBP (mmHg)</td>
<td>108.4 ± 7.0</td>
<td>108.3 ± 8.6</td>
<td></td>
</tr>
<tr>
<td>Mean DBP (mmHg)</td>
<td>69.6 ± 7.2</td>
<td>69.5 ± 8.4</td>
<td>0.946</td>
</tr>
<tr>
<td>Mean HR (beats/min)</td>
<td>71.0 ± 6.5</td>
<td>70.8 ± 7.9</td>
<td>0.910</td>
</tr>
<tr>
<td>Vasopressor use</td>
<td>12 (34.3)</td>
<td>17 (51.5)</td>
<td>0.234</td>
</tr>
<tr>
<td>Intraoperative input and output</td>
<td></td>
<td></td>
<td>0.234</td>
</tr>
<tr>
<td>Crystalloid (ml)</td>
<td>462.9 ± 216.0</td>
<td>539.4 ± 304.6</td>
<td></td>
</tr>
<tr>
<td>Colloid (ml)</td>
<td>64.3 ± 150.3</td>
<td>33.3 ± 110.9</td>
<td>0.340</td>
</tr>
<tr>
<td>Estimated blood loss (ml)</td>
<td>146.3 ± 160.8</td>
<td>123.6 ± 136.1</td>
<td>0.534</td>
</tr>
<tr>
<td>Urine output (ml)</td>
<td>143.7 ± 149.2</td>
<td>201.8 ± 208.0</td>
<td>0.188</td>
</tr>
<tr>
<td>Total remifentanil dose (μg)</td>
<td>338.7 ± 195.0</td>
<td>388.8 ± 294.1</td>
<td>0.414</td>
</tr>
<tr>
<td>Total rocuronium dose (mg)</td>
<td>38.5 ± 4.7</td>
<td>49.2 ± 63.2</td>
<td>0.388</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>95.4 ± 49.7</td>
<td>111.8 ± 68.5</td>
<td>0.261</td>
</tr>
<tr>
<td>Anesthesia time (min)</td>
<td>119.4 ± 49.9</td>
<td>138.5 ± 70.9</td>
<td>0.208</td>
</tr>
<tr>
<td>PACU length of stay (min)</td>
<td>33.6 ± 12.2</td>
<td>37.8 ± 18.6</td>
<td>0.284</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number (%). Dual group: ketorolac and fentanyl delivered by a dual-chamber PCA, Single group: fentanyl alone delivered by a PCA. ASA PS: American Society of Anesthesiologists physical status, PONV: postoperative nausea and vomiting, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, PACU: post-anesthesia care unit.

Postoperative NRS scores for pain showed no significant intergroup differences. It decreased over time, and significant differences were found at postoperative 2 h compared to the PACU values in each group (Fig. 3). Rescue fentanyl doses at PACU were similar between the two groups (90.7 ± 39.8 and 82.6 ± 34.5 μg in the dual and the single group, respectively; P = 0.372); however, less fentanyl was administered via intravenous PCA during the postoperative period in the dual group than in the single group (66.0 ± 77.8 vs. 383.6 ± 70.1 μg, P < 0.001). The proportion of patients who required rescue analgesics in the ward was similar between the two groups (Table 2). Tramadol was additionally administered to 12 (34.3%) and 11 patients (33.3%) in the dual and single group, respectively, at postoperative 0–2 h (P = 0.934).

### Discussion

This study found that two different analgesics, ketorolac and fentanyl, could be administered safely using a newly designed dual-chamber intravenous PCA that was able to significantly reduce postoperative PONV while providing adequate pain control. The strength of this study is that it achieved multimodal analgesia with ketorolac and fentanyl via the dual-chamber intravenous PCA and evaluated its efficacy on postoperative analgesia and side effects compared to conventional opioid PCA. Oh et al. [10] used the same PCA device for postoperative analgesia and demonstrated the effect of the dual administration of ketorolac and fentanyl. The difference was that there was no basal infusion of opioids in our dual group that was administered only when the patient re-
Fig. 2. The incidence distribution of PONV in both groups. Dual group: ketorolac and fentanyl delivered by a dual-chamber PCA, Single group: fentanyl alone delivered by a PCA. PACU: post-anesthesia care unit, PONV: postoperative nausea and vomiting, PCA: patient-controlled analgesia, NA: not available. *Five patients in the single group discontinued the intravenous PCA at postoperative 2–6 h. †Two patients in the dual group and 13 patients in the single group discontinued the intravenous PCA at postoperative 6–12 h.

Fig. 3. Postoperative NRS for pain in both groups. Dual group: ketorolac and fentanyl delivered by a dual-chamber PCA, Single group: fentanyl alone delivered by a PCA. PACU: post-anesthesia care unit, NRS: numerical rating scale. *P < 0.001 vs. NRS at PACU of each group.

https://doi.org/10.4097/kja.23217
Table 2. Proportion of the Patients Who Required Postoperative Rescue Analgesics

<table>
<thead>
<tr>
<th>Time</th>
<th>Dual group (n = 35)</th>
<th>Single group (n = 33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2 h</td>
<td>22 (62.9)</td>
<td>26 (78.8)</td>
<td>0.150</td>
</tr>
<tr>
<td>2–6 h</td>
<td>13 (37.1)</td>
<td>19 (57.6)</td>
<td>0.092</td>
</tr>
<tr>
<td>6–12 h</td>
<td>8 (22.9)</td>
<td>10 (30.3)</td>
<td>0.487</td>
</tr>
<tr>
<td>12–24 h</td>
<td>3 (8.6)</td>
<td>8 (24.2)</td>
<td>0.079</td>
</tr>
</tbody>
</table>

Values are presented as number (%). Dual group: ketorolac and fentanyl delivered by a dual-chamber PCA, Single group: fentanyl alone delivered by a PCA.

The selective use of opioids in intravenous PCA in combination with ketorolac resulted in significantly reduced opioid-related side effects and improved analgesic efficacy.

In our study, the amount of fentanyl administered via intravenous PCA was reduced by one-sixth that is consistent with previous studies reporting that intranasal or intravenous ketorolac administration reduced opioid consumption in patients on a PCA morphine pump [11,12]. With this reduced opioid consumption, patients in the dual group experienced fewer opioid-related side effects, particularly PONV, without compromising the analgesic quality. The value of multimodal analgesia with NSAID and opioids for fewer postoperative adverse effects and better analgesic quality is clinically significant, as it is reportedly associated with shorter hospital stays and improved recovery [13–17].

Multimodal analgesia is an important method for managing postoperative pain to avoid excessive opioid consumption and its adverse effects [18]. The rationale for multimodal analgesia is to achieve sufficient analgesia by the additive or synergistic effects of different combined classes of analgesics that act via different mechanisms [15]. NSAIDs may be used to reduce postoperative opioid consumption and the incidence of opioid-related adverse events [12,19]; however, these studies evaluated the effect of perioperative single-dose intravenous NSAID administration on postoperative outcomes. NSAIDs can be used as the sole analgesic in minor surgeries. However, breakthrough pain should be managed separately with more potent opioids, limiting the widespread use of intravenous PCA composed of NSAIDs.

Jung et al. [4] previously reported that basal infusion of fentanyl-based intravenous PCA increased fentanyl consumption with more side effects; however, no benefit was observed in reducing pain intensity. The single group in our study also used fentanyl-based intravenous PCA, including basal infusion, and the results were similar to those of Jung et al. [4]. The quality of postoperative analgesia did not improve even when more fentanyl was administered to the single group via intravenous PCA than to the dual group. In addition, approximately 55% of the patients in the single group discontinued intravenous PCA; thus, their postoperative pain management might have been inappropriate.

Interestingly, the mean NRS scores for pain were significantly reduced at postoperative 2 h in both groups. In addition, the requirement for rescue analgesics did not differ between the two groups. This means that the demand for analgesics is lower than expected for less-invasive pelviscopic operations. Controlling breakthrough pain with an opioid while administering ketorolac as a basal continuous infusion can be an appropriate intravenous PCA option in gynecologic pelviscopic surgery.

The pH of mixtures of two or more drugs decreases over time, and the concentration of ketorolac decreases significantly [9]. In addition, even if the stability of drugs in vitro is confirmed, it does not ensure pharmacodynamic and pharmacokinetic safety after administration to the patient’s body [9]. The chemical and microbiological stabilities of the various analgesic drug mixtures were evaluated according to their clinical combinations. Some studies have demonstrated the stability and compatibility of mixed drugs for a considerable period [20,21], whereas others have yet to draw firm conclusions because the results may be affected by the type or condition of the mixed drugs [22,23]. In this study, dual-chamber PCA enabled ketorolac to be infused as a basal analgesic drug, and fentanyl was administered as a bolus injection for breakthrough pain. Thus, the aforementioned safety issues can be resolved.

This study had several limitations. First, it was conducted at a single tertiary university hospital, and all patients were female who underwent pelviscopic gynecologic surgery that might have contributed to a selection bias. Second, the majority of our patients in both groups exhibited Apfel scores of 3 and 4; thus, the combined administration of ketorolac and fentanyl via dual-chamber intravenous PCA may not have significant effects in patients with fewer risk factors for PONV. Third, the direct effect of the dual-chamber NSAID and fentanyl PCA on hospital stay and quality of recovery was not assessed, as this study primarily focused on the immediate postoperative outcomes. Finally, all data were analyzed in the FAS population, except the incidence distribution of PONV (Fig. 2) that was analyzed only in patients who had used intravenous PCA at a designated period. Patients who discontinued intravenous PCA owing to PONV were excluded from the follow-up period. This caused the post-hoc power to decrease to 71.6% at postoperative 6–12 h. However, the final PONV incidence and intravenous PCA discontinuation rates over the entire observation period included all enrolled patients and met our hypothesis.

In conclusion, the two different analgesics, continuous ketoro-
lact and intermittent fentanyl bolus, administered via a dual-chamber intravenous PCA, showed fewer side effects with adequate analgesia compared to those associated with conventional intravenous fentanyl PCA in gynecologic patients undergoing pelviscopic surgery.

**Funding**

This study was supported from the HB medical Research Fund.

**Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

**Data Availability**

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Author Contributions**

Insun Park (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Validation; Visualization; Writing – original draft)

Seukyoung Hong (Data curation)

Su Yeon Kim (Data curation; Formal analysis)

Jung-Won Hwang (Conceptualization; Project administration; Writing – review & editing)

Sang-Hwan Do (Conceptualization; Supervision; Validation; Writing – review & editing)

Hyo-Seok Na (Conceptualization; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – review & editing)

**Supplementary Material**

Supplementary Table 1. Incidence of PONV.

**ORCID**

Insun Park, https://orcid.org/0000-0002-6413-752X

Seukyoung Hong, https://orcid.org/0009-0005-1863-4700

Su Yeon Kim, https://orcid.org/0000-0002-6167-4952

Jung-Won Hwang, https://orcid.org/0000-0002-0887-6889

Sang-Hwan Do, https://orcid.org/0000-0001-5452-4166

Hyo-Seok Na, https://orcid.org/0000-0003-0986-3243

**References**


Effect of local anesthetic volume (20 vs. 40 ml) on the analgesic efficacy of costoclavicular block in arthroscopic shoulder surgery: a randomized controlled trial

Yumin Jo1,2, ChaHyun Oh1,2, Woo-Yong Lee2, Hyung-Jin Chung2, Hanmi Park1, Juyeon Park1, Jieun Lee1, Yoon-Hee Kim1, YoungKwon Ko1,3, Woosuk Chung1, Boohwi Hong1,3

Departments of 1Anesthesiology and Pain Medicine, 2Orthopedic Surgery, Chungnam National University Hospital, Chungnam National University College of Medicine, 3Biomedical Research Institute, Chungnam National University Hospital, Daejeon, Korea

Introduction

The interscalene brachial plexus block has been the gold standard for shoulder surgery because of its excellent perioperative analgesic efficacy [1]. However, as the course of the phrenic nerve runs close to the brachial plexus at the interscalene level, hemidiaphragm-
matic paresis (HDP) is almost unavoidable when using this approach [2].

Various diaphragm-sparing alternatives to interscalene blocks have been studied [3]. Among them, costoclavicular block (CCB) that is performed under the clavicle showed reduced HDP with non-inferior analgesic efficacy compared to interscalene block [4]. Recently, a cadaveric study demonstrated that local anesthetic injected into the costoclavicular space can reach the suprascapular space [5]. Twenty milliliters of dye were injected into the costoclavicular space, spread cephalad to the brachial plexus in the suprascapular area, consistently reaching the suprascapular nerve and all trunks of the brachial plexus while sparing the phrenic nerve.

However, the promising results of CCB in shoulder surgery do not seem to be reliably reproduced in our clinical experience [6]. In our previous report, the analgesic efficacy of CCB was not consistent, and a few patients required rescue blockades due to severe pain immediately after surgery. As the suprascapular spreading of local anesthetic and the resulting suprascapular nerve block could be a major determinant for effective analgesia via CCB, we hypothesized that a larger volume of local anesthetic could provide sufficient analgesia by achieving reliable suprascapular spreading. In this study, we compared the analgesic efficacy of two volumes of local anesthetic (20 vs. 40 ml) for CCB in arthroscopic shoulder surgery.

Materials and Methods

Study design and participants

This single-center, prospective, randomized, parallel-group clinical trial was conducted at the Chungnam National University Hospital, Republic of Korea, and adhered to the tenets of the Declaration of Helsinki, 2013. After obtaining approval from the Chungnam National University Hospital Institutional Review Board (Daejeon, Korea, CNUH IRB 2021-04-068, Chairperson: Prof. Jeong Lan Kim) on June 14, 2021, we prospectively registered the protocol in the Clinical Trial Registry of Korea (KCT0006290, principal investigator: Boohwi Hong) on June 23, 2021 [https://cris.nih.go.kr]. Written informed consent was obtained from all participants prior to enrollment.

Patients between the ages of 20 and 80, with American Society of Anesthesiologists (ASA) physical status classifications I–III and scheduled for elective arthroscopic rotator cuff repair between July 2021 and March 2022 (with the first patient enrolled on July 19, 2021) were screened for eligibility. Exclusion criteria encompassed refusal to participate, a body mass index (BMI, kg/m²) of 30 or higher, significant pulmonary disease, sepsis, pregnancy, allergy to amide local anesthetics, infection at the surgical site, history of neck surgery, peripheral neuropathy, chronic pain syndrome, and cognitive impairment. Research data were collected and managed using the Research Electronic Data Capture (REDCap®; https://projectredcap.org) software hosted at Chungnam National University Hospital. REDCap® is a secure web-based platform designed to facilitate data capture in research [7]. This manuscript was written in line with the Consolidated Standards of Reporting Trials guidelines [8].

Randomization and blinding

We utilized a group assigning function in the REDCap® program based on a pre-uploaded sequence of randomization that was generated using blocks of two and four [9]. This was done to conceal the allocation and ensure the allocation sequence was revealed sequentially by a single dedicated researcher (Y.J.) on each case. Patients were randomly assigned to one of the following groups: 20 ml of 0.75% ropivacaine (CCB20) or 40 ml of 0.375% ropivacaine (CCB40). The researcher who conducted the group allocation prepared the study drugs and performed all blocks immediately after the induction of general anesthesia and was excluded from the study thereafter. Other individuals who participated in the surgery and research, including outcome assessors, attending anesthesiologists, surgeons, and nurses, were blinded to the group assignment.

Study flow and anesthetic procedures

Baseline pulmonary function was assessed using a handheld spirometer (CONTEC™ SP10 BP Spirometer; Healthcare4all Ltd.) in the ward prior to the day of surgery. On the day of the surgery, patients received premedication with intramuscular midazolam (0.05 mg/kg) before entering the operating room. The diaphragm was assessed using ultrasound as a baseline measurement. General anesthesia was then administered with standard ASA monitoring. Anesthesia induction involved intravenous (i.v.) propofol (1.5 mg/kg), rocuronium (0.8 mg/kg), and remifentanil (1 µg/kg), followed by maintenance with sevoflurane and continuous infusion of remifentanil (0.025–0.2 µg/kg/min) adjusted to maintain blood pressure and pulse rate within ± 20% of baseline. After induction, CCB was performed according to the group allocation. All surgeries were performed by a single experienced surgeon (W.L.) using three portals (posterior, lateral, and minor anterolateral) and one optional anterior portal in the beach chair position. Paracetamol (1 g) and nefopam (20 mg) were administered during surgery. At the end of the surgery, neuromuscular
blockade was reversed with 200 mg of sugammadex, and the patients were extubated after confirming adequate ventilation. Immediate postoperative outcomes, including evaluations of the diaphragm and pulmonary functions, upper extremity function, and pain, were assessed sequentially prior to discharge from the post-anesthesia care unit (PACU) with confirmation of a fully cooperative status. Upper extremity assessments were carried out by evaluating hand grip strength (patients were asked to squeeze the investigator’s hand) and hand sensory loss (rubbing the palm and back of the hand). A successful block was defined as the loss of full strength and normal sensation to the light touch in the hand. The overall flow of the study protocol is provided in Supplementary Fig. 1.

**Costoclavicular block**

Our institution has extensive experience with the CCB, the subject of this study, as demonstrated in our previous studies [10,11]. Patients were placed in a supine position with the ipsilateral limb abducted at an angle of 60°–90°. The infraclavicular area was scanned with an ultrasound probe placed parallel immediately below the clavicle. With gentle tilting to the cephalad direction, the probe was projected toward costoclavicular space, which is defined as the space between the posterior surface of the clavicle and the second rib. Then the image was optimized until the location and relationships of all three cords were identified lateral to the axillary artery [12]. We performed the injections using an in-plane technique and in the lateral-to-medial direction. To ensure the spread of local anesthetic around all three cords of the costoclavicular space, we used separate sequential injections [13,14]. After gently puncturing the paraneural sheath, we dissected the space between the cords using 1–2 ml test doses of injectate while avoiding any swelling signs of the cords. Once we confirmed proper needle placement, we injected 10–15 ml of local anesthetic for the CCB20 group and 20–30 ml for the CCB40 group between the medial and posterior cords. The needle was then slightly withdrawn until its tip was adjacent to the lateral cord, and the remaining volume was injected. All blocks were performed by experienced anesthesiologists using a high-resolution ultrasound system (X-Porte, FUJIFILM SonoSite®, Inc.) with a corresponding high-frequency (15–6 MHz) linear probe (HFL50xp, FUJIFILM SonoSite®, Inc.) and an echogenic needle (SonoPlex®, PAJUNK®). Every injection was divided into small aliquots, each containing 1–2 ml, and any over-pressurization during injection was avoided.

**Ultrasound assessment of supraclavicular spreading**

First, we performed a pre-procedural scanning on the supraclavicular area for the sequential verifications from the roots, trunk formation, and branching of the suprascapular nerve from the superior trunk [15]. Immediately after the blockade, the supraclavicular area was re-scanned using the same linear probe with minimal contact pressure. Starting from the corner pocket image, where the inferior trunk of the brachial plexus lies on the first rib, the courses of each trunk and suprascapular nerve were traced using cephalad and caudad tilting and the sliding movement of the probe. Adequate spread of the local anesthetic was confirmed by observing the areas where the local anesthetic was visible between the superior and middle trunk or around the suprascapular nerve itself after branching (Supplemental Fig. 2). Other images showing absence or spreading only to the space between the middle and inferior trunks were considered inadequate spreading.

**Postoperative pain management**

Patient-controlled analgesia (PCA) devices (Accumate®, Woo Young Meditech) were used to administer bolus doses of fentanyl 15 μg (10 min of lockout time without basal infusion; total fentanyl dose of 1000 μg). After oral intake was tolerated, all patients received multimodal analgesia consisting of naproxen (500 mg) and tapentadol (50 mg) twice daily. If intolerable pain (numeric rating scale [NRS] ≥ 4) persisted despite these measures, i.v. pethidine (25 mg) was used as rescue analgesia.

**Ultrasound assessment of the diaphragm and pulmonary function test**

The ultrasound assessment of the diaphragm was performed in a supine position. Two approaches were used for the evaluation of diaphragmatic movement. First, diaphragm excursion (DE) between full inspiration and expiration was measured using M-mode with a 5–2 MHz curved probe (C60xp, FUJIFILM Sonosite®, Inc.). The liver or spleen was used as the acoustic window under the rib at the anterior axillary line. Second, the diaphragm thickness fraction (DTF, %) was assessed at the mid axillary line just inferior to the edge of the pleura with a 15–6 MHz linear probe (HFL50xp, FUJIFILM Sonosite®, Inc.) [16]. DTF was calculated as follows: 100 × (thickness at inspiration / thickness at expiration) / thickness at expiration. Complete HDP was defined by either of the following criteria: 75%–100% decrease in DE, less than 5% in DTF, or occurrence of paradoxical movement of the diaphragm. Partial HDP was defined by either of the following...
criteria: a 25%–75% decrease in DE or a 5%–20% in DTE. Thus, the absence of any of these criteria is required to indicate the absence of HDP. All ultrasound assessments of the diaphragm were performed by a dedicated researcher (B.H.) blinded to the study groups.

The pulmonary function test was conducted by researchers who were trained in operating handheld spirometers in a semi-recumbent position and were blinded to the group allocation. Forced expiratory volume in 1 s, forced vital capacity, and peak expiratory flow were measured. The third spirometry and ultrasound measurements were recorded after two sets of pre-tests.

Outcome measures

The primary outcome was the rate of complete analgesia (0 on the NRS of pain) at rest 1 h postoperatively. The secondary outcomes included NRS at rest 1 h postoperatively, ultrasound assessment of supraclavicular spreading, time to first use of PCA, postoperative cumulative opioid consumption during 48 h, pain-related experience within 24 h postoperatively assessed with a brief questionnaire, the incidence of HDP, and the changes in pulmonary function.

Data regarding the use of PCA were collected using the AccuLinker (data extraction program of Accumate® 1200 version 1.1; Woo Young Meditech) that records the exact time and dose of every administration performed by the device [17]. The dose of pethidine used as rescue analgesia was converted to 33.3 μg of fentanyl and integrated into the calculation of postoperative cumulative opioid consumption.

Statistical analysis

In a preliminary analysis of our previous study [6], it was observed that approximately 70% of the patients reported a pain score greater than 0 at rest 1 h postoperatively after CCB when 20 ml of local anesthetic was used. We expected that using 40 ml of local anesthetic would demonstrate the incidence of any pain by up to 20%. To detect a difference in the proportion of 50% (70% vs. 20%), with a significance level of 0.05 and a power of 90%, a sample size of 23 patients in each group was calculated. Accounting for a potential dropout rate of about 20%, we planned to include 28 patients in each group.

All statistical analyses were performed using R software, version 4.2.2 (R Foundation for Statistical Computing). Continuous variables were analyzed using the independent t-test (mean ± SD) or Mann–Whitney U test (median [Q1, Q3]), depending on the results of the Shapiro–Wilk tests for the normality of data distribution. Categorical variables were analyzed using χ² or Fisher’s exact test (expected count < 5) and reported as numbers (%). An alluvial plot was utilized to illustrate the relationship between the volume of local anesthetic (group), supraclavicular spreading of injectate, and postoperative pain. A nonparametric rank-based method was used to analyze the longitudinal change in opioid consumption across different groups [18]. The time to the first dose of PCA was determined using Kaplan–Meier survival analysis and compared using log-rank tests [19]. Factors associated with immediate postoperative pain and HDP were explored using linear and logistic models as appropriate. Statistical significance was set at a two-tailed P value of < 0.05.

Results

From July 19, 2021, to March 29, 2022, 69 consecutive patients were assessed for eligibility. Of these, five were excluded (three for refusal and two for BMI) based on the predetermined criteria. Additionally, four patients were excluded due to changes in the surgical plan (open) before group allocation. The remaining 60 patients were randomly allocated to the CCB20 or CCB40 group. All the enrolled patients were included in the final analysis (Fig. 1). The baseline patient and clinical characteristics are shown in Table 1. There were no failed blocks according to the predefined criteria. No serious block-related complaints or complications such as dyspnea, desaturation, and pneumothorax were observed during the trial.

The rate of complete analgesia, indicated by 0 on the NRS, at the PACU was 23.3% (7/30) in the CCB20 group and 33.3% (10/30) in the CCB40 group (risk difference 10%, 95% CI [−13, 32], P = 0.567; Fig. 2). The pain score at 1 h was not significantly different between the groups (3 [1, 5] in CCB20 vs. 2 [0, 4] in CCB40, P = 0.395; Table 2). Sonographic assessment of the supraclavicular spreading showed no significant difference between the groups. The association between the groups, supraclavicular spreading, and immediate postoperative pain are shown in Fig. 3. While most cases with complete analgesia were associated with adequate spreading of local anesthetic, complete analgesia was not always achieved despite adequate spreading. Univariable and multivariable linear regression analyses showed that ultrasound observation of supraclavicular spreading was the only significant factor associated with immediate postoperative pain score (Table 3).

There were no significant differences in the results of the pain-related questionnaire between the groups (Supplementary Table 1). No significant difference was observed in the cumulative opioid consumption between the groups during the postoperative period (P = 0.627; Supplementary Fig. 3). In addition, no signifi-
cant interaction was found between the groups and the measurement time points \( (P = 0.371; \text{Supplementary Fig. 3}) \).

Time to first request of analgesia did not differ significantly (median 6.9 h, 95% CI [2.9, 16.1] h in CCB20 vs. 5.5 h, 95% CI [3.7, 13.4] h in CCB40, \( P = 0.640; \text{Supplementary Fig. 4} \)).

DE data from one patient in the CCB40 group (left-sided procedure) was excluded because of difficulty in visualization. DTF was evaluated in all patients. Complete HDP was observed in four patients in the CCB40 group and zero in the CCB20 group that was not significantly different \( (P = 0.121; \text{Supplementary Fig. 1}) \).

---

**Fig. 1.** Consolidated Standards of Reporting Trials (CONSORT) flow diagram. CCB20 group: costoclavicular block with 20 ml of 0.75% ropivacaine, CCB40 group: CCB with 40 ml of 0.375% ropivacaine. HDP: hemidiaphragmatic paresis.

**Table 1.** Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CCB20 group (n = 30)</th>
<th>CCB40 group (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>59.9 ± 9.8</td>
<td>60.0 ± 7.9</td>
</tr>
<tr>
<td>Sex (M)</td>
<td>14 (46.7)</td>
<td>16 (53.3)</td>
</tr>
<tr>
<td>Operation side (left)</td>
<td>12 (40.0)</td>
<td>13 (43.3)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>159.6 ± 9.2</td>
<td>162.1 ± 8.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.1 (58.0, 73.0)</td>
<td>63.4 (59.0, 70.4)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.1 ± 2.9</td>
<td>24.5 ± 2.4</td>
</tr>
<tr>
<td>ASA classification (&gt; II)</td>
<td>6 (20.0)</td>
<td>2 (6.7)</td>
</tr>
<tr>
<td>Surgery time (min)</td>
<td>111.6 ± 23.9</td>
<td>117.8 ± 32.8</td>
</tr>
<tr>
<td>Anesthesia time (min)</td>
<td>142.2 ± 27.6</td>
<td>150.5 ± 31.7</td>
</tr>
<tr>
<td>Intraoperative remifentanil (μg/kg/min)</td>
<td>0.035 (0.031, 0.043)</td>
<td>0.034 (0.029, 0.041)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, number (%), or median (Q1, Q3). CCB20 group: costoclavicular block with 20 ml of 0.75% ropivacaine, CCB40 group: CCB with 40 ml of 0.375% ropivacaine. BMI: body mass index, ASA: American Society of Anesthesiologists physical status.
Table 2. Primary Outcome (Complete Analgesia), Incidence of HDP, and the Evaluation of Supraclavicular Spreading of Local Anesthetic

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CCB20 group (n = 30)</th>
<th>CCB40 group (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete analgesia (NRS 0)</td>
<td>7 (23.3)</td>
<td>10 (33.3)</td>
<td>0.567</td>
</tr>
<tr>
<td>Pain at postoperative 1 h (NRS)</td>
<td>3.0 (1.0, 5.0)</td>
<td>2.0 (0.0, 4.0)</td>
<td>0.395</td>
</tr>
<tr>
<td>HDP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial or complete</td>
<td>5 (16.7)</td>
<td>10 (33.3)</td>
<td>0.233</td>
</tr>
<tr>
<td>Complete</td>
<td>0 (0.0)</td>
<td>4 (13.3)</td>
<td>0.121</td>
</tr>
<tr>
<td>Supraclavicular spreading*</td>
<td>17 (56.7)</td>
<td>18 (60.0)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or median (Q1, Q3). CCB20 group: costoclavicular block with 20 ml of 0.75% ropivacaine, CCB40 group: CCB with 40 ml of 0.375% ropivacaine. HDP: hemidiaphragmatic paresis. NRS: numeric rating scale. *Adequate supraclavicular spreading, defined as spreading of local anesthetic between the superior and middle trunk or directly affecting the suprascapular nerve itself after branching, was confirmed by ultrasound scanning at the supraclavicular fossa after CCB.

Table 3. Linear Regression Analysis for Factors Associated with Immediate Postoperative Pain Score

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Univariable model Coefficient (95% CI)</th>
<th>Multivariable model* Coefficient (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>-0.01 (−0.08, 0.07)</td>
<td>−0.04 (−0.12, 0.04)</td>
</tr>
<tr>
<td>Sex (M)</td>
<td>-0.07 (−1.32, 1.19)</td>
<td>0.90 (−1.18, 2.97)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>-0.02 (−0.09, 0.06)</td>
<td>−0.10 (−0.23, 0.03)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>0.01 (−0.06, 0.08)</td>
<td>0.02 (−0.08, 0.12)</td>
</tr>
<tr>
<td>Surgery time (h)</td>
<td>0.24 (−1.09, 1.57)</td>
<td>0.11 (−1.35, 1.57)</td>
</tr>
<tr>
<td>Group (CCB40)</td>
<td>−0.53 (−1.78, 0.72)</td>
<td>−0.29 (−1.51, 0.94)</td>
</tr>
<tr>
<td>Supraclavicular spreading†</td>
<td>−1.92 (−3.09, −0.75)†</td>
<td>−2.16 (−3.43, −0.90)†</td>
</tr>
</tbody>
</table>

CCB40: costoclavicular block with 40 ml of 0.375% ropivacaine. *All the variables listed in the table were included. †P value < 0.05.
The univariable analysis did not reveal any significant predictors for the occurrence of HDP (partial or complete; Supplementary Table 3). The pulmonary function test of one patient in the CCB20 group was withheld due to poor cooperation during the examination. No significant differences between the groups were observed in the reduction rates of pulmonary function (Supplementary Table 4).

Discussion

In this trial, we hypothesized that the larger the volume of local anesthetic used during CCB, the greater the spread into the supraclavicular area, thereby achieving complete analgesia during arthroscopic shoulder surgery. However, we found that neither adequate spreading of the local anesthetic nor complete analgesia was guaranteed by a larger volume of local anesthetic. In addition, despite its significant association with lower pain scores, the sonographic finding of supraclavicular spreading of local anesthetic was not a reliable indicator of complete analgesia.

The density of nociceptors in the shoulder joint is highest in the subacromial bursa, anterior glenohumeral capsule, and ligaments that are innervated by the suprascapular, axillary, lateral pectoral, and upper subscapular nerves [20,21]. The lateral pectoral (lateral cord), subscapular (posterior cord), and axillary (posterior cord) nerves can be directly covered by a CCB. Meanwhile, the suprascapular nerve branching off from the superior trunk can only be blocked by the supraclavicular spreading of the local anesthetic [5]. Thus, the severe pain that manifested in several patients in this study can be partially explained by inadequate supraclavicular spreading. Additionally, the lateral pectoral nerve can also be spared by inadequate spreading. According to a previous meta-analysis, the lateral pectoral nerve arises most frequently from the anterior divisions of the upper and middle trunks before forming the cords [22].

However, it should be noted that while supraclavicular spreading determined by post-procedure ultrasound showed a certain degree of association with lower pain score, it did not guarantee complete analgesia in this study. There could be several explanations for this. Firstly, the binary determinations of adequate versus inadequate spreading in sonographic imaging and complete versus incomplete analgesia may not be realistic classifications. This stringent classification may have limitations in representing a more nuanced spectrum of local anesthetic spreading and the corresponding quality of blockade. Secondly, in some cases, the suprascapular nerve can branch off early and course further away from the plexus. This might explain why some patients still suffer from pain despite being determined to have proper local anesthetic spread between the superior and middle trunk. Thirdly, there may be at least some degree of ambiguity and/or subjectivity in the visual evaluation of sonographic findings. Unfortunately, the exact cause of insufficient shoulder analgesia cannot be concluded in this study. Further research using detailed assessments of each major contributing nerve after CCB is needed [23].

Table 2). The pulmonary function test of one patient in the CCB20 group was withheld due to poor cooperation during the examination. No significant differences between the groups were observed in the reduction rates of pulmonary function (Supplementary Table 4).

Fig. 3. Alluvial plot for relation of group, supraclavicular spreading of local anesthetic, and complete analgesia in immediate postoperative period. Note that while most cases with complete analgesia were associated with the adequate supraclavicular spreading of local anesthetics, complete analgesia was not always achieved despite adequate supraclavicular spreading. CCB20: costoclavicular block with 20 ml of 0.75% ropivacaine, CCB40: CCB with 40 ml of 0.375% ropivacaine.
According to previous dose-finding studies of CCB, approximately 20 ml of local anesthetic is required for surgical anesthesia in forearm and hand surgeries [24,25]. Since even twice the volume of injectate during CCB showed no significant improvement in supraclavicular spreading in the current study, other factors affecting proper coverage of the shoulder joint should be considered. One of the possible factors is the intraplexus fascial septum [14] that separates the two compartments (i.e., either the anterior that contains the lateral cord, or the posterior that contains the medial and posterior cord) and may affect spreading. Because we injected a larger volume into the posterior compartment, whether supraclavicular spreading is better if a larger volume is injected into the anterior compartment needs to be confirmed. In addition, as shown in this study, direct observation of the supraclavicular spread of the injectate via ultrasound would be helpful, and additional measures to supplement inadequate coverage (e.g., suprascapular nerve block) can be sought in advance.

Although the costoclavicular space is contiguous with the supraclavicular space, CCB has shown a lower HDP rate than the supraclavicular block in previous studies [10,11,26]. However, the occurrence of HDP (4%–11% incidence) is not completely avoidable with CCB. In line with the insignificant volume effect on supraclavicular spreading, the HDP rate was irrelevant to the injectate volume. Although complete HDP was observed only in CCB40, no statistical significance in group difference was found. Also, supraclavicular spreading was not a significant determinant of HDP either. However, since HDP is not the main outcome of this study, it cannot be confirmed, and additional well-designed studies are needed.

While it is true that CCB is a diaphragm-sparing technique when compared to other approaches performed above the clavicle [27], caution should be exercised when comparing studies due to the differences in the definition of HDP used in each study. Our findings appear to conflict with a prior study that reported no cases of HDP when utilizing CCB in shoulder surgery [4]. However, the definition of HDP in that study only focused on a very severe case of complete HDP absence, or paradoxical movement of the diaphragm that makes it challenging to compare with the results of other studies that define complete HDP as less than 25% of the baseline DE value.

Anatomical variations in the phrenic nerve can contribute to varying degrees of partial HDP. Duplication or lateral displacement of the phrenic nerve and its accessory variations may result in variable degrees of HDP due to supraclavicular spreading during CCB [28,29]. Therefore, it may be important to distinguish whether the main branch of the phrenic nerve that originates from C4 is blocked. From this perspective, using all-or-nothing criteria of prior study may be more clinically relevant [4].

This study has several limitations that should be considered when interpreting the results. First, the 40 ml volume of local anesthetic may not be large enough for supraclavicular spreading. Second, the primary outcome of the zero-pain score may have been too strict. Considering the benefit of the low risk of HDP after CCB, mild pain that is well tolerated by the patient may be acceptable, especially in patients with limited respiratory capacity. Third, intermediate or superficial cervical plexus block was not performed in this study. During interscalene or supraclavicular blocks, the C4 dermatome can also be blocked by superior spreading, which is hardly expected during CCB [30]. Although the cape region that is covered by the cervical plexus is not the main source of pain in arthroscopic shoulder surgery, the incomplete analgesia reported in this study may be partially explained by this issue. Fourth, the results cannot be generalized to other shoulder procedures, such as total shoulder replacement or fixation of humerus fractures that might follow different healing processes and consequent pain trajectories. Fifth, bias due to the disclosure of group assignment to the physician who performed the blockades cannot be excluded. Lastly, given that the evaluation of lung function took place after general anesthesia, differentiating the distinct impact of the block from that of general anesthesia might present a challenge.

In conclusion, 40 ml of local anesthetic does not guarantee supraclavicular spread during CCB and does not show a greater rate of complete analgesia than 20 ml of local anesthetic in arthroscopic shoulder surgery. Due to the inconsistent analgesic effects observed even with a high volume of local anesthetic, CCB does not seem to be an ideal analgesic technique for shoulder surgery. Further research exploring techniques that provide both effective analgesia and diaphragm-sparing in shoulder surgery is needed.

Funding

This work was supported by the National Research Foundation of Korea (NRF-2022R1C1C1007982) of Chungnam National University.

Conflicts of Interest

Woosuk Chung has been an editor for the Korean Journal of Anesthesiology since 2020. However, he was not involved in any process of review for this article, including peer reviewer selection, evaluation, or decision-making. There were no other potential conflicts of interest relevant to this article.
Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Yumin Jo (Conceptualization; Data curation; Project administration; Writing – original draft)
Chahyun Oh (Conceptualization; Formal analysis; Methodology; Writing – original draft; Writing – review & editing)
Woo-Yong Lee (Methodology; Project administration; Resources)
Hyung-Jin Chung (Investigation; Methodology; Project administration)
Hanmi Park (Data curation; Project administration)
Juyeon Park (Data curation; Project administration)
Jieun Lee (Data curation; Project administration; Resources)
Yoon-Hee Kim (Supervision; Writing – review & editing)
Youngkwon Ko (Supervision; Writing – review & editing)
Woosuk Chung (Resources; Supervision; Validation; Writing – review & editing)
Boohwi Hong (Conceptualization; Formal analysis; Funding acquisition; Software; Visualization; Writing – original draft; Writing – review & editing)

Supplementary Materials

Supplementary Fig. 1. Study protocol. Diaphragm evaluation using ultrasound and spirometry was performed before and after surgery.
Supplementary Fig. 2. Ultrasound-guided observation of brachial plexus at the supraclavicular area. (A) Pre-block, the suprascapular nerve lies laterally within the superior trunk at the corner pocket image. (B) Local anesthetic is spread around trunks and suprascapular nerve after the costoclavicular block.
Supplementary Fig. 3. Cumulative opioid consumption during the postoperative 48 hours.
Supplementary Fig. 4. The proportion of patients not requiring the first dose of patient-controlled analgesia (PCA) stratified by group.
Supplementary Table 1. Questionnaire about the experience at 24 hours postoperatively stratified by group.
Supplementary Table 2. Sonographic assessments of diaphragm function.
Supplementary Table 3. Logistic regression analysis for factors associated with hemidiaphragmatic paresis (HDP).

ORCID

Yumin Jo, https://orcid.org/0000-0002-4847-0250
Chahyun Oh, https://orcid.org/0000-0001-8344-4245
Woo-Yong Lee, https://orcid.org/0000-0001-8706-6026
Hyung-Jin Chung, https://orcid.org/0000-0003-0650-8975
Hanmi Park, https://orcid.org/0000-0002-4677-8737
Juyeon Park, https://orcid.org/0000-0002-2864-6538
Jieun Lee, https://orcid.org/0000-0002-1317-8452
Yoon-Hee Kim, https://orcid.org/0000-0002-8282-610X
Youngkwon Ko, https://orcid.org/0000-0002-0178-6346
Woosuk Chung, https://orcid.org/0000-0002-6409-2325
Boohwi Hong, https://orcid.org/0000-0003-2468-9271

References

Randomized controlled trial of the effect of general anesthetics on postoperative recovery after minimally invasive nephrectomy

Hyun-Kyu Yoon, Somin Joo, Susie Yoon, Jeong-Hwa Seo, Won Ho Kim, Ho-Jin Lee

Department of Anesthesiology and Pain Medicine, Seoul National University Hospital, Seoul, Korea

Background: General anesthetic techniques can affect postoperative recovery. We compared the effect of propofol-based total intravenous anesthesia (TIVA) and desflurane anesthesia on postoperative recovery.

Methods: In this randomized trial, 150 patients undergoing robot-assisted or laparoscopic nephrectomy for renal cancer were randomly allocated to either the TIVA or desflurane anesthesia (DES) group. Postoperative recovery was evaluated using the Korean version of the Quality of Recovery-15 questionnaire (QoR-15K) at 24 h, 48 h, and 72 h postoperatively. A generalized estimating equation (GEE) was performed to analyze longitudinal QoR-15K data. Fentanyl consumption, pain severity, postoperative nausea and vomiting, and quality of life three weeks after discharge were also compared.

Results: Data were analyzed for 70 patients in each group. The TIVA group showed significantly higher QoR-15K scores at 24 and 48 h postoperatively (24 h: DES, 96 [77, 109] vs. TIVA, 104 [82, 117], median difference 8 [95% CI: 1, 15], P = 0.029; 48 h: 110 [95, 128] vs. 125 [109, 130], median difference 8 [95% CI: 1, 15], P = 0.022), however not at 72 h (P = 0.400). The GEE revealed significant effects of group (adjusted mean difference 6.2, 95% CI: 0.39, 12.1, P = 0.037) and time (P < 0.001) on postoperative QoR-15K scores without group-time interaction (P = 0.051). However, there were no significant differences in other outcomes, except for fentanyl consumption, pain severity, postoperative nausea and vomiting, and quality of life three weeks after discharge were also compared.

Conclusions: Propofol-based TIVA showed only a transient improvement in postoperative recovery than desflurane anesthesia, without significant differences in other outcomes.

Keywords: Enhanced recovery after surgery; General anesthetics; Inhalation anesthesia; Intravenous anesthesia; Perioperative medicine; Postoperative period.

Introduction

General anesthetic techniques that are divided into inhalation and intravenous (IV) anesthesia can affect postoperative recovery. The most well-known difference between the two techniques may be the decrease in postoperative nausea and vomiting (PONV) for propofol-based total intravenous anesthesia (TIVA) compared with inhalation anesthesia [1]. Previous studies have also reported that propofol-based TIVA yields better outcomes than inhalation anesthesia in terms of postoperative morbidity [2–4]. Further, propofol-based TIVA may be associated with improvements in oncologic outcomes compared with inhalation anesthesia [5]. However, propofol-based TIVA has not yet been strongly recommended in perioperative guidelines due to the lack of strong evidence.
Materials and Methods

This prospective, randomized, single-blinded trial was approved by the Institutional Review Board (IRB) of Seoul National University Hospital (2003-177-1113). Before patient enrollment, the study protocol was registered with ClinicalTrials.gov (NCT04447105). This study was performed in accordance with Good Clinical Practice Guidelines and Consolidated Standards of Reporting Trials (CONSORT) guidelines [14]. The study adhered to the tenets outlined in the 2013 Declaration of Helsinki, and all patients provided written informed consent. Enrollment occurred at the university teaching hospital in South Korea between June 2020 and July 2021.

Patient selection

We screened adult patients (age: 19 to 80 years) with renal cancer scheduled to undergo elective minimally invasive nephrectomy for study eligibility. Patients with the following features were excluded: 1) American Society of Anesthesiologists (ASA) physical status ≥ III, 2) non-malignancy or receiving concurrent surgeries, 3) history of allergic reaction to anesthetics or analgesics included in the protocol of this study, 4) history of chronic pain defined as having taken analgesics or anticonvulsants for more than three months, 5) requirement of mechanical ventilation for ≥ 2 h after surgery, 6) poorly controlled psychological diseases that precluded cooperation, and 7) difficulty understanding the informed consent process or questionnaires in the Korean language.

Randomization and blinding

After enrollment, block randomization (block size: 4 and 6) was used to randomly allocate patients to the propofol-based TIVA (TIV A group) or desflurane anesthesia (DES group) at a 1:1 ratio using R software (Version: 3.6.1, R Development Core Team). Randomization was conducted by an anesthesiologist who was not involved in this study. Patients and the outcome assessor were blinded to group assignments, but the attending anesthesiologists could not be blinded due to the differences in intraoperative anesthetic techniques between the groups. Information regarding the allocation order stored in an opaque envelope was delivered to the attending anesthesiologists on the day of surgery.

Anesthetic management

Without premedication, anesthesia was induced with a 1.0–2.0 mg/kg bolus dose of propofol (Fresofol MCT 1%, Fresenius Kabi Korea Ltd.) and maintained with desflurane (Suprane, Baxter Healthcare) in the DES group. In the TIVA group, anesthesia was induced and maintained with a target-controlled infusion (TCI) of propofol (Fresofol MCT 2%, Fresenius Kabi Korea Ltd.) using an infusion pump (Orchestra®; Fresenius Vial) using the Marsh pharmacokinetic model. Other than the anesthetics used to maintain general anesthesia, the following anesthetic management procedure was identical in both groups. During induction, 5 mg of dexamethasone and 0.075 mg of palonosetron were administered for PONV prophylaxis. Remifentanil was started using a TCI using the Minto pharmacokinetic model with a target of effect-site concentration of 3.0 ng/ml, then was adjusted to maintain arterial pressure within 20% of baseline ward pressure. Rocuronium was used to maintain deep neuromuscular block under monitoring with acceleromyography. The bispectral index and mean arterial blood pressure were maintained within 40–60 and 60–90 mmHg, respectively. For early postoperative pain control, 1 g of IV acetaminophen was injected over 30 min at the point of insertion of the Jackson–Pratt drains. A loading dose of IV fentanyl (50 µg) was administered following skin closure for IV patient-controlled analgesia (IV-PCA). Patients were extubated after administration of sugammadex for the reversal of neuromuscular blockade, following which they were transferred to the post-anesthesia care unit (PACU).
Postoperative management in the PACU and ward

Patients in the PACU were permitted to utilize IV-PCA delivered via a semi-electronic infusion pump (AutoMed 3200®, ACE Medical). The bolus dose of fentanyl and lockout interval were 20 μg and 10 min, respectively, and there was no basal infusion. Patients were instructed to use IV-PCA when they had a numeric rating scale (NRS) pain score ≥ 3. At the PACU, patients who reported a pain level of NRS ≥ 7 were given 50 μg of IV fentanyl, regardless of whether they were using IV-PCA or not. PONV was categorized into four groups: no symptoms, mild (occasional symptoms but tolerable without medication), moderate (frequent or persistent symptoms requiring medication), and severe (vomiting). Rescue antiemetics were administered upon the patient’s request or when they reported moderate to severe PONV. Such treatment involved the administration of 10 mg of metoclopramide in the PACU. In the ward, initial rescue antiemesis treatment involved the administration of 0.3 mg of ramosetron, followed by 10 mg of metoclopramide as the second rescue treatment when necessary. Water sips were permitted on the morning of the postoperative day (POD) 1, and a liquid and soft-blended diet were initiated in stages on the same day. An oral extended-release tramadol 37.5 mg/acetaminophen 325 mg combination tablet was routinely administered at 12-h intervals from the morning of POD 1 until discharge. If a patient’s pain persisted at a rating of NRS ≥ 7 despite active use of IV-PCA (four times/h), a rescue analgesic was administered. During the first 8 h postoperatively, the initial rescue analgesic was 50 μg of IV fentanyl and then 1 g of IV acetaminophen.

After taking a routine oral analgesic (the morning of POD 1), the initial rescue analgesic was 650 mg of oral acetaminophen, and an alternative rescue analgesic was 50 μg of IV fentanyl. However, when the patient complained of PONV, 1 g of IV acetaminophen was administered at the discretion of the attending physicians. Ward ambulation was also initiated on the morning of POD 1 after radical nephrectomy and 24 h after partial nephrectomy. The Foley catheter was removed at the start of ward ambulation. During the follow-up period (until POD 3), transdermal analgesics, IV opioids other than fentanyl, and oral analgesics other than the tramadol/acetaminophen combination tablet were not allowed.

Outcome measures

The day before surgery, the investigators asked the patients to complete the QoR-15K and the EuroQoL 5-dimension 5-level scale (EQ-5D-5L) to measure baseline status [15]. The QoR-15K consists of 15 short-form instrument items, and these items can be classified into the following five categories: physical comfort (five items), emotional state (four items), psychological support (two items), physical independence (two items), and pain (two items). Each item is evaluated using an 11-point numerical rating scale (0–10), and a higher score means a better recovery. The following baseline and intraoperative variables were recorded: sex, age, body mass index, the Physiological and Operative Severity Score for the enUmeration of Mortality and Morbidity (POSSUM score) [16], ASA physical status, Apfel score [17], type of surgery (radical vs. partial), type of approach (laparoscopic vs. robot-assisted), estimated blood loss (ml), intraoperative crystalloid and colloid administration (ml/kg), intraoperative transfusion, operative time (min), and intraoperative remifentanil consumption (μg). The primary outcome was the QoR-15K score measured at 24 h postoperatively. Secondary outcomes included the QoR-15K score measured at 48 h and 72 h postoperatively; the interval of fentanyl consumption during the first 24 h and 24–48 h postoperatively; resting and movement-evoked pain intensity using an 11-point NRS at 24, 48, and 72 h postoperatively; the occurrence of PONV at 24, 48, and 72 h postoperatively; and quality of life at three weeks after discharge as measured using the EQ-5D-5L in the outpatient clinic. Considering the confusion caused by certain points of the QoR-15K for respondents [9], all QoR-15K questionnaires were completed under the two experienced investigator’s guidance. In addition, because we determined that the QoR-15K was not suitable for evaluating the quality of recovery after discharge, we opted to use the EQ-5D-5L questionnaire to evaluate the quality of recovery at the outpatient clinic three weeks after discharge. Patients completed the questionnaire after discharge independently without assistance from the investigators. We also compared the administration of rescue analgesics other than fentanyl, serum high-sensitivity C-reactive protein on POD 3 as a systemic inflammatory marker, postoperative complications classified using the Clavien–Dindo classification during hospitalization evaluated at the time of discharge [18], acute kidney injury diagnosed based on Kidney Disease: Improving Global Outcomes criteria [19], and length of hospital stay between the two groups. All outcomes were evaluated by physicians that were not involved in this study and were blinded to the group assignment.

Statistical analysis

Based on our previous study [9], we assumed a QoR-15K score of 95 ± 20 at 24 h after minimally invasive nephrectomy under inhalation anesthesia. Although we planned to investigate a QoR-15K at 48 and 72 h postoperatively, we could not consider it in the
sample size calculation due to the lack of relevant data. Considering a QoR-15K score of 10 as the minimal clinically important difference (MCID) at 24 h postoperatively [20], the sample size calculation using G*Power (version 3.1.9; Franz Faul, University of Kiel) yielded 64 patients per group to achieve a two-tailed significance of 0.05 and a power of 80%. Considering the dropout rate of 15%, a total of 150 patients were required for enrolment.

Continuous variables are reported as the mean ± standard deviation or median [interquartile range (IQR)] and were compared using Student’s t-test or the Mann-Whitney U test according to the normality of the data. Categorical variables are reported as frequencies or percentages and were compared using the chi-square or Fisher’s exact test based on their expected frequencies. The effect size and 95% CI were also calculated.

To compare the differences in QoR-15K scores at each time point, including the primary outcome (QoR-15K score at 24 h postoperatively), we used the Mann–Whitney U test. We also performed a generalized estimating equation (GEE) that is more flexible than repeated-measures analysis of variance to analyze repeated QoR-15K score measurements [21]. If there was no significant interaction between the group and time in the GEE, we calculated the adjusted mean difference of the QoR-15K score between the two groups, excluding the interaction term from the model. If a significant interaction between group and time was observed in the GEE, then post hoc pairwise multiple comparisons using least squares mean with the Bonferroni correction were performed to calculate the adjusted mean difference of QoR-15K score between the two groups at each time point. The GEE analysis was also performed, with Bonferroni correction, for each dimension of the QoR-15K.

All tests were two-sided, and the level of statistical significance was set at P < 0.05. All statistical analyses were conducted using R software (Version: 3.6.1, R Development Core Team).

Results

Among 246 eligible patients, 96 were excluded, following which the remaining 150 patients were randomly allocated to the TIVA or DES group (Fig. 1). During the study period, ten patients were additionally excluded due to the cancellation of the operation on the day of surgery (n = 4), ASA Physical Status of III on the day of surgery (n = 1), requirement of mechanical ventilation after massive intraoperative bleeding (n = 1), refusal to complete the questionnaire after surgery (n = 3), and postoperative cognitive dysfunction (n = 1). In total, 140 patients were included in the final analysis. Table 1 summarizes the baseline characteristics of the included participants that did not significantly differ between the TIVA and DES groups, except for the amount of remifentanil administered intraoperatively (median difference: 270 [169, 376] μg, P < 0.001).

Fig. 2 and Supplementary Tables 1–4 show the comparisons of QoR-15K scores between the two groups. Eight patients (TIVA group: n = 5, DES group: n = 3) were discharged before 72 h postoperatively; thus, they could not complete the QoR-15K at that point. The TIVA group showed significantly higher QoR-15K scores at 24 and 48 h postoperatively (24 h: DES, 96 [77, 109] vs. TIVA, 104 [82, 117], median difference 8 [95% CI: 1, 15], P = 0.029; 48 h: DES, 110 [95, 128] vs. TIVA, 125 [109, 130], median difference 8 [95% CI: 1, 15], P = 0.022), however not at 72 h (DES group, 125 [113, 137] vs. TIVA group, 129 [115, 140], median difference 3 [95% CI: −3, 8], P = 0.400). During the entire study period, the GEE revealed significant effects of group (adjusted mean difference 6.2, [95% CI: 0.39, 12.1], P = 0.037) and time (P < 0.001) on postoperative QoR-15K scores, without group-time interaction (P = 0.051). Among the five dimensions of the QoR-15K, only the pain dimension was significantly better in the TIVA group than in the DES group during the study period (Table 2). A significant interaction was observed between time and group in the psychological support and physical independence dimensions, leading to a post hoc analysis. The analysis revealed a significant difference between the two groups only in the physical independence dimension at 24 h postoperatively and in the psychological support dimension at 48 h postoperatively.

Table 3 and Supplementary Table 5 show the comparison of other postoperative outcomes between the two groups. Fentanyl consumption during the first 24 h postoperatively was significantly lower in the TIVA group than in the DES group (adjusted median difference −40 μg, [corrected 95% CI: −250, −30 μg], Bonferroni corrected P = 0.008). However, no other postoperative outcomes differed between the two groups. One hundred and four patients (74.3%) completed the EQ-5D-5L questionnaire three weeks after hospital discharge (Supplementary Table 6). There was no significant difference in any item of the EQ-5D-5L before surgery and after hospital discharge between the two groups.

Discussion

The difference in the postoperative quality of recovery between the two groups varied depending on the time after surgery. Although propofol-based TIVA significantly improved the quality of recovery at 24 and 48 h after minimally invasive nephrectomy compared with desflurane anesthesia, their effect size was smaller than the predefined MCID. Furthermore, this difference did not remain at 72 h postoperatively. There was no significant difference
246 Patients assessed for eligibility

96 Excluded
- 26 Declined to participate
- 45 ASA III or more
- 9 Antipsychotics or anticonvulsants
- 6 Joint operation
- 6 Angiomyolipoma
- 3 Dementia
- 1 Others

26 Declined to participate
45 ASA III or more
9 Antipsychotics or anticonvulsants
6 Joint operation
6 Angiomyolipoma
3 Dementia
1 Others

200 Randomized

75 Assigned to the desflurane group

3 Excluded
- 2 Cancelled operation
- 1 Intraoperative massive bleeding due to vessel injury

72 Received allocated intervention

2 Excluded
- 2 Patients refused to respond

70 Included in the final analysis

75 Assigned to the propofol group

3 Excluded
- 2 Cancelled operation
- 1 Not meeting inclusion criteria; ASA III

72 Received allocated intervention

2 Excluded
- 1 Patient refused to respond
- 1 Patients could not complete the questionnaire due to postoperative cognitive dysfunction

70 Included in the final analysis

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram. ASA: American Society of Anesthesiologists.

between the two groups in any other postoperative clinical outcomes, including quality of life, at three weeks after discharge.

Several studies have investigated the effect of general anesthetic techniques on postoperative recovery using the QoR-40 [22–28]. An RCT including female patients undergoing thyroid surgery reported the superiority of propofol-based TIVA for early postoperative recovery, mainly due to the reduction in PONV [22]. However, differences in patient characteristics and insufficient PONV prophylaxis made this result difficult to apply to other surgeries, and subsequent RCTs have yielded conflicting results [23–28]. Moreover, in most previous studies, outcomes were assessed only within POD 1, except in two recently published RCTs [27,28].

One involving patients undergoing pancreatectomy reported that postoperative recovery was significantly better on POD 3 in the propofol-based TIVA group than in the DES group [27]. However, the clinical implications of a significant difference only on POD 3 may be debatable, considering the relatively long length of hospital stay following pancreatectomy. Rather, this difference seen only on POD 3 might have resulted from the transient effect of type of general anesthetic techniques, similar to our result. Another recent RCT for laparoscopic hysterectomy reported no significant difference between the two techniques in terms of postoperative recovery [28]. However, the study only included relatively young female patients, making the results difficult to gener-
### Table 1. Baseline and Perioperative Characteristics of the Propofol-based Total Intravenous Anesthesia (TIVA) and Desflurane Anesthesia (DES) Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DES group (n = 70)</th>
<th>TIVA group (n = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>59.0 (48.0, 65.0)</td>
<td>60.0 (53.0, 67.0)</td>
</tr>
<tr>
<td>Female sex</td>
<td>21 (30.0)</td>
<td>27 (38.6)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.0 (23.7, 28.2)</td>
<td>24.7 (22.7, 27.1)</td>
</tr>
<tr>
<td><strong>Baseline medical status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASA physical status (I/II)</td>
<td>21 (30.0)/49 (70.0)</td>
<td>15 (21.4)/55 (78.6)</td>
</tr>
<tr>
<td>Apfel score (1/2/3/4)</td>
<td>31 (44.3)/21 (30.0)/17 (24.3)/1 (1.4)</td>
<td>25 (35.7)/21 (30.0)/21 (30.0)/3 (4.3)</td>
</tr>
<tr>
<td><strong>POSSUM</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physiological score</td>
<td>20 (15, 22)</td>
<td>20 (16, 21)</td>
</tr>
<tr>
<td>Operative severity score</td>
<td>8 (8, 9)</td>
<td>8 (8, 9)</td>
</tr>
<tr>
<td>Preoperative serum hs-CRP (mg/dl)</td>
<td>0.1 (0.0, 0.2)</td>
<td>0.1 (0.0, 0.1)</td>
</tr>
<tr>
<td><strong>Surgical variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extent of surgery: Radical/Partial</td>
<td>12 (17.1)/58 (82.9)</td>
<td>16 (22.9)/54 (77.1)</td>
</tr>
<tr>
<td>Type of surgery: Laparoscopic/Robot-assisted</td>
<td>12 (17.1)/58 (82.9)</td>
<td>15 (21.4)/55 (78.6)</td>
</tr>
<tr>
<td><strong>Intraoperative variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>90 (75, 115)</td>
<td>90 (75, 105)</td>
</tr>
<tr>
<td>Intraoperative remifentanil (μg)</td>
<td>653 (500, 1000)</td>
<td>979 (800, 1200)</td>
</tr>
<tr>
<td>Estimated blood loss (ml)</td>
<td>130 (60, 200)</td>
<td>100 (50, 150)</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3) or number of patients (%). BMI: body mass index, ASA: American Society of Anesthesiologists, POSSUM: physiological and operative severity score for the enumeration of mortality and morbidity, hs-CRP: high-sensitivity C-reactive protein.

**Fig. 2.** Comparison of scores of the QoR-15K between the propofol-based TIVA and DES groups. The box plot displays the median and IQR of the QoR-15K scores in the TIVA and DES groups. The upper and lower whiskers on the plot represent the maximum and minimum values, respectively, excluding outliers that are depicted on the plot as round symbols. The statistical significance is also indicated on the plot. DES: desflurane anesthesia, IQR: interquartile range, QoR-15K: Korean version of the Quality of Recovery-15, TIVA: total intravenous anesthesia. *P < 0.05; †This included 67 patients in the DES group and 65 patients in the TIVA group.
alize. Additionally, unlike this study, our study found a transient but significant improvement in early postoperative recovery in the TIVA group, consistent with several previous studies [22–25].

Our study differs from previous investigations in that we aimed to mitigate the impact of the antiemetic effect of propofol-based TIVA by implementing multimodal PONV prophylaxis in both groups in accordance with recent guidelines [1]. Furthermore, we included patients undergoing minimally invasive cancer surgeries. Given the growing interest in the effects of anesthetic type on oncologic outcomes [5,29,30], our study may provide additional

Table 2. Comparison of Each Dimension* of the Korean Version of the Quality of Recovery-15 (QoR-15K*) between the Propofol-based Total Intravenous Anesthesia (TIV A) and Desflurane Anesthesia (DES) Groups via the Generalized Estimating Equation (GEE)

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Adjusted mean difference†</th>
<th>Corrected 95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical comfort (0–50) during the study period</td>
<td>2.0</td>
<td>−0.3, 4.2</td>
<td>0.087</td>
</tr>
<tr>
<td>Emotional state (0–40) during the study period</td>
<td>1.6</td>
<td>−0.7, 4.0</td>
<td>0.168</td>
</tr>
<tr>
<td>Psychological support (0–20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h postoperatively</td>
<td>0.5</td>
<td>−0.6, 1.7</td>
<td>0.813†</td>
</tr>
<tr>
<td>48 h postoperatively</td>
<td>1.0</td>
<td>0.1, 2.1</td>
<td>0.021†</td>
</tr>
<tr>
<td>72 h postoperatively</td>
<td>0.4</td>
<td>−0.3, 0.1</td>
<td>0.480†</td>
</tr>
<tr>
<td>Physical independence (0–20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h postoperatively</td>
<td>1.6</td>
<td>1.0, 3.0</td>
<td>0.033†</td>
</tr>
<tr>
<td>48 h postoperatively</td>
<td>1.0</td>
<td>−1.4, 3.4</td>
<td>0.930†</td>
</tr>
<tr>
<td>72 h postoperatively</td>
<td>−0.5</td>
<td>−2.7, 1.8</td>
<td>&gt; 0.999†</td>
</tr>
<tr>
<td>Psychological support (0–20)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h postoperatively</td>
<td>1.6</td>
<td>1.0, 3.0</td>
<td>0.033†</td>
</tr>
<tr>
<td>48 h postoperatively</td>
<td>1.0</td>
<td>−1.4, 3.4</td>
<td>0.930†</td>
</tr>
<tr>
<td>72 h postoperatively</td>
<td>−0.5</td>
<td>−2.7, 1.8</td>
<td>&gt; 0.999†</td>
</tr>
<tr>
<td>Pain (0–20) during the study period</td>
<td>1.5</td>
<td>0.3, 3.0</td>
<td>0.013</td>
</tr>
</tbody>
</table>

*The QoR-15K consists of 15 short-form instrument items, and these items can be classified into the following five dimensions: physical comfort (5 items), emotional state (4 items), psychological support (2 items), physical independence (2 items), and pain (2 items). Each item is evaluated using an 11-point numerical rating scale (0–10), and a higher score means a better recovery. †Adjusted mean differences are expressed as the TIV A group versus the DES group.

Table 3. Comparison of Secondary Outcomes Other than the Quality of Recovery between the Propofol-based TIVA and DES Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>DES group (n = 70)</th>
<th>TIV A group (n = 70)</th>
<th>Effect size* (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h postoperatively</td>
<td>3 (2, 5)</td>
<td>3 (1, 5)</td>
<td>−1 (−1, 0)†</td>
<td>0.453†</td>
</tr>
<tr>
<td>48 h postoperatively</td>
<td>2 (1, 3)</td>
<td>2 (1, 3)</td>
<td>0 (−1, 0)†</td>
<td>0.345†</td>
</tr>
<tr>
<td>72 h postoperatively†</td>
<td>2 (0, 3)</td>
<td>1 (0, 2)</td>
<td>0 (−1, 0)†</td>
<td>0.234†</td>
</tr>
<tr>
<td>Movement-evoked pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 h postoperatively</td>
<td>7 (5, 8)</td>
<td>7 (5, 8)</td>
<td>0 (−1, 1)†</td>
<td>&gt; 0.999†</td>
</tr>
<tr>
<td>48 h postoperatively</td>
<td>5 (4, 7)</td>
<td>5 (3, 6)</td>
<td>0 (−1, 0)†</td>
<td>0.480†</td>
</tr>
<tr>
<td>72 h postoperatively†</td>
<td>3 (2, 5)</td>
<td>3 (2, 5)</td>
<td>0 (−1, 0)†</td>
<td>0.564†</td>
</tr>
<tr>
<td>Intravenous fentanyl consumption (μg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 24 h</td>
<td>500 (300, 740)</td>
<td>355 (210, 500)</td>
<td>−140 (−250, −30)†</td>
<td>0.008†</td>
</tr>
<tr>
<td>24–48 h</td>
<td>170 (60, 460)</td>
<td>120 (40, 320)</td>
<td>−20 (−100, 40)†</td>
<td>0.512†</td>
</tr>
<tr>
<td>Rescue analgesics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 24 h</td>
<td>12 (17.1)</td>
<td>5 (7.1)</td>
<td>−0.10 (−0.23, 0.03)†</td>
<td>0.201†</td>
</tr>
<tr>
<td>24–48 h</td>
<td>6 (8.6)</td>
<td>5 (7.1)</td>
<td>−0.01 (−0.12, 0.09)†</td>
<td>&gt; 0.999†</td>
</tr>
<tr>
<td>48–72 h</td>
<td>6 (8.6)</td>
<td>5 (7.1)</td>
<td>−0.01 (−0.13, 0.10)†</td>
<td>&gt; 0.999†</td>
</tr>
<tr>
<td>PONV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 24 h</td>
<td>14 (20.0)</td>
<td>16 (22.9)</td>
<td>0.03 (−0.14, 0.19)†</td>
<td>&gt; 0.999†</td>
</tr>
<tr>
<td>24–48 h</td>
<td>12 (17.1)</td>
<td>7 (10.0)</td>
<td>−0.07 (−0.21, 0.07)†</td>
<td>0.645†</td>
</tr>
<tr>
<td>48–72 h</td>
<td>5 (7.5)</td>
<td>10 (15.4)</td>
<td>0.07 (0.05, 0.20)†</td>
<td>0.507†</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3) or number of patients (%). DES: desflurane anesthesia, NRS: numeric rating scale, PONV: postoperative nausea and vomiting, TIVA: total intravenous anesthesia. *Median or % differences are expressed as the TIVA group versus the DES group. †Bonferroni adjustments with corrections of the 95% CIs were applied to multiple comparisons. A Bonferroni corrected P < 0.05 was considered statistically significant. ‡This included 67 patients in the DES group and 65 patients in the TIVA group.
meaningful information regarding anesthetic selection in patients undergoing cancer surgeries. We also reduced the impact of confounding factors on postoperative recovery using a homogeneous sample of patients and a standardized perioperative protocol. Lastly, we used the QoR-15, which has higher clinical feasibility than the QoR-40 [31] and was the first validated measurement for postoperative recovery under the standardized criteria [13]. Therefore, our results may provide more reliable information regarding the effect of general anesthetic techniques on postoperative recovery.

In this study, the main perceived advantages of propofol-based TIVA compared to desflurane anesthesia were its opioid-sparing effect and improvement of pain dimension in the QoR-15K. Propofol may improve postoperative pain through its anti-inflammatory and antioxidant effects and antagonistic effects at NMDA receptors that can play an important role in pain signaling [2,32]. Several meta-analyses have supported the superiority of propofol-based TIVA for improving postoperative pain compared with inhalation anesthesia [2,33,34]. However, since the analgesic effect of propofol-based TIVA can vary depending on the degree of surgical trauma and postoperative pain management, our results should be interpreted cautiously. In an aforementioned RCT that addressed laparoscopic hysterectomy outcomes, no differences in postoperative recovery were observed between propofol-based TIVA and sevoflurane anesthesia [28]. In this study, postoperative pain intensity was low, indicating that propofol-based TIVA may not have induced a significant difference in postoperative pain outcomes. Additionally, regional analgesia—not included in our study—can negate the analgesic and opioid-sparing effects of propofol-based TIVA [35], which may further contribute to insignificant differences in QoR-15 scores between the two groups.

Our findings suggested that propofol-based TIVA improved postoperative recovery during the early postoperative period, which is also in line with the opinion of anesthesiologists who participated in a relevant survey (79% somewhat to strongly agreed that TIVA leads to the superior quality of recovery) [36]. However, considering its transient and marginal effect during hospitalization and the time course of postoperative recovery in our patients, it may be difficult to show that propofol-based TIVA leads to significant improvements in other postoperative outcomes.

Our study has several limitations. First, as this study was a single-blinded RCT, some biases may have influenced our results. However, although attending anesthesiologists could not be blinded, the investigator who evaluated postoperative outcomes was completely blinded to the group allocation. Second, the sample size was calculated based on the QoR-15K score at 24 h postoperatively, according to our previous study [9], although this was not sufficiently powered to detect significant differences in other outcomes. Additionally, we considered a QoR-15K score of 10 as the MCID, greater than the previously reported MCID of 8 for the QoR-15 [37]. In the planning stage of this study, we initially considered a QoR-15K score of 8 to be MCID based on the previous study [37]. However, considering that the difference in the QoR-15K scores between the two groups may decrease over time after surgery [22], we had set the MCID of 10 at 24 h postoperatively as the primary outcome that was a greater value than 8. Thus, we recalculated the sample size before patient enrollment after the approval of IRB. Third, our study was conducted at a single tertiary university hospital and thus may not reflect perioperative management at other institutions. Fourth, there was a significant difference in the total amount of intraoperative remifentanil used between the two groups. The type of general anesthesia technique and amount of intraoperative remifentanil could have affected postoperative pain severity and opioid consumption [32]. Although we assumed that this difference would have been due to the vasodilatory or analgesic effect of desflurane [38,39], we found it difficult to explain the mechanism behind this difference from our results. However, since there was no significant difference in postoperative pain severity, but rather, less postoperative opioid consumption in the TIVA group, the difference in intraoperative remifentanil amount would not have had a significant effect on our primary and secondary outcomes. Lastly, since we followed the conventional discharge criteria determined by attending surgeons, this may explain why a significant difference in postoperative recovery during the early postoperative period did not lead to a significant difference in the length of hospital stay. Further research is required to investigate the clinical impact of these two anesthetic techniques under a discharge protocol adjusted according to the degree of postoperative recovery. Despite these limitations, to our best knowledge, this is the first study to evaluate the impact of general anesthetic techniques on the quality of postoperative recovery, as measured using the QoR-15K in patients undergoing minimally invasive cancer surgeries.

In conclusion, our findings indicate that propofol-based TIVA provides better early postoperative recovery at 24 and 48 h postoperatively than desflurane anesthesia. However, this transient and marginal improvement did not last until 72 h postoperatively. Additionally, this transient and slight improvement led to no significant differences in other postoperative outcomes, including quality of life, at the early discharge phase of our study. However, considering our modest sample size, further studies with sufficient power are needed to establish a standardized anesthetic technique to improve postoperative recovery.
Acknowledgements

We would like to thank the Division of Statistics in the Medical Research Collaborating Center at the Seoul National University Hospital for helping with statistical analyses.

Funding

None.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Hyun-Kyu Yoon (Data curation; Visualization; Writing – original draft)
Somin Joo (Data curation; Formal analysis)
Susie Yoon (Formal analysis; Visualization; Writing – original draft)
Jeong-Hwa Seo (Data curation; Formal analysis)
Won Ho Kim (Formal analysis; Writing – review & editing)
Ho-Jin Lee (Conceptualization; Data curation; Supervision; Writing – original draft; Writing – review & editing)

Supplementary Materials

Supplementary Table 1. Comparison of the Korean version of the Quality of Recovery-15 (QoR-15K) scores at the preoperative phase between the propofol-TIVA and DES groups.
Supplementary Table 2. Comparison of the Korean version of the Quality of Recovery-15 (QoR-15K) scores at 24 h postoperatively between the propofol-based TIVA and DES groups.
Supplementary Table 3. Comparison of the Korean version of the Quality of Recovery-15 (QoR-15K) scores at 48 h postoperatively between the propofol-based TIVA and DES groups.
Supplementary Table 4. Comparison of the Korean version of the Quality of Recovery-15 (QoR-15K) scores at 72 h postoperatively between the propofol-based TIVA and DES groups.
Supplementary Table 5. Comparison of postoperative outcomes, other than primary and secondary outcomes, between the propofol-based TIVA and DES groups.
Supplementary Table 6. Comparisons of EQ-5D-5L scores on the day before surgery (preoperative) and at three weeks postoperatively (early post-discharge) between the propofol-based TIVA and DES groups.

ORCID

Hyun-Kyu Yoon, https://orcid.org/0000-0001-5424-3559
Somin Joo, https://orcid.org/0000-0001-8807-7229
Susie Yoon, https://orcid.org/0000-0001-5281-5904
Jeong-Hwa Seo, https://orcid.org/0000-0001-7644-2727
Won Ho Kim, https://orcid.org/0000-0003-1748-1296
Ho-Jin Lee, https://orcid.org/0000-0002-7134-5044

References


Programmed intermittent epidural bolus as an ideal method for labor analgesia: a randomized controlled trial

Doyeon Kim¹, Jeayoun Kim², Hyeonju Choo³, Duck Hwan Choi⁴

Department of Anesthesiology and Pain Medicine, ¹CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, ²Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, ³Inha University Hospital, Inha University School of Medicine, Incheon, ⁴Dongtan Sacred Heart Hospital, Hallym University School of Medicine, Hwaseong, Korea

Background: Although programmed intermittent epidural bolus (PIEB) is effective for labor analgesia, an appropriate flow rate has not been established. Therefore, we investigated the analgesic effect based on different epidural injection flow rates.

Methods: Nulliparous women scheduled for spontaneous labor were enrolled in this randomized trial. After injection of intrathecal 0.2% ropivacaine 3 mg with fentanyl 20 μg, participants were randomized to three study groups. Epidural analgesics, 10 ml during one hour, were administered with patient controlled epidural analgesia as follows (0.2% ropivacaine 60 ml, fentanyl 180 μg, and 0.9% saline 40 ml): continuous (n = 28, 10 ml/h for continuous infusion), PIEB (n = 29, 240 ml/h for bolus infusion of 10 ml), or manual (n = 28, 1200 ml/h for bolus injection of 10 ml). The primary outcome was hourly consumption of the epidural solution. The time interval between labor analgesia and the first breakthrough pain was investigated.

Results: The median (Q1, Q3) hourly consumption of epidural anesthetics was significantly different among the groups (continuous: 14.3 [8.7, 16.9] ml, PIEB: 9.4 [6.2, 9.8] ml, manual: 8.6 [7.6, 9.9] ml; P < 0.001). The time to breakthrough pain for the PIEB group was longer than that for the other groups (continuous: 78.5 [35.8, 185.0] min, PIEB: 200.0 [88.5, 441.5] min, manual: 60.5 [37.3, 162.0] min, P = 0.027).

Conclusions: PIEB, with a low-flow rate, provided more adequate labor analgesia than a continuous epidural infusion or manual injection with a high-flow rate.

Keywords: Analgesia; Anesthesia; Injections; Obstetrics; Pain; Pregnancy.

Introduction

Epidural analgesia is considered the gold standard for labor analgesia. Although provider-administered manual epidural infusion is classically performed as labor analgesia, with advances in technology, new methods, such as continuous epidural infusion and programmed intermittent epidural bolus (PIEB), have been introduced. Both are widely used in clinical situations for labor analgesia in combination with an epidural bolus [1].

PIEB is a method of automatically injecting a local anesthetic into the epidural space [2]. It provides superior analgesia and decreases motor blockade compared with conventional continuous epidural infusion [3]. PIEB is known to have an effective analgesic effect because it distributes the local anesthetic more uniformly in the epidural space with a large volume and high flow rate [4]. However, no standard for the appropriate flow range...
of PIEB has been established to date. Although Klumpner et al. [5] have reported that the higher the infusion rate, the higher the pressure generated during PIEB, Lange et al. [6] demonstrated that a small difference in epidural infusion flow rates (100 ml/h vs. 300 ml/h) did not contribute to satisfactory labor analgesia. Furthermore, because providing a high flow rate above a certain level is difficult owing to the pressure limitations of the machine itself, additional research is needed to establish a satisfactory epidural infusion flow rate.

Based on this, we hypothesized that a high-flow epidural bolus infusion of local anesthetics would be more efficient than a low-flow bolus infusion during labor analgesia. Therefore, we aimed to compare the effects of epidural analgesics infused at different flow rates on labor analgesia.

Materials and Methods

Ethics

This randomized, parallel-group, single-blind study was approved by the Institutional Review Board of Samsung Medical Center, Seoul, Republic of Korea (No. SMC 2019-06-085-002, chairperson Young Keun On, registration date: 11/09/2019) and was registered in the Clinical Trial Registry of Korea (https://cris.nih.go.kr, registration no. KCT0004389, principal investigator: Duck Hwan Choi, date of registration: 28/10/2019) a written informed consent was obtained from all participants before study enrolment. All the procedures were performed in accordance with the Declaration of Helsinki, 2013.

Patients

The study was conducted between November 2019 and December 2020. Nulliparous women with gestational age ≥ 36 weeks, single-twin pregnancy, American Society of Anesthesiologists physical status of I or II scheduled for spontaneous or induced vaginal delivery with cervical dilatation between 2 and 5 cm, and regular contractions occurring every 3–5 min were included. The exclusion criteria were as follows: women who received opioids or sedatives, received opioids within 4 h prior to labor analgesia, hypersensitivity, allergy to local ropivacaine or fentanyl, preeclampsia, and premature rupture of membranes.

Randomization and blindness

One statistician who was not involved in this study generated a random allocation sequence. Participants were randomly assigned to one of the three study groups using a computer-generated randomization sequence: continuous, PIEB, or manual. Randomization and group allocation were performed in a 1:1:1 ratio with a block size of three. One of the authors assigned the groups using the sealed opaque envelope technique. All investigators were blinded to the assigned groups.

Study protocol

A combined spinal epidural analgesia (CSE) procedure for labor analgesia was performed by residents under the supervision of an experienced obstetrical anesthesiologist. Prior to the procedure, the patient’s intravenous route was secured, and standard monitoring was performed, including blood pressure, heart rate, pulse oximetry, respiration rate, fetal heart rate, and uterine contractions. At the L3–4 interspace with the patient in the lateral decubitus position, a lumbar puncture was performed using a 25-gauge Whitacre needle (BD® Whitacre spinal needle, 25 G × 3.50IN TW, BD). After confirming the free flow of cerebrospinal fluid, intrathecal agents (0.2% ropivacaine 3 mg with fentanyl 20 μg) were administered to relieve labor pain immediately. The epidural space was then located using a 17-gauge Tuohy needle at the L3–4 or L4–5 level with the loss of resistance to the air technique. An epidural catheter (FlexTip Plus® Epidural Catheterization Set, 19 G, Arrow Electronics) was inserted 5–6 cm into the epidural space, confirmed by negative aspiration of blood and cerebrospinal fluid and flushed with 4 mg of 0.2% ropivacaine. All the procedures were performed using aseptic techniques.

According to the assigned group, an ambulatory infusion pump (Accumate® 1200, Wooyoung Meditech Co., Ltd.), comprising 60 ml of 0.2% ropivacaine, fentanyl 180 μg, and 40 ml of 0.9% saline, was used. Prior to the start of this trial, an ambulatory infusion pump device was tested using an infusion device analyzer (IDA-4 Plus Multi-Channel Infusion Device Analyzer, Fluke® Biomedical) to confirm its applicability. Patient-controlled epidural analgesia (PCEA) was prepared by a nurse who was not involved in the trial.

The details of drug delivery protocol according to the assigned group were as follows. In the continuous group, PCEA + basal continuous epidural infusion 10 ml/h was started 30 min after the labor analgesia procedure. When the bolus button was pressed by the patient, 5 ml of the local anesthetic was injected. Continuous basal epidural infusion was continued, regardless of the bolus dose.

In the PIEB group, PCEA + PIEB 10 ml during one hour (240 ml/h for bolus infusion of 10 ml) and infusion were started 60 min after the labor analgesia procedure. When the bolus button was pressed by the patient, 5 ml of local anesthetic was injected.
and a PIEB was injected after 15 min.

In the manual group, PCEA + provider-administered intermittent epidural boluses of 10 ml during one hour (1,200 ml/h for bolus injection of 10 ml) and manual injection was started 60 min after the labor analgesia procedure. In the manual group, an experienced anesthesiologist injected 10 ml of ropivacaine with a fentanyl mixture at a constant rate for 30 s through an epidural catheter. When the bolus button was pressed by the patient, 5 ml of the local anesthetic was injected. A provider-administered epidural bolus was injected at set intervals regardless of the bolus dose.

Labor pain was measured using an 11-point numerical rating scale (NRS: 0 = no pain and 10 = the worst pain imaginable). The participants were informed that the PCEA bolus could be used for labor analgesia. Breakthrough pain was defined as pain requiring a bolus infusion of PCEA while receiving epidural anesthetics according to the assigned group. When breakthrough pain with an NRS score ≥ 4 occurred during PCEA infusion, rescue medications were injected as follows: 0.2% ropivacaine 14 mg was administered into the epidural space. If the pain did not subside, 50 mg of 1% lidocaine was administered. The delivery method was switched from vaginal delivery to Cesarean section in cases where failure to progress in labor occurred even after more than 4 h of labor or when the mother requested it.

Patients’ age, height, weight, body mass index, gestational age, cervical dilatation at the time of labor analgesia, total labor duration, any adverse effects associated with labor analgesia (e.g., nausea, vomiting, numbness, paraplegia, postdural puncture headache, and local anesthetic systemic toxicity), duration of second stage, incidence and NRS score of breakthrough pain, use of oxytocin, preoperative blood pressure, heart rate, NRS score after the labor analgesia procedure, conversion rate to Cesarean section, and patient satisfaction using a Likert scale were also recorded.

Outcomes

The primary outcome was the hourly consumption of epidural analgesics during the labor analgesia procedure among the three groups. The secondary outcomes were the differences in the time interval to the first breakthrough pain, NRS score for breakthrough pain, degree of sensory and motor nerve blockade, and NRS score 4 h after labor analgesia among the three study groups. Considering the duration of intrathecal anesthetics injected during the labor analgesia procedure, we investigated the degree of sensory and motor blockade 4 h after the labor analgesia procedure. Neonatal outcomes including birth weight and Apgar scores were also recorded.

The degree of sensory blockade was recorded using a cold sensation, and the degree of motor blockade was investigated using the Breen-modified Bromage score (1 = complete block, unable to move feet or knees; 2 = almost complete block, only able to move feet; 3 = partial block, only able to move below knees; 4 = detectable weakness of hip flexion while supine; 5 = no detectable weakness of hip flexion while in supine but cannot stand due to hip weakness, full flexion of knees; and 6 = can stand and perform partial knee bend) [7].

Statistical analyses

A power calculation was based on a previous study that investigated the effect of PCEA plus automated mandatory boluses (PIEB) for reducing the hourly consumption of local anesthetics during labor (mean ± standard deviation [SD]: control group, 7.5 ± 2.0 ml vs. PIEB group, 6.5 ± 3.4 ml) [8]. We hypothesized that the difference in hourly local anesthetic consumption among the three groups would be clinically significant at a minimum of 1 ml. Thus, we calculated that 28 patients per group would provide a power of 80% at a significance level of 5%, under the assumption that the difference in local anesthetic consumption among the three groups was clinically significant. Considering a dropout rate of 10%, a minimum of 31 patients in each group (n = 93) were required to participate in the study.

Continuous variables are expressed as mean ± SD, median (Q1, Q3), or median (min, max), while normality was assessed using the Shapiro–Wilk test. For motor blockade and NRS score 4 hours after labor analgesia induction, the min and max values were additionally described. Categorical variables are expressed as numbers (percentages). A one-way analysis of variance or Kruskal–Wallis test was used as appropriate to determine the differences in continuous variables among the study groups, including hourly consumption of epidural analgesics, time interval to the first breakthrough pain, NRS score for breakthrough pain after labor analgesia, degree of sensory and motor nerve blockade, NRS score at 4 h after the labor analgesia procedure, and obstetric and neonatal outcomes. In case of statistical differences among the three groups, multiple comparisons were performed using Bonferroni correction. Categorical variables, including the incidence of breakthrough pain and mode of delivery, were analyzed using Pearson’s chi-square test. The partitioned chi-square test was used for multiple pairwise comparisons. Bonferroni correction was used to adjust P values for multiple comparisons. Statistical analyses were performed using SPSS® version 25 (IBM® Inc.), and P < 0.05 was considered significant.
Results

Altogether, 96 parturient women were examined for eligibility, and three were excluded for not meeting the inclusion criteria (n = 1) and declining to participate (n = 2). Additionally, eight women withdrew from the trial because they did not want to continue participating. Finally, 85 participants completed the trial as follows: continuous group (n = 28), PIEB group (n = 29), and manual group (n = 28) (Fig. 1). When labor analgesia was administered, no difference in cervical dilation was observed among the three study groups (continuous: 3 [3, 3] cm, PIEB: 3 [3, 3] cm, manual: 3 [3, 3] cm), respectively; all the participants received oxytocin. The NRS scores before labor analgesia were comparable in all three groups (continuous: 6 [5, 8], PIEB: 6 [5, 7], manual: 5 [5, 6]). The demographic data were similar between the study groups (Table 1).

No differences in the duration of PCEA application were observed among the three groups (P = 0.285) (Table 2). However, the hourly consumption of epidural analgesics was significantly different among the three study groups (continuous: 14.3 [4.7, 12.9] ml, PIEB: 9.4 [6.2, 9.8] ml, manual: 8.6 [7.6, 9.9] ml; P < 0.001). Moreover, significant differences in the hourly consumption of epidural analgesics were observed between the continuous group and the other groups (continuous vs. PIEB, P < 0.001; PIEB vs. manual, P = 0.413; and continuous vs. manual, P < 0.001) (Fig. 2).

Participants requiring PCEA bolus infusion due to breakthrough pain were 22 (78.9%) in the continuous group, 19 (65.5%) in the PIEB group, and 14 (50.0%) in the manual group (P = 0.081). The NRS scores at the time of complaining of breakthrough pain were not significant among the three groups (continuous: 4.0 [0.2], PIEB: 4.0 [1.0], and manual: 3.5 [1.0], P = 0.195). The PIEB group expressed breakthrough pain after a significantly longer time than the manual group (continuous: 78.5 [35.8, 185.0] min, PIEB: 200.0 [88.5, 441.5] min, manual: 60.5 [37.3, 162.0] min; P = 0.027) (Table 2).

No significant differences in the degree of sensory and motor blockade were observed among the study groups 4 h after labor analgesia induction (sensory blockade, P = 0.974; motor blockade, P = 0.224). Two cases of motor nerve blockage were recorded 4 h after infusion: one each in the continuous and manual groups. The NRS scores were not significantly different among the three groups 4 h after labor analgesia induction (P = 0.066).

Obstetric and neonatal outcomes are presented in Table 3. A significant difference in the mode of delivery was observed among the three groups (continuous: 18 [64%], PIEB: 27 [93%], and manual: 18 [64%], P = 0.021). In pairwise comparisons, the mode

---

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram. PIEB: programmed intermittent bolus infusion.
of delivery did not indicate a significant difference according to the epidural injection method (continuous vs. PIEB, P = 0.069; PIEB vs. manual, P = 0.081; manual vs. continuous, P > 0.99).

Although three participants complained of numbness in the lower extremities immediately after labor analgesia induction, they recovered within 4 h. Two participants in the continuous group required 14 mg of 0.2% ropivacaine as an epidural rescue medication. No adverse events occurred during the study period.

### Table 1. Participants’ Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Continuous group (n = 28)</th>
<th>PIEB group (n = 29)</th>
<th>Manual group (n = 28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>34 (32, 36)</td>
<td>33 (30, 35)</td>
<td>32 (28, 36)</td>
<td>0.108</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163 (160, 166)</td>
<td>163 (160, 168)</td>
<td>161 (157, 165)</td>
<td>0.133</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69 (65, 76)</td>
<td>67 (64, 72)</td>
<td>68 (62, 77)</td>
<td>0.444</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.4 (24.9, 28.3)</td>
<td>25.4 (23.7, 27.5)</td>
<td>26.0 (24.4, 29.8)</td>
<td>0.407</td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>39.6 (38.6, 40.2)</td>
<td>39.3 (38.5, 40.3)</td>
<td>39.3 (38.7, 39.6)</td>
<td>0.580</td>
</tr>
<tr>
<td>ASA PS, I</td>
<td>28 (100)</td>
<td>28 (96.6)</td>
<td>28 (100)</td>
<td>0.604</td>
</tr>
<tr>
<td>Pre-labor analgesia data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical dilation (cm)</td>
<td>3 (3, 3)</td>
<td>3 (3, 3)</td>
<td>3 (3, 3)</td>
<td>0.795</td>
</tr>
<tr>
<td>Use of oxytocin</td>
<td>28 (100)</td>
<td>29 (100)</td>
<td>28 (100)</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>120 (110, 128)</td>
<td>114 (104, 129)</td>
<td>117 (108, 130)</td>
<td>0.542</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>68 (62, 78)</td>
<td>70 (64, 78)</td>
<td>67 (64, 70)</td>
<td>0.796</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>87 (78, 95)</td>
<td>85 (79, 96)</td>
<td>86 (80, 87)</td>
<td>0.860</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>65 (61, 75)</td>
<td>64 (60, 72)</td>
<td>71 (63, 80)</td>
<td>0.137</td>
</tr>
<tr>
<td>Pain, NRS score (11-point)</td>
<td>6 (3, 8)</td>
<td>6 (3, 7)</td>
<td>5 (5, 6)</td>
<td>0.030</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3) or number (%). PIEB: programmed intermittent epidural bolus, BMI: body mass index. ASA PS: American Society of Anesthesiologists physical status, NRS: numerical rating scale, 0 = no pain and 10 = the worst pain imaginable.

### Table 2. Labor Analgesia-related Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Continuous group (n = 28)</th>
<th>PIEB group (n = 29)</th>
<th>Manual group (n = 28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCEA usage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total consumption (ml)</td>
<td>109 (77, 136)</td>
<td>75 (50, 95)</td>
<td>73 (55, 100)</td>
<td>0.003*†</td>
</tr>
<tr>
<td>Duration of application (min)</td>
<td>417 (294, 489)</td>
<td>488 (308, 775)</td>
<td>442 (328, 665)</td>
<td>0.285</td>
</tr>
<tr>
<td>Breakthrough pain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>22 (78.9)</td>
<td>19 (65.5)</td>
<td>14 (50.0)</td>
<td>0.081</td>
</tr>
<tr>
<td>Pain, NRS score (11-point)</td>
<td>4.0 (3.8, 4.0)</td>
<td>4.0 (3.0, 4.0)</td>
<td>3.5 (3.0, 4.0)</td>
<td>0.195</td>
</tr>
<tr>
<td>Time to express the breakthrough pain (min)</td>
<td>78.5 (35.8, 185.0)</td>
<td>200.0 (88.5, 441.5)</td>
<td>60.5 (37.3, 162.0)</td>
<td>0.027*†</td>
</tr>
<tr>
<td>Four hours after labor analgesia induction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory blockade</td>
<td>T7 (5, 8)</td>
<td>T7 (5, 9)</td>
<td>T7 (6, 8)</td>
<td>0.974</td>
</tr>
<tr>
<td>Motor blockade</td>
<td>6 (4, 6)</td>
<td>6 (6, 6)</td>
<td>6 (5, 6)</td>
<td>0.224</td>
</tr>
<tr>
<td>Pain, NRS score (11-point)</td>
<td>0 (0, 3)</td>
<td>0 (0, 3)</td>
<td>0 (0, 2)</td>
<td>0.066</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3), medians (min, max) or number (%). PIEB: programmed intermittent epidural bolus, PCEA: patient-controlled epidural analgesia, NRS: numerical rating scale, 0 = no pain and 10 = the worst pain imaginable. *P < 0.05, continuous vs. PIEB. †P < 0.05, continuous vs. manual. Bonferroni correction is used for multiple comparison. ‡The degree of motor blockade is graded using the Breen-modified Bromage score (1 = complete block, unable to move feet or knees; 2 = almost complete block, only able to move feet; 3 = partial block, simply able to move knees; 4 = detectable weakness of hip flexion while in supine; 5 = no detectable weakness of hip flexion while in supine, full flexion of knees; and 6 = can stand and perform a partial knee bend) [7]. §Values are presented as medians (min, max).

### Discussion

This randomized clinical trial demonstrated that PIEB or manual infusion of epidural analgesics effectively reduced the hourly consumption of epidural analgesics rather than continuous epidural infusion in labor analgesia. Moreover, the time taken to express the first breakthrough pain after labor analgesia induction was significantly longer in the PIEB group than in the other groups.
Numerous studies have demonstrated that intermittent epidural bolus injection provides superior labor analgesic effects compared with continuous infusion, reducing local anesthetic consumption and increasing maternal satisfaction [8–13]. A systematic review has indicated that larger bolus doses of diluted epidural anesthetics are required for superior analgesia [14]. In this context, Wong et al. [15] demonstrated that administration of larger doses of epidural anesthetics at long time intervals reduces the consumption of bupivacaine and increases maternal satisfaction (2.5 ml/15 min vs. 5 ml/30 min vs. 10 ml/60 min). Most previous studies on PIEB compared bolus volumes and time intervals. However, studies comparing differences in the flow rate of administered drugs are lacking.

Lange et al. [6], who investigated the difference in the effect of the PIEB according to the flow rate (100 ml/h vs. 300 ml/h), have reported that the hourly consumption of epidural analgesics was not improved by high-flow epidural administration. In line with this, our results revealed no significant difference in epidural analgesic consumption between the PIEB and manual injections. As our study and that of Lange et al. [6] differed slightly because Lange et al. conducted a study using only the PIEB machine, the difference in infusion pressure between the groups might not be significant. Considering that analgesic consumption may be related to the flow rate of epidural analgesics, we provided a higher infusion flow rate (1,200 ml/h) via manual injection. Additionally, the flow rate of the PIEB group was selected as the maximum value that could be set in the machine (240 ml/h). Hence, the flow rate in the PIEB group was sufficient to provide effective labor analgesia compared with the high flow rate in the manual group. In Lange et al.’s study, the authors suggested that several factors may affect these results, including the size of the epidural catheter, number of orifices, dose and concentration of the local anesthetic, and infusion rate of the bolus drug. To exclude the influence of

![Fig. 2. Hourly consumption of epidural analgesics. Box-and-whisker plots (Tukey) indicate the median (Q1, Q3) with maximum and minimum values. The dots indicate outliers. PIEB: programmed intermittent epidural bolus.](https://doi.org/10.4097/kja.23173)

<table>
<thead>
<tr>
<th>Table 3. Obstetric and Neonatal Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Obstetric outcome</td>
</tr>
<tr>
<td>Duration of labor (min)</td>
</tr>
<tr>
<td>Duration of second stage (min)</td>
</tr>
<tr>
<td>Mode of delivery</td>
</tr>
<tr>
<td>Normal delivery</td>
</tr>
<tr>
<td>Instrumental</td>
</tr>
<tr>
<td>Cesarean section</td>
</tr>
<tr>
<td>Satisfaction score, Likert scale*</td>
</tr>
<tr>
<td>Neonatal outcome</td>
</tr>
<tr>
<td>Birth weight (g)</td>
</tr>
<tr>
<td>Apgar score</td>
</tr>
<tr>
<td>1 min</td>
</tr>
<tr>
<td>5 min</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3) or frequencies (%). In the case of Cesarean section, the duration of labor is calculated as the time from the starting of labor to the time of entering the operating room. Participants who delivered by Cesarean section are excluded from the calculation of the duration of secondary stage of labor. PIEB: programmed intermittent epidural bolus. *Likert scale score: 1 = strongly dissatisfied, 2 = dissatisfied, 3 = neutral, 4 = satisfied, and 5 = strongly satisfied.
external circumstances, we equally administered epidural analgesics, epidural catheters, and PCEA machines to each group in this study. Consequently, the flow rate of the epidural bolus injection for adequate labor analgesia may not need to be excessively high. Effective labor analgesia can be provided within the range of the flow rate provided by the machine.

PIEB has a superior analgesic effect compared to continuous infusion because the drugs are distributed at high pressures in the epidural space and effectively block sensory nerves. Because most PCEA machines allow the limit of high rates as 200–300 ml/h, this is insufficient to assess the effectiveness of high-flow vs. low-flow epidural infusion. We expected that manual infusion would increase the diffusion range by promoting better drug flow within the epidural space. However, our findings demonstrated that the labor analgesic effect of manual injection was not different from that of PIEB. Although this study did not establish the flow rate range that can provide optimal labor analgesic effects, the infusion flow rate into the epidural space did not need to be as high as that of manual infusion. Therefore, parous women may likely achieve sufficient analgesic effects with the PIEB machine.

Interruption of labor analgesia is associated with a greater diffusion surface area than continuous infusions [16]. Thus, local anesthetics do not remain in a specific epidural space for a long time and are distributed in a large area at a fast rate during PIEB. By contrast, because the concentration of local anesthetics is more easily elevated in the extraneural space than in the intraneural space during continuous infusion, motor blockade frequently occurs [3,17]. Preserving the motor function during labor analgesia maintains the pelvic muscle tone. This enables smooth pushing during the delivery process and reduces the transition to instrumental delivery. Although numerous studies have compared motor blockade according to the epidural injection method, the results have been inconsistent. Capogna et al. [3] have demonstrated that the incidence of motor blockade was lower with PIEB than with continuous infusion. Meanwhile, no significant difference in the degree of motor blockade was observed between the PIEB and continuous infusion in this study. This discrepancy may be related to the type of local anesthetic used. Previous studies using similar concentrations of ropivacaine as ours did not demonstrate a difference in the incidence of motor blockade between continuous epidural analgesia and PIEB [8,11,18]. These evidences support the involvement of the type and concentration of local anesthetic in the incidence of motor blockade. When selecting a labor analgesic regimen using epidural analgesia, applying it in clinical practice would be desirable, considering that the use of a low concentration and large volume of local anesthetic promotes effective labor analgesia without motor blockade [19].

As mentioned above, no significant difference in the incidence of motor blockade was observed regardless of the method of epidural infusion of the local anesthetic used in this study. However, the rate of conversion to Cesarean section was significantly lower in the PIEB group. Our results contradict those of Huang et al. [20], who have reported no difference in the conversion rate of the mode of delivery between PIEB and continuous infusion. In particular, no significant difference in the mode of delivery conversion rate according to the epidural infusion method was indicated in studies using the same local anesthetic at a concentration similar to this study [8,11,21]. Since we used low and high doses of the local anesthetic in this study, the local anesthetic could have been more effectively distributed in the epidural space in the PIEB group than in the other groups. By contrast, a higher dose of local anesthetic could have been distributed in the extraneural space in the continuous-infusion group. A previous meta-analysis investigating the rate of assisted vaginal delivery according to the concentration of local anesthetics (high vs. low) supports our suggestion [22].

This study has several limitations. First, we used the CSE method rather than the simple epidural analgesia as the labor analgesia method, and the same intrathecal agent was administered to all the participants. Thus, the outcomes of our study may have been affected by the extended duration and range of the intrathecal drugs. However, the duration of intrathecal ropivacaine administration was less than 100 min [23]. Considering that all groups in our study applied PCEA for more than 390 min, the effects of intrathecal agents would disappear when our secondary outcome was measured. Second, different results may have been obtained depending on the specifications of the PCEA machine used at each institute. Third, each local anesthetic used for labor analgesia has a different viscosity [24]. Future studies are required to investigate the effects of different PCEA machines and local anesthetics on the flow rate and infusion pressure generated when the local anesthetic is distributed into the epidural space. Finally, the infusion flow rate might not have been constant in the manual group. The epidural space is a potential space where the pressure and volume of the injected medication can affect the distribution of agents. Therefore, the pressure generated by the infusion of epidural agents may have individual differences that may have influenced the study outcomes. However, these effects occurred not only in the manual group, but also in the other two groups. Considering that the study design was a randomized trial, the influence of the epidural space may be evenly distributed among all the participants.

In conclusion, PIEB with ropivacaine provided adequate analgesia and did not require the high flow provided by manual injec-
tion for labor analgesia. Future research is warranted to determine the ideal flow rate of PIEB.

Acknowledgements

The authors would like to thank Dr. Seonwoo Kim for providing statistical advice.

Funding

None.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Doyeon Kim (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing)
Jeayoun Kim (Data curation; Formal analysis)
Hyeonju Choo (Data curation; Formal analysis)
Duck Hwan Choi (Conceptualization; Methodology; Project administration; Supervision; Validation; Writing – review & editing)

ORCID

Doyeon Kim, https://orcid.org/0000-0003-3823-7321
Jeayoun Kim, https://orcid.org/0000-0002-7263-0867
Hyeonju Choo, https://orcid.org/0000-0002-9280-3788
Duck Hwan Choi, https://orcid.org/0009-0002-5194-7037

References

16. Kaynar AM, Shankar KB. Epidural infusion: continuous or bo-


Background: Alveoli tend to collapse in patients with acute respiratory distress syndrome (ARDS). Endotracheal aspiration may increase alveolar collapse due to the loss of end-expiratory lung volume (EELV). We aimed to compare the loss of EELV after open and closed suction in patients with ARDS.

Methods: This randomized crossover study included 20 patients receiving invasive mechanical ventilation for ARDS. Open and closed suction were applied in a random order. Lung impedance was measured using electric impedance tomography. The change in end-expiratory lung impedance (EELI) end of suction and at 1, 10, 20, and 30 min after suction, was used to represent the change in EELV. Arterial blood gas analyses and ventilatory parameters such as the plateau pressure (P_{plat}), driving pressure (P_{drive}), and compliance of the respiratory system (C_{RS}) were also recorded.

Results: Less volume loss was noted after closed suction than after open suction (mean ΔEELI: −2661 ± 1937 vs. −4415 ± 2363; mean difference: −1753, 95% CI [−2662, −844], P = 0.001). EELI returned to baseline 10 min after closed suction but did not return to baseline even 30 min after open suction. After closed suction, the P_{plat} and P_{drive} decreased while the C_{RS} increased. Conversely, the P_{plat} and P_{drive} increased while the C_{RS} decreased after open suction.

Conclusions: Endotracheal aspiration may result in alveolar collapse due to loss of EELV. Given that closed suction is associated with less volume loss at end-expiration without worsening ventilatory parameters, it should be chosen over open suction in patients with ARDS.

Keywords: Critical care; Electric impedance; Lung volume measurements; Positive-pressure respiration; Respiratory distress syndrome; Suction.

Introduction

The purpose of mechanical ventilation is to provide adequate gas exchange while preventing lung injury. Alveolar collapse at end-expiration is a common phenomenon in various respiratory conditions, including acute respiratory stress syndrome (ARDS) [1]. Adequate positive end-expiratory pressure (PEEP) is crucial for preventing alveolar collapse and atelectotrauma.

As intubated patients are unable to clear secretions from the airways spontaneously, the airways must be cleaned periodically. Endotracheal aspiration, which is one of the most
common procedures performed in the intensive care unit (ICU), clears the respiratory tract, prevents atelectasis, and improves oxygenation [2]. Although endotracheal aspiration is essential for intubated patients, it can have harmful effects such as oxygen desaturation and alveolar derecruitment [3,4].

Endotracheal aspiration can be performed either using open suction, in which the patient is disconnected from the ventilator, or closed suction, in which a sterile catheter is inserted into the ventilator circuit without disconnection. Under open suction, an abrupt drop in airway pressure due to disconnection from the ventilator and negative pressure aspiration may cause alveolar derecruitment and collapse. Because the patient remains connected to the ventilator in closed aspiration, this technique protects against alveolar derecruitment and results in less volume loss [5]. Heinze et al. [6] showed that the functional residual capacity (FRC) is reduced after endotracheal suctioning, regardless of whether closed or open suction is used, and remains low 20 min after aspiration. Although end-expiratory lung volume (EELV) loss is lower in closed suction than in open suction, slower recovery has been observed when closed suction is used in post-cardiac surgery patients [7].

EELV can be easily and accurately measured at the bedside using electric impedance tomography (EIT). The basic principle of electric impedance is based on alternating current injection and voltage measurements using surface electrodes placed around the chest wall. The electrical properties of the chest change with inspiration and expiration owing to variations in air content, and changes in impedance resulting from ventilation can be measured using an electric impedance device [8]. These changes in impedance represent changes in EELV because of the strong linear relationship between impedance and EELV [9].

Studies examining the effect of the endotracheal aspiration method on EELV have been conducted in surgical patients [6,7]; however, the effect is unclear in cases such as ARDS where the alveoli are more prone to collapse. This study compared the effects of the endotracheal aspiration method on EELV in patients with ARDS.

### Materials and Methods

This randomized crossover study was conducted between September 15 and October 30, 2022, at the ICU of the University of Health Sciences Turkey, Dr. Suat Seren Chest Disease and Surgery Training and Research Hospital, which is a tertiary hospital specializing in pulmonary diseases. Our study was approved by the Ethics Committee of the University of Health Sciences, Dr. Suat Seren Chest Disease and Thoracic Surgery Teaching and Research Hospital (IRB number: 2022/2-7). Written informed consent was obtained from all participants or their next of kin. The study was registered at ClinicalTrials.gov under the number NCT05537974 and was conducted in accordance with the Declaration of Helsinki, 2013.

### Participants

Patients aged ≥ 18 years who underwent invasive mechanical ventilation due to ARDS were included in the study. ARDS was diagnosed according to the Berlin criteria [10]. Patients were excluded from the study if they were hemodynamically unstable (systolic blood pressure < 90 mmHg or mean arterial pressure < 60 mmHg), had an air-leak condition such as pneumothorax, had high FiO₂ levels (> 60%), or had a cardiac pacemaker.

### Study protocol

The suction procedures were performed in a random order with a 60-min washout period between. Patients were randomized after intubation using sealed envelopes. A flowchart of the study is shown in Fig. 1.

An electrical impedance tomography belt (PulmoVista® 500, Dräger Medical GmbH) with 16 electrodes was placed around each patient's chest between the fifth or sixth intercostal space. All patients were intubated with an 8.0-mm or 8.5-mm diameter endotracheal tube and mechanically ventilated (Galileo GOLD; Hamilton Medical AG) using a lung-protective ventilation strategy in continuous volume mandatory ventilation mode. The tidal volume (Vₜ) was set at 4–8 ml/kg, plateau pressure (Pₚₚₚ) at < 30 cmH₂O, and FiO₂ was titrated to maintain a SaO₂ of 88%–92%. The PEEP level was set by an intensivist who was blinded to the study.

All suctioning was performed within the first 24 h after intubation. Before suctioning, patients were ventilated with 100% oxygen for 60 s. The negative aspiration pressure was set at 150 mmHg [4]. A 14 F suction catheter was used for both open (Bıçakcılar Medical Equipment) and closed (Shaoxing Reborn Medical Device) suctioning. The patient was disconnected from the ventilator for open suction but not for closed suction. For both open and closed suction, the aspiration catheter was advanced until resistance was met and was then withdrawn 1 cm before aspiration. During endotracheal suctioning, negative pressure was applied twice for 5 s. All suction maneuvers were performed by the intensivists.
Measurements

End expiratory lung impedance (EELI) was measured using EIT at baseline (1 min before suctioning) and at 1, 10, 20, and 30 min after suctioning. Changes in EELI were used to represent changes in EELV, as a strong linear relationship between lung impedance and volume was established by Hinz et al. [9]. In that study, the EELV was measured using the open-circuit nitrogen washout maneuver, and an increase in the EELV was induced by a stepwise increase in the PEEP. A linear relationship between the increase in EELV and changes in EELI were seen (\( R^2 = 0.95 \)) [9].

Oxygen saturation was measured via pulse oximetry, and pulse and arterial blood pressures were recorded. Arterial blood gas levels were measured before and 30 min after suctioning. Mechanical ventilatory parameters, such as the \( V_t \), \( P_{plat} \), PEEP, FiO\(_2\), driving pressure (\( P_{drive} \)), and static compliance of the respiratory system (\( C_{RS} \)), were also recorded. All measurements were performed under passive conditions (patients were sedated and ventilation was thus not triggered). The ventilatory settings were maintained constant before, during, and after the suction maneuvers were performed.

Statistical analysis

Continuous variables are represented as the mean ± SD if they are normally disturbed and as the median (Q1, Q3) if they are not normally disturbed. The change in EELI compared to baseline was used to represent the change in EELV. The differences between the baseline and post-suction values (\( \Delta \text{EELI} \) values) in open and closed suction were compared using paired t-tests because of the normal distribution of the data. Differences in the respiratory variables (\( P_{plat} \), \( P_{drive} \), etc.) were compared using the Wilcoxon signed-rank test because the data were not normally distributed. Statistical significance was set at \( P < 0.05 \). The sample size was based on a 20% difference in the reduction in EELI between the groups. Twenty patients were thus required to determine this difference with 80% power at a 5% significance level. It was assumed that the paired difference in the EELI (open minus closed) had a normal distribution, with an SD of 30%.

Results

Twenty patients with ARDS were included in the study. Thirteen (65%) of the participants were male, and the mean age was 64.2 ± 14.1 years. All patients had ARDS due to pneumonia (60% bacterial and 40% viral). The clinical features and baseline charac-
teristics of the participants are summarized in Table 1. All measurements were successfully recorded for all patients, and there were no missing data.

The baseline electrical impedance values were comparable between open and closed suction. More volume loss after suctioning was found with open suction than with closed suction. The mean $\Delta$EELI was $-4415 \pm 2363$ impedance units in open suction and $-2661 \pm 1937$ impedance units in closed suction (mean difference: $-1753, 95\% \text{ CI } [-2662, -844], P = 0.001$). EELI values returned to baseline 10 min after closed suction and remained above baseline (mean EELI at 10, 20, and 30 min: 110, 158, and 247 impedance units above baseline, respectively). However, EELI values did not reach baseline even 30 min after open suction (mean $\Delta$EELI at 10, 20, and 30 min: $-548, -300$, and $-182$ impedance units) (Table 2). The mean changes in lung impedance ($\Delta$EELI) at each time point after open and closed suction are shown in Fig. 2.

The baseline mechanical ventilatory parameters were similar between open and closed suction. However, 30 min after aspiration, the $P_{\text{plat}}$ and $P_{\text{drive}}$ decreased and $C_{RS}$ increased under closed suction, whereas after open suction, the $P_{\text{plat}}$ and $P_{\text{drive}}$ increased and $C_{RS}$ decreased (Table 3). Arterial blood gas parameters were not significantly different 30 min after aspiration in either group, except for the $\text{PaO}_2/\text{FiO}_2$ ratio, which increased slightly after closed suction (median $\Delta\text{PaO}_2/\text{FiO}_2$: 15 vs. 2; $P = 0.016$).

Discussion

Our study showed that open suction resulted in greater volume loss than closed suction in patients with ARDS. The EELI returned to baseline values 10 min after closed suction and remained above the baseline; however, even 30 min after open suction, baseline values were not achieved. These results indicate that closed suction is more protective against EELV than open suction in patients with ARDS.

Table 1. Demographic Features and Baseline Characteristics of Participants

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All participants ($n = 20$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>$64.2 \pm 14.1$</td>
</tr>
<tr>
<td>Male</td>
<td>13 (65)</td>
</tr>
<tr>
<td>Ideal body weight (kg)</td>
<td>70 (60, 71)</td>
</tr>
<tr>
<td>Body mass index (kg/$m^2$)</td>
<td>26.9 (24.5, 30.1)</td>
</tr>
<tr>
<td>APACHE-2 score</td>
<td>22 (17, 25)</td>
</tr>
<tr>
<td>Cause of ARDS</td>
<td></td>
</tr>
<tr>
<td>Bacterial pneumonia</td>
<td>12 (60)</td>
</tr>
<tr>
<td>Viral pneumonia</td>
<td>8 (40)</td>
</tr>
<tr>
<td>Comorbid disease</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (30)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (20)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Solid organ malignancy</td>
<td>4 (20)</td>
</tr>
</tbody>
</table>

Baseline characteristics

- $P_{\text{plat}}$ (cmH$_2$O): 27.5 (21.5, 28.4)
- $P_{\text{mean}}$ (cmH$_2$O): 16.8 (14, 18)
- PEEP (cmH$_2$O): 12 (10.5, 14)
- $P_{\text{drive}}$ (cmH$_2$O): 13.9 (9, 16)
- $V_t$ (ml): 445 (405, 480)
- $C_{RS}$ (ml/cmH$_2$O): 27.9 (22.1, 29.8)
- pH: 7.38 (7.35, 7.43)
- $\text{PaO}_2$ (mmHg): 75 (69, 88)
- $\text{PaCO}_2$ (mmHg): 49 (41, 56)
- $\text{SaO}_2$ (%): 92 (91, 95)
- Lactate (mmol/L): 1.4 (1.0, 1.9)
- $\text{PaO}_2/\text{FiO}_2$: 172 (132, 198)

Values are presented as mean ± SD, number (%), or median (Q1, Q3). APACHE: Acute Physiology and Chronic Health Evaluation, ARDS: acute respiratory distress syndrome, $P_{\text{plat}}$: plateau pressure, $P_{\text{mean}}$: mean airway pressure, PEEP: positive end-expiratory pressure, $P_{\text{drive}}$: driving pressure, $V_t$: tidal volume, $C_{RS}$: compliance of respiratory system.

Table 2. Comparison of Changes in EELI* after Open and Closed Suction

<table>
<thead>
<tr>
<th>Variable</th>
<th>Open suction</th>
<th>Closed suction</th>
<th>Mean difference in EELI†</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean $\Delta$EELI</td>
<td>$\Delta$EELI, %</td>
<td>Mean $\Delta$EELI</td>
<td>$\Delta$EELI, %</td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4800</td>
<td>NA</td>
<td>4834</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>End of suction</td>
<td>$-4415$</td>
<td>$-96.0$</td>
<td>$-2661$</td>
<td>$-52.1$</td>
<td>$-1753 \pm 1942$</td>
</tr>
<tr>
<td>1st min</td>
<td>$-865$</td>
<td>$-17.1$</td>
<td>$-831$</td>
<td>$-19.9$</td>
<td>$-33 \pm 785$</td>
</tr>
<tr>
<td>10th min</td>
<td>$-548$</td>
<td>$-8.8$</td>
<td>110</td>
<td>$-4.1$</td>
<td>$-658 \pm 1402$</td>
</tr>
<tr>
<td>20th min</td>
<td>$-300$</td>
<td>$-4.7$</td>
<td>158</td>
<td>$-0.25$</td>
<td>$-458 \pm 878$</td>
</tr>
<tr>
<td>30th min</td>
<td>$-182$</td>
<td>$-1.0$</td>
<td>247</td>
<td>3.0</td>
<td>$-429 \pm 768$</td>
</tr>
</tbody>
</table>

EELI: end-expiratory lung impedance. *Changes in end-expiratory lung impedance represent change in end-expiratory lung volume. †EELI value in open suction minus EELI value in closed suction.

We found that closed suction led to less volume loss at the end of expiration than open suction. In previous studies, open suction was associated with greater volume loss in postoperative patients.
and those with lung injury [5, 7, 11]. Our findings are thus consistent with those of previous studies. However, our findings also showed slower recovery of the EELV after closed aspiration. Corley et al. [7] reported that although less volume loss was found with closed suction, the EELV recovered more slowly with closed suction than with open suction. By contrast, we found that EELV recovery was faster with closed suction than with open suction. This may be explained by a couple of factors. First, the participants in our study were ARDS patients whose alveoli tended to collapse, while the participants in Corley et al. [7]’s study were post-cardiac surgery patients who may have had relatively better lung conditions at baseline. Second, the participants in our study were ventilated with higher PEEP levels than those in the study conducted by Corley et al. Opening the lungs to atmospheric pressure during open suction may have caused more volume loss owing to the release effect in ventilated patients with a higher PEEP level than those with a lower PEEP level. Third, recruitment of collapsed alveoli due to the loss of EELV may be more difficult in patients with ARDS than in postoperative patients.

We found that respiratory parameters, such as the $P_{\text{plat}}$, $P_{\text{mean}}$, and $C_{\text{RS}}$, improved 30 min after closed aspiration. We also found that open suction negatively affected these ventilatory parameters. Although closed aspiration has been associated with less EELV loss, the effect of closed aspiration on ventilator parameters could not be observed in previous studies. Cereda et al. [5] found similar ventilatory parameters before and after closed and open suction. A greater loss of EELV after open suction may lead to greater alveolar derecruitment. More alveoli collapsed owing to higher volume loss during open suction, and some may have remained collapsed after open suction. Therefore, the tidal volume may have been distributed to fewer alveoli compared to baseline, which may have resulted in the worsening of ventilator parameters with open suction.

Oxygenation did not change after open suction. The oxygen saturation and $\text{PaO}_2$ at baseline and 30 min after open suction were similar. We observed that oxygenation improved after closed suction. The change in the $\text{PaO}_2$/FiO$_2$ ratio was higher with closed compared to open suction at 30 min post-aspiration. Cereda et al. [5] reported that oxygen saturation decreases rapidly after open aspiration in patients with acute lung injury but does not change during closed aspiration. However, Cereda et al. did not apply any hyperoxygenation or hyperinflation maneuvers prior to suction. A prospective crossover study conducted by Demir et al. [12] found a significant decrease in $\text{SaO}_2$ and $\text{PaO}_2$ after endotracheal aspiration without preoxygenation compared with endotracheal aspiration with preoxygenation. In our study, we applied hyperoxygenation before both open and closed suction; therefore, the better $\text{PaO}_2$/FiO$_2$ ratio observed after closed suction may have been due to the prevention of alveolar collapse and alveolar recruitment due to secretion clearance.

Our results support the use of closed aspiration in patients with ARDS, especially at higher PEEP levels. The results of previous studies on the effect of closed suction on EELV have been inconsistent. Fernandez et al. [11] showed that closed suction causes

![Fig. 2. Mean changes in end-expiratory lung impedance (EELI) after open and closed suction. Open suction caused greater end-expiratory volume loss than closed suction. EELI reached baseline after 10 min of closed suction but did not reach baseline after 30 min of open suction.](image)

Table 3. Changes in Respiratory Parameters Compared to Baseline

<table>
<thead>
<tr>
<th>Respiratory variable</th>
<th>Open suction</th>
<th>Closed suction</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta P_{\text{plat}}$ (cmH$_2$O)</td>
<td>$1.0 (0.25, 1.75)$</td>
<td>$-1.0 (-2.0, 0.30)$</td>
<td>$0.001$</td>
</tr>
<tr>
<td>$\Delta P_{\text{mean}}$ (cmH$_2$O)</td>
<td>$1.0 (0.0, 1.75)$</td>
<td>$-1.0 (-2.0, 0.30)$</td>
<td>$0.002$</td>
</tr>
<tr>
<td>$\Delta C_{\text{RS}}$ (cmH$_2$O)</td>
<td>$0.0 (0.0, 0.0)$</td>
<td>$0.0 (-0.75, 0.0)$</td>
<td>$0.200$</td>
</tr>
<tr>
<td>$\Delta C_{\text{plat}}$ (ml/cmH$_2$O)</td>
<td>$-1.10 (-2.0, -0.5)$</td>
<td>$1.25 (0.1, 1.97)$</td>
<td>$0.002$</td>
</tr>
<tr>
<td>$\Delta \text{PaO}_2$/FiO$_2$</td>
<td>$2 (-14.0, 23)$</td>
<td>$15 (6, 33)$</td>
<td>$0.016$</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3). $P_{\text{plat}}$: plateau pressure, $P_{\text{mean}}$: driving pressure, $P_{\text{mean}}$: mean airway pressure, $C_{\text{RS}}$: compliance of respiratory system.
less volume loss than open suction, and that volume loss caused by closed suction recovered after 10 min. Heinze et al. [6] found that the FRC remained low 20 min after aspiration. Differences in patient populations, aspiration times, and lung volume measurement methods complicates accurate comparisons of these results. Although the differences between closed and open aspiration were relatively small, the cumulative effect may be greater because endotracheal aspiration is more frequently performed. Because the application of a closed suction system is not a costly maneuver, it is worth considering the potential benefits.

Our study had some limitations. First, this was a crossover study with a small number of participants. Because we did not use the open-circuit nitrogen washout maneuver or spirometry to measure EELV, we could not report the absolute change in EELV. Rather, we used the ΔEELI as a surrogate for the ΔEELV because a strong and linear association between the ΔEELI and ΔEELV has been shown [9]. The EELV can be computed using the EELI; however, the EELV calculated from EIT may result in an over- or underestimation of the EELV compared to that with the nitrogen washout technique [13]. The cause of ARDS in all patients was pneumonia; therefore, the effect of the aspiration method on EELV may differ in patients with ARDS due to extrapulmonary pathologies. Additionally, we focused on the effect that the suctioning method had on EELV and ventilatory parameters in the short term; however, long-term outcomes remain unclear.

This study has several implications for clinical practice. Patients with ARDS who are ventilated with higher levels of PEEP and closed suction may be less susceptible to EELV loss and worsening of other ventilatory parameters.

In conclusion, endotracheal aspiration may lead to alveolar collapse due to the loss of EELV. Instead of open suction, closed suction may be a better alternative for patients with ARDS because it results in less volume loss at end-expiration without worsening of the ventilatory parameters.

Funding

None.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Süleyman Yildirim (Conceptualization; Methodology; Project administration; Writing – original draft; Writing – review & editing)
Saba Mukaddes Saygili (Conceptualization; Data curation; Formal analysis)
Onur Süneçli (Conceptualization; Data curation; Formal analysis; Visualization)
Cenk Kirakli (Conceptualization; Methodology; Supervision; Writing – original draft; Writing – review & editing)

ORCID

Suleyman Yildirim, https://orcid.org/0000-0001-9856-3431
Saba Mukaddes Saygili, https://orcid.org/0000-0002-4460-5453
Onur Süneçli, https://orcid.org/0000-0002-1195-7292
Cenk Kirakli, https://orcid.org/0000-0001-6013-7330

References

7. Corley A, Spooner AJ, Barnett AG, Caruana LR, Hammond NE, Fraser JE. End-expiratory lung volume recovers more slowly after closed endotracheal suctioning than after open suctioning: a

https://doi.org/10.4097/kja.23194


Electroencephalographic spectrogram–guided total intravenous anesthesia using dexmedetomidine and propofol prevents unnecessary anesthetic dosing during craniotomy: a propensity score–matched analysis

Feng-Sheng Lin¹, Po-Yuan Shih¹, Chao-Hsien Sung², Wei-Han Chou¹, Chun-Yu Wu³

¹Department of Anesthesiology, National Taiwan University Hospital, Taipei, ²Department of Anesthesiology, Fu Jen Catholic University Hospital, New Taipei City, ³Department of Anesthesiology, National Taiwan University Hospital Hsinchu Branch, Hsinchu, Taiwan

Background: The bispectral index (BIS) may be unreliable to gauge anesthetic depth when dexmedetomidine is administered. By comparison, the electroencephalogram (EEG) spectrogram enables the visualization of the brain response during anesthesia and may prevent unnecessary anesthetic consumption.

Methods: This retrospective study included 140 adult patients undergoing elective craniotomy who received total intravenous anesthesia using a combination of propofol and dexmedetomidine infusions. Patients were equally matched to the spectrogram group (maintaining the robust EEG alpha power during surgery) or the index group (maintaining the BIS score between 40 and 60 during surgery) based on the propensity score of age and surgical type. The primary outcome was the propofol dose. Secondary outcome was the postoperative neurological profile.

Results: Patients in the spectrogram group received significantly less propofol (1585 ± 581 vs. 2314 ± 810 mg, P < 0.001). Fewer patients in the spectrogram group exhibited delayed emergence (1.4% vs. 11.4%, P = 0.033). The postoperative delirium profile was similar between the groups (profile P = 0.227). Patients in the spectrogram group exhibited better in-hospital Barthel’s index scores changes (admission state: 83.6 ± 27.6 vs. 91.6 ± 17.1; discharge state: 86.4 ± 24.3 vs. 85.1 ± 21.5; group–time interaction P = 0.008). However, the incidence of postoperative neurological complications was similar between the groups.

Conclusions: EEG spectrogram–guided anesthesia prevents unnecessary anesthetic consumption during elective craniotomy. This may also prevent delayed emergence and improve postoperative Barthel index scores.

Keywords: Anesthesia adjuvants; Bispectral index monitor; Consciousness monitors; Craniotomy; Dexmedetomidine; Electroencephalography; Intravenous anesthesia.

Introduction

Dexmedetomidine has unique pharmacological effects, including anesthetic-sparing [1,2], postanesthetic recovery–facilitating [3], postoperative delirium–preventing [4], and potent anti-inflammatory effects [1,5]. Dexmedetomidine is often used in combination with other anesthetics, such as propofol, to provide multimodal general anesthesia.
[6] and improve postoperative recovery [7]. Processed electroencephalogram (EEG) indices such as the bispectral index (BIS), which uses an algorithm to analyze and interpret raw EEG data, are widely used tools for monitoring anesthetic depth [8]; however, processed EEG indices may be unreliable when dexmedetomidine is administered because patients who received dexmedetomidine can present profound slow EEG oscillations (a low BIS score) but remains arousable [8–10].

Recently, we reported that the intraoperative co-administration of dexmedetomidine and propofol combined with goal-directed hemodynamic therapy may have neuroprotective effects, including reducing postoperative neurological complications and preventing postoperative delirium in patients undergoing craniotomy [1]. As a result, we have adopted this regimen as our institutional standard practice for such patients. Furthermore, we observed substantial propofol-sparing effects when dexmedetomidine and propofol were co-administered under the guidance of BIS value [1]. Because each anesthetic produces distinct brain states that are readily visible in an EEG spectrogram and can be easily interpreted by anesthesiologists [8], anesthetic titration based on an EEG spectrogram may provide additional information for anesthetic depth monitoring and may avoid the conventional ‘one-index—fits-all’ approach, which often ignores the influence of anesthetic drug combination [8,11]. Theoretically, the anesthetic exposure in cases that involve the coadministration of dexmedetomidine can be more precise through the use of an EEG spectrogram than the use of BIS value. Therefore, we have changed our institutional anesthetic propofol from BIS guidance to the EEG spectrogram guidance and we hypothesize that propofol consumption during craniotomy with total intravenous anesthesia using dexmedetomidine and propofol would be lower when general anesthesia is guided by EEG spectrogram than when it is guided by BIS values. Based on these context, this retrospective analysis was conducted to test our hypothesis and investigate the potential benefits of EEG spectrogram use on postoperative outcomes.

**Materials and Methods**

This retrospective observational cohort study was approved by the Research Ethics Committee of National Taiwan University Hospital (approval number: 202211078RINC; approval date: December 8, 2022) and was registered at clinicaltrials.gov (NCT05656547). The requirement for written informed consent was waived by the research ethic committee. Adult patients undergoing elective craniotomy for brain tumor resection, aneurysm clipping, intracranial bypass, or microvascular decompression who received intraoperative EEG spectrogram–guided total intravenous anesthesia with propofol and dexmedetomidine between January 1, 2021, and October 31, 2022, were identified from the institutional database. Identifying information was omitted from the study, thus ensuring patient anonymity. Eighty patients undergoing craniotomy from our previous trial conducted between April 2017 and April 2020 who received intraoperative BIS score guided anesthesia using the same regimens [1], namely propofol and dexmedetomidine were identified as the control cohort for the present study. This study adhered to applicable STROBE guidelines [12].

**Anesthesia**

The standardized institutional anesthetic protocol for craniotomy involves the administration of total intravenous anesthesia, utilizing a combination of propofol and dexmedetomidine. Prior to 2021, the anesthetic protocol relied on the intraoperative BIS value for management. In contrast, after 2021, the protocol shifted to being guided by the EEG spectrogram. The specific details of these anesthetic protocols are outlined below: A BIS monitor was situated contralateral to the surgical side in an aseptic manner. General anesthesia was performed and maintained by total intravenous anesthesia using a target-controlled infusion of propofol (Schnider model) with an initial dose of effect site concentration with 4.0–5.0 μg/ml during induction. Remifentanil infusion or fentanyl boluses were administered during surgery at the attending anesthesiologist’s discretion. The muscle relaxant was not added after anesthesia induction to facilitate the neurophysiological monitoring [13]. The attending anesthesiologist titrated the propofol concentration to maintain the targeted anesthetic depth. Patients receiving BIS-guided anesthesia were placed into the index group titrating anesthetics to maintain a BIS value between 40–60 [1]. Patients receiving EEG spectrogram–guided anesthesia were placed into the spectrogram group. In the EEG spectrogram–guided protocol, the anesthetic depth was managed based on the following principles proposed by our neuroanesthesia team:

(1) Following anesthesia induction and prior to surgical stimulation, the patient’s maximal frontal alpha power occurring at the peak of the slow oscillation (referred to as the peak-max state) [14,15] was determined. This period was free of noxious stimuli, and the minimal target-controlled propofol infusion effect site concentration required to maintain the peak-max state was identified as the lower limit of propofol dose titration throughout the surgery (Fig. 1). We inferred that titrating the propofol dosage to maintain robust EEG alpha power as the peak-max state, which is the signature of propofol-based general anesthesia [8] as well as to...
avoid burst suppression [16].

(2) Incremental doses of iv. propofol or remifentanil infusion, as well as additional iv. fentanyl boluses, were administrated to prevent sudden EEG spectrogram patterns coincident with noxious stimuli, namely the beta arousal, delta arousal and alpha dropout [17]. The administration of incremental target-controlled propofol infusion concentration or opioid boluses (Fig. 2) was at the discretion of the attending anesthesiologists, who based their decisions on the principle of differentiating between the loss of peak-max alpha power without obvious sources of noxious stimuli (indicating the need for more propofol) or the alpha dropout combined with beta/delta arousal patterns with obvious sources of increased noxious stimuli (e.g., scalp dissection) or with concurrent hemodynamic changes (indicating the need for more opioid).

(3) An infusion of dexmedetomidine (0.5 mg/kg/h) was started immediately before anesthesia in each patient. Patients in the index group received a constant rate infusion (0.5 mg/kg/h) of dexmedetomidine [1]. The dexmedetomidine infusion rate was also recommended to maintain the dose of 0.5 mg/kg/h in patients of the spectrogram group as we previously indicated potential neuroprotective effects and anti-inflammatory effects with this therapeutic dose [1,5]. However, because excessive dexmedetomidine may profoundly enhance the effects of propofol anesthesia and may markedly reduce the propofol-induced EEG alpha power [18], the infusion rate may be titrated in patients in the spectrogram group at the attending anesthesiologist’s discretion to maintain robust EEG alpha power and prevent excessively deep anesthesia in cases where the peak-max alpha power was not obtained after titrating down the propofol dose to the lowest acceptable limit (Fig. 3).

For analgesia, each patient routinely received a scalp nerve block containing 10 ml of 0.5% levobupivacaine with a 1:200,000 epinephrine mixture for each side of the scalp before the skin incision [19,20]. Neurophysiological monitoring techniques were used to enhance surgical safety. The fourth-generation Vigileo/FloTrac system (Edwards Lifesciences) was regularly employed to enhance intraoperative cardiac index; this was grounded in our prior positive outcomes with goal-directed fluid therapy for craniotomy [1,21], involving the iterative administration of 250 ml colloid infusions (Voluven® Fresenius Kabi) [1,22].

Postoperative care

After surgery, all patients were immediately transferred to the same neurosurgical intensive care unit (ICU). We characterized “delayed emergence” when the patient’s record revealed the time gap between the end of surgery and the first motor response to command was greater than 30 minutes.

Postoperative neurological complications were identified and characterized through an analysis of medical records. At our institution, specialized neurosurgeons and neurosurgical care-focused nurses conducted patient evaluations a minimum of two times per day. Any newly emerged postoperative neurological symp-
Fig. 2. Illustration of the administration of incremental target-controlled propofol infusion concentration or opioid boluses: The first arrow (labelled "A") represents a mild reduction in alpha power. After increasing the target-controlled propofol infusion effect site concentration, the alpha power returns to its prior level. The second arrow (labelled "B") shows a gradual increase in beta power (beta arousal), accompanied by a drop in alpha power, as well as increases in heart rate and arterial pressure. Following the administration of remifentanil boluses, the beta power decreases and the alpha power returns.

Fig. 3. Illustration that shows the administration of a titrated-down dose of dexmedetomidine to prevent excessive anesthesia depth. The attending anesthesiologist observed a decrease in alpha power, but the target-controlled propofol infusion effect-site concentration had already been titrated to the lower acceptable limit. As a result, the dexmedetomidine dose was reduced at 15:30 (indicated by an arrow marker and labeled as "A"). Following this adjustment, the alpha power was restored (the second arrow; labeled as "B").

toms and indicators were diligently recorded. Severe neurological complications were defined to include mortality, intracerebral hemorrhage necessitating surgical intervention, hydrocephalus requiring surgery, a Glasgow Coma Scale score of 13 or lower, failure to successfully transition off mechanical ventilation, and significant motor deficit (indicated by a reduction of at least 2 points in the motor score) [1,23]. The modified Barthel Index was used to assess short-term neurological disabilities [24] which was routinely assessed upon administration and discharge. The occurrence of postoperative delirium was assessed at least twice daily to document any indicative signs in the neurosurgical ICU and ward at our institute. A trained physician, who was unaware of the patient's group allocation, meticulously reviewed the medical records and diagnosed delirium following the criteria outlined in

https://doi.org/10.4097/kja.23118
Statistical analysis

To adjust for selection bias, 1:1 propensity score matching using the nearest neighbor method was performed using a logistic regression model including age, body mass index and surgery type, factors that substantially influence the administration of anesthesia and postoperative neurological outcomes [27,28]. To assess the effects of matching on the improvement of patient allocation balance, we calculated the standardized mean difference (SMD) [29]. Based on the pilot data, which consisted of the first 20 patients who received an EEG spectrogram-guided anesthesia protocol transition at our institute (and were not included in the analysis of the present study), the mean propofol dose was approximately 1800 mg (with a standard deviation of approximately 500 mg). Notably, this was 500 mg lower than the mean propofol dose administered to patients guided by the BIS value in our previous study [1]. A sample size of 60 patients per group is necessary to achieve a power of 0.9 and a two-sided type I error rate of 0.05. Fisher's exact test or the Χ² test was performed to analyze dichotomous data, and Student's t test and the Mann–Whitney U test were used for normally distributed continuous data and nonparametric ordinal data, respectively. Statistical analyses were performed using MedCalc Statistical Software version 20 (MedCalc Software Ltd.).

Results

In total, 98 patients who underwent elective craniotomy with EEG spectrogram–guided anesthesia at our center between January 2021 and October 2022 were enrolled in this study. Combined with the 80 patients in our previous report, a total of 178 patients were included for matching. Propensity score matching, in which the patients were matched 1:1 by age and operation time, yielded 70 patients in the spectrogram group and 70 patients in the index group. Patient characteristics before and after matching are summarized in Table 1. Following the matching process, the SMDs of the majority of baseline characteristics were reduced. Notably, the SMD of body mass index, which is a major factor influencing the intraoperative propofol dose, between the two study groups was significantly reduced, from 0.26 to 0.02.

Intraoperative profiles

The intraoperative profiles of the two groups are summarized

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Spectrogram group (n = 70)</th>
<th>Index group (n = 70)</th>
<th>SMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before match</td>
<td>56.2 ± 15.1</td>
<td>55.5 ± 14.9</td>
<td>0.05</td>
</tr>
<tr>
<td>After match</td>
<td>54.9 ± 14.2</td>
<td>56.1 ± 15.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Sex (M)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before match</td>
<td>41 (41.8)</td>
<td>30 (37.5)</td>
<td>0.09</td>
</tr>
<tr>
<td>After match</td>
<td>28 (40)</td>
<td>27 (38.6)</td>
<td>0.03</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before match</td>
<td>24.1 ± 4.2</td>
<td>25.4 ± 4.3</td>
<td>0.26</td>
</tr>
<tr>
<td>After match</td>
<td>24.7 ± 3.7</td>
<td>24.6 ± 4.0</td>
<td>0.02</td>
</tr>
<tr>
<td>Education level (yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before match</td>
<td>12.4 ± 3.8</td>
<td>12.2 ± 3.9</td>
<td>0.06</td>
</tr>
<tr>
<td>After match</td>
<td>12.4 ± 3.8</td>
<td>12.1 ± 4.0</td>
<td>0.09</td>
</tr>
<tr>
<td>ASA classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before match</td>
<td>11 (11.2)</td>
<td>5 (6.3)</td>
<td>0.18</td>
</tr>
<tr>
<td>After match</td>
<td>5 (7.1)</td>
<td>4 (5.7)</td>
<td>0.06</td>
</tr>
<tr>
<td>II</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before match</td>
<td>58 (59.2)</td>
<td>48 (60.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>After match</td>
<td>41 (58.6)</td>
<td>42 (60.0)</td>
<td>0.03</td>
</tr>
<tr>
<td>III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before match</td>
<td>33 (33.7)</td>
<td>27 (33.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>After match</td>
<td>24 (34.3)</td>
<td>24 (34.3)</td>
<td>0.00</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before match</td>
<td>38 (38.8)</td>
<td>19 (23.8)</td>
<td>0.33</td>
</tr>
<tr>
<td>After match</td>
<td>26 (37.1)</td>
<td>21 (30.0)</td>
<td>0.15</td>
</tr>
<tr>
<td>Coronary arterial disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before match</td>
<td>6 (6.1)</td>
<td>4 (5.0)</td>
<td>0.05</td>
</tr>
<tr>
<td>After match</td>
<td>2 (2.9)</td>
<td>3 (4.3)</td>
<td>0.07</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before match</td>
<td>5 (5.1)</td>
<td>5 (6.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>After match</td>
<td>3 (4.3)</td>
<td>3 (4.3)</td>
<td>0.00</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before match</td>
<td>16 (16.3)</td>
<td>13 (16.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>After match</td>
<td>10 (14.3)</td>
<td>10 (14.3)</td>
<td>0.00</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before match</td>
<td>12 (12.2)</td>
<td>16 (20.05)</td>
<td>0.21</td>
</tr>
<tr>
<td>After match</td>
<td>10 (14.3)</td>
<td>11 (15.7)</td>
<td>0.04</td>
</tr>
<tr>
<td>Surgery type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor excision</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before match</td>
<td>82 (83.7)</td>
<td>55 (78.6)</td>
<td>0.36</td>
</tr>
<tr>
<td>After match</td>
<td>57 (81.4)</td>
<td>52 (74.3)</td>
<td>0.17</td>
</tr>
<tr>
<td>Aneurysm clipping</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before match</td>
<td>4 (4.1)</td>
<td>11 (13.8)</td>
<td>0.34</td>
</tr>
<tr>
<td>After match</td>
<td>3 (4.3)</td>
<td>8 (11.4)</td>
<td>0.27</td>
</tr>
<tr>
<td>Intracranial bypass</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before match</td>
<td>3 (3.1)</td>
<td>8 (10.0)</td>
<td>0.28</td>
</tr>
<tr>
<td>After match</td>
<td>3 (4.3)</td>
<td>6 (8.6)</td>
<td>0.17</td>
</tr>
<tr>
<td>Microvascular decompression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before match</td>
<td>9 (9.2)</td>
<td>6 (7.5)</td>
<td>0.06</td>
</tr>
<tr>
<td>After match</td>
<td>7 (10.0)</td>
<td>4 (5.7)</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number (%). SMD: standardized mean difference, ASA: American Society of Anesthesiologists.
in Table 2. The two groups had comparable operation times, blood loss, and transfusion profiles. Patients in the spectrogram group received significantly less propofol than did those in the index group (1585 ± 581 vs. 2314 ± 810 mg, respectively, P < 0.001; Table 2). Patients in the index group received 0.5 μg/kg/h of dexmedetomidine, whereas patients in the spectrogram group received 0.40 ± 0.11 μg/kg/h. The median (Q1, Q3) intraoperative BIS values were higher in the spectrogram group than in the index group [44 (41, 49) vs. 41 (37, 45), respectively, P = 0.117; Table 2]. No significant differences in fentanyl equivalent doses were observed between the two groups (Table 2).

Average intraoperative cardiac index, mean arterial pressure, and crystalloid solution volume values were similar between the groups (Table 2). By comparison, patients in the spectrogram group revealed a significant lower intraoperative heart rate (P = 0.028). Intraoperative norepinephrine doses were not significantly different between the study groups (8.7 ± 16.1 vs. 4.4 ± 16.4 μg in the spectrogram and index groups, respectively, P = 0.117; Table 2). Patients in the spectrogram group received significantly less nicardipine than did patients in the index group (median [Q1, Q3]; 0 [0, 0.7] vs. 2.0 [0.3, 5.5] mg, respectively, P < 0.001; Table 2). Patients in the spectrogram group received significantly less colloid than did patients in the index group (405 ± 340 vs. 659 ± 350 ml, respectively, P < 0.001; Table 2) and had a smaller median (Q1, Q3). intraoperative urine output (800 [400, 1200] vs. 1200 [800, 1825] ml, respectively, P < 0.001; Table 2).

### Postoperative outcomes

Postoperative outcomes for each group are summarized in Table 3. The median (Q1, Q3) number of days in hospital was 8 (6, 10) in the spectrum group versus 9 (6, 14) in the index group (P = 0.098; Table 2). The number of days in the ICU was similar between the groups. The incidence of postoperative neurological complications was similar between the groups.

The percentage of patients with delayed emergence was lower in the spectrogram group than in the index group (1.4% vs. 11.4%, P = 0.033; Table 3). Regarding postoperative delirium, one patient in the spectrogram group and two patients in the index group could not be assessed because they were comatose. The two groups had comparable postoperative delirium profiles. In total, 2 patients in the spectrogram group and 4 patients in the index group had an ICDSC score ≥ 4 (delirium), and 64 and 58 patients in the spectrogram and index groups, respectively, had an ICDSC score of 0 (P = 0.227). The in-hospital Barthel’s index scores showed more favorable changes in the spectrum group compared to the index group. Specifically, at admission, the scores were 83.6 ± 27.6 in the spectrum group and 91.6 ± 17.1 in the index group.

### Table 2. Intraoperative Profile

<table>
<thead>
<tr>
<th>Intraoperative Profile</th>
<th>Spectrogram group (n = 70)</th>
<th>Index group (n = 70)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surgical profile</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>241 ± 110</td>
<td>246 ± 105</td>
<td>0.804</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td>150 (50, 400)</td>
<td>125 (100, 300)</td>
<td>0.754</td>
</tr>
<tr>
<td>Patient needing transfusion</td>
<td>11 (15.7)</td>
<td>13 (18.6)</td>
<td>0.823</td>
</tr>
<tr>
<td>Red blood cell transfusion (unit)</td>
<td>0.7 ± 2.0</td>
<td>0.5 ± 1.1</td>
<td>0.398</td>
</tr>
<tr>
<td><strong>Anesthetic profile</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol dose (mg)</td>
<td>1585 ± 581</td>
<td>2314 ± 810</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Dexmedetomidine dose (μg/kg/h)</td>
<td>0.46 ± 0.09</td>
<td>0.5 (fixed dose)</td>
<td>NA</td>
</tr>
<tr>
<td>Fentanyl equivalence (μg)</td>
<td>200 (125, 1504)</td>
<td>250 (175, 733)</td>
<td>0.746</td>
</tr>
<tr>
<td>Average bispectral index score</td>
<td>44 (41, 49)</td>
<td>41 (37, 45)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Hemodynamic profile</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average cardiac index (L/min/m²)</td>
<td>2.8 (2.5, 3.1)</td>
<td>2.7 (2.4, 3.4)</td>
<td>0.681</td>
</tr>
<tr>
<td>Average mean arterial pressure (mmHg)</td>
<td>82.4 ± 8.5</td>
<td>84.5 ± 7.8</td>
<td>0.137</td>
</tr>
<tr>
<td>Average heart rate (beats/min)</td>
<td>65 (58, 74)</td>
<td>71 (64, 78)</td>
<td>0.028</td>
</tr>
<tr>
<td>Nicardipine dose (mg)</td>
<td>0 (0, 0.7)</td>
<td>2.0 (0.3, 5.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Norepinephrine dose (μg)</td>
<td>8.7 ± 16.1</td>
<td>4.4 ± 16.4</td>
<td>0.117</td>
</tr>
<tr>
<td><strong>Fluid balance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crystalloid infusion (ml)</td>
<td>1693 (1210, 2180)</td>
<td>1784 (1250, 2276)</td>
<td>0.659</td>
</tr>
<tr>
<td>Colloid infusion (ml)</td>
<td>405 ± 340</td>
<td>659 ± 350</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Urine output (ml)</td>
<td>800 (400, 1200)</td>
<td>1200 (800, 1825)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, median (Q1, Q3) or number (%). NA: not applicable.
Table 3. Postoperative Outcomes

<table>
<thead>
<tr>
<th>Postoperative outcome</th>
<th>Spectrogram group (n = 70)</th>
<th>Index group (n = 70)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital stay (day)</td>
<td>8 (6, 10)</td>
<td>9 (6, 14)</td>
<td>0.098</td>
</tr>
<tr>
<td>ICU stay (day)</td>
<td>1 (1, 2)</td>
<td>1 (1, 2)</td>
<td>0.372</td>
</tr>
<tr>
<td>Neurological complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number</td>
<td>12 (17.1)</td>
<td>18 (25.7)</td>
<td>0.303</td>
</tr>
<tr>
<td>Severe complication</td>
<td>4 (5.7)</td>
<td>9 (12.9)</td>
<td>0.243</td>
</tr>
<tr>
<td>Delayed emergence</td>
<td>1 (1.4)</td>
<td>8 (11.4)</td>
<td>0.033</td>
</tr>
<tr>
<td>Delirium profile</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICDSC score = 0 (no delirium)</td>
<td>64 (94.2)</td>
<td>58 (85.2)</td>
<td>0.227</td>
</tr>
<tr>
<td>ICDSC score 1–3 (subclinical delirium)</td>
<td>2 (2.9)</td>
<td>4 (5.9)</td>
<td></td>
</tr>
<tr>
<td>ICDSC score ≥ 4 (delirium)</td>
<td>2 (2.9)</td>
<td>6 (8.9)</td>
<td></td>
</tr>
<tr>
<td>Barthel index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission</td>
<td>83.6 ± 27.6</td>
<td>91.6 ± 17.1</td>
<td></td>
</tr>
<tr>
<td>Discharge</td>
<td>86.4 ± 24.3</td>
<td>85.1 ± 21.5</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3), number (%) or mean ± SD. *One patient in the spectrogram group and two patients in the index group could not be assessed because they were comatose. ICU: intensive care unit, ICDSC: intensive care delirium screening checklist.

At discharge, the scores were 86.4 ± 24.3 in the spectrum group and 85.1 ± 21.5 in the index group. The group-time interaction analysis revealed a significant difference between the two groups (P = 0.008; Table 3).

Discussion

In the present study, we observed that anesthetic doses were markedly lower in patients receiving EEG spectrogram-guided anesthesia than in those receiving BIS value-guided anesthesia. The reduced anesthetic dose appears to correlate with a lower incidence of delayed emergence and higher Barthel index scores at discharge and may reduce postoperative subsyndromal delirium.

Coadministration of dexmedetomidine is effective in lowering propofol requirements for total intravenous anesthesia [30]. Accordingly, our previous study indicated that the coadministration of dexmedetomidine led to a propofol dose reduction of approximately 20% based on BIS value-guided anesthesia [1]. Furthermore, the scalp block was applied in each patient and this markedly reduced anesthetic requirement [31]. The present study indicates that an EEG spectrogram-guided anesthetic protocol elicits additional propofol-sparing effects (approximately overall 31.5%) compared with a BIS value-guided anesthetic protocol. The median averaged BIS values in the spectrum group were maintained only 10% higher than the average value maintained in the index group. Several factors may cause erroneous BIS scores and the large differences in anesthetic doses. First, electromyographic artefacts resulting from electrocautery at the surgical site and cranial nerve stimulator may cause transient increase BIS index values (we provided an example in the Supplementary Fig. 1) [32,33]. Second, dexmedetomidine may also affect BIS values. Kasuya et al. [34] observed lower BIS values at a given observational sedation level in volunteers sedated with dexmedetomidine than in those sedated with propofol. Similarly, Xi et al. [35] observed lower BIS values in patients sedated with dexmedetomidine than in those sedated with propofol at moderate and deep sedation levels. Dexmedetomidine may induce slow EEG oscillations, thereby reducing BIS values at a given sedation level. This may explain why BIS values for both groups in the present study were relatively low. In addition, we observed that the range of the average BIS values was wider in the spectrogram group compared to the index group, with values ranging from 27 to 72 in the spectrogram group and 31 to 56 in the index group. Furthermore, it’s important to note that the averaged BIS value was calculated in 5-minute intervals from the electronic medical records, rather than being an average of continuous data. As a result, the BIS data provided in the present study may potentially underestimate the true difference between spectrogram-guided anesthesia and index-guided anesthesia. This finding highlighted that by monitoring the EEG spectrogram, anesthesiologists may not strictly adhere to maintaining the BIS value within the common recommended 40–60 range and this approach of using EEG spectrogram guidance appears to be effective in reducing unnecessary intraoperative anesthetic requirements during craniotomy.

In addition, propofol doses varied less in the spectrogram group than in the index group, suggesting that EEG spectrogram-guided anesthesia facilitated a more accurate propofol titration than did BIS value-guided anesthesia. The anesthetic-sparing ef-
fect of EEG spectrogram–guided anesthesia was also observed in a trial involving children by Long et al. [36], in which the EEG spectrogram–guided protocol required 10% less sevoflurane than did the standard care protocol. The anesthetic-sparing effect is more prominent in our study than in that by Long et al., possibly because the present study coadministered two hypnotic agents, whereas only one hypnotic agent, sevoflurane, was administered in the study by Long et al. This emphasizes the necessity of having an EEG spectrogram available in the context of multimodal general anesthesia [6].

In the present study, we observed several favorable postoperative outcomes, including the prevention of delayed emergence, better Barthel index scores, and prevention of subsyndromal delirium among patients in the spectrogram group. Dutta et al. [30] reported that the administration of dexmedetomidine in combination with propofol in BIS value–guided anesthesia significantly reduced the propofol requirement but increased the risk of early postoperative sedation. In the present study, patients receiving EEG spectrogram–guided anesthesia were less likely to experience delayed emergence than were those receiving BIS value–guided anesthesia, possibly because of the reduced propofol dose. The prevention of delayed emergence is crucial for patients undergoing craniotomy for early neurological assessment and immediate optimization of treatment after surgery. This may contribute to the better in-hospital Barthel index change in the spectrogram group.

The use of processed EEG indices monitor aims to precisely control the anesthetic depth and this often is related with a reduction of anesthetic dosage in real world practice [37,38]. Furthermore, there is a great interest of application of the EEG monitoring to prevent postoperative delirium [39]. However, one of the current landmark trial, namely the ENGAGE trial, revealed that use of BIS value to guide anesthesia reduces intraoperative anesthetic consumption by up to 0.11 minimum alveolar concentration but does not prevent postoperative delirium [40]. In the postoperative delirium substudy of BALANCE trial, the postoperative delirium incidence was lower among patients received a lighter anesthesia (BIS 50) than those received a deeper anesthesia (BIS 35) [41]. Although the spectrum group received substantially less (35%) propofol than did the index group, the incidence of postoperative delirium was the same for both groups. Patients undergoing craniotomy may be more susceptible to postoperative delirium than patients undergoing other types of surgery because craniotomy causes cerebral injuries such as neuroinflammation, focal tissue ischemia, and tissue edema [42,43]. Therefore, a reduction in anesthesia alone is not sufficient to prevent delirium after craniotomy. However, no patient in the spectrogram group and five patients in the index group (0% vs. 7.4%) had subsyndromal delirium (ICDSC score of 1–3). Intraoperative low frontal EEG alpha power is associated with postoperative subsyndromal delirium [44] and propofol reduces EEG alpha power [45]. Therefore, propofol dose may be correlated with the incidence of subsyndromal delirium. As postoperative subsyndromal delirium prognosticates poor outcomes [46], an EEG spectrogram–guided anesthetic protocol may be beneficial to prevent this complication for patients undergoing craniotomy. However, we observed no significant differences in postoperative neurological complication between the two groups because neurological complications in patients undergoing craniotomy are more likely to be related with the surgery than the anesthesia.

Regarding the intraoperative hemodynamic profiles, patients in the spectrogram group required less colloid to maintain intraoperative cardiac output than did those in the index group, possibly because the spectrum group received less propofol. As the propofol concentration increases, the mean systemic filling pressure increases [47], and the venous return decreases [48] which requires amount of intravenous fluid required to maintain cardiac output. However, intraoperative fluid requirement may be related with more complex interactions between hemodynamic Dexmedetomidine induces biphasic changes in arterial pressure with both hypertensive and hypotensive effects; a high maintenance dose may induce higher arterial pressure than a low maintenance dose [49]. Patients in the spectrogram group received a smaller maintenance dose of dexmedetomidine than did those in the index group and therefore required less intraoperative nicardipine than did patients in the index group.

This study has several limitations. First, maintaining the alpha power was a qualitative rather than a quantitative goal and the values of alpha power was not allowable to be exported from the EEG device. Therefore, it is unable to compare the alpha power between the two study groups. Furthermore, despite the proposal of the EEG spectrogram–guided protocol, calculating the actual protocol compliance was challenging due to the retrospective design. Second, there is an age-dependent decline in alpha power of the EEG. As the average age of our cohort was below 60 years old, our protocol and results should not be completely extrapolated to the geriatric population. Third, intraoperative nociception may not be optimally monitored by the combination of EEG spectrogram and hemodynamic changes [17], and thus we considered the implication of scalp block crucial in our protocol to reduce inadequate nociception control. Hence, our protocol may not be suitable for patients who did not receive a scalp block. Forth, we did not have sufficient resources to save the details of EEG data. Relevant parameters, such as the intraoperative burst suppression...
time were not available. However, because the spectrogram group received less propofol, we assumed that the spectrogram group had a lower accumulated suppression time than did the index group. Fifth, the primary outcome of the present study is propofol consumption. Secondary outcomes, including the incidence of postoperative delirium and the length of hospital stay, were not sufficiently powered to detect significant differences. Furthermore, the retrospective design may increase the risk of unexplored factors influencing outcomes other than the anesthetic consumptions such as the differences in the Barthel indices as well as the differences in intraoperative iv. fluid requirements. Sixth, the surgical type was not optimally balanced between the two study groups. For instance, there were more patients undergoing aneurysm clipping in our previous trial (index group) than in the spectrogram group. This difference may be attributed to the growing trend towards using endovascular coiling instead of surgical clipping for the treatment of unruptured cerebral aneurysms in recent years [50]. Consequently, fewer patients in the spectrogram group (where surgery was performed in a more recent period) underwent aneurysm clipping. Furthermore, electroencephalographic spectrogram-guided anesthesia is a relatively new clinical practice, resulting in a relatively small number of patients in the spectrogram database at our institute, making it challenging to achieve optimal matching. Despite these challenges, the SMD of the surgical type still decreased after the matching process. The primary outcome, namely the propofol dose, was more closely related to age and body mass index than the surgical type [27,28], and the SMDs of age and body mass index were below 0.1, indicating good balanced matching [29].

In conclusion, this study demonstrated that for patients undergoing craniotomy and receiving total intravenous anesthesia using dexmedetomidine and propofol, less propofol is required when anesthesia administration is guided by an EEG spectrogram than when it is guided by a BIS monitor. Precise anesthetic dosing may also prevent delayed emergence, improve postoperative Barthel index scores, and reduce intraoperative fluid requirements.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Feng-Sheng Lin (Data curation; Investigation; Writing – original draft; Writing – review & editing)
Po-Yuan Shih (Conceptualization; Investigation; Methodology; Software; Visualization; Writing – review & editing)
Chao-Hsien Sung (Data curation; Investigation; Methodology; Software)
Wei-Han Chou (Formal analysis; Writing – original draft; Writing – review & editing)
Chun-Yu Wu (Conceptualization; Data curation; Formal analysis; Writing – original draft; Writing – review & editing)

Supplementary Material

Supplementary Fig. 1. An example of electrocautry interference on the BIS value during craniotomy.

ORCID

Feng-Sheng Lin, https://orcid.org/0000-0001-7798-9716
Po-Yuan Shih, https://orcid.org/0000-0002-1096-9179
Chao-Hsien Sung, https://orcid.org/0000-0002-0461-2050
Wei-Han Chou, https://orcid.org/0000-0001-6868-3985
Chun-Yu Wu, https://orcid.org/0000-0002-9544-8654

References


Lin et al. - EEG spectrogram lowers TIVA dose


Total postoperative opioid dose is an independent risk factor for prolonged postoperative ileus after laparoscopic colorectal surgery: a case-control study

Hui Ju¹, Kai Shen², Jiaxin Li¹, Yi Feng¹

Departments of ¹Anesthesiology, ²Gastroenterologic Surgery, Peking University People's Hospital, Beijing, China

Background: Prolonged postoperative ileus (PPOI) is a major complication of colorectal surgery. Increased opioid consumption has been proposed to increase the risk of PPOI. This study aimed to test the hypothesis that an increased total postoperative opioid dose (TPOD) is associated with the increased incidence of PPOI.

Methods: For this matched case-control study, patients who underwent elective laparoscopic colorectal procedures at the Peking University People's Hospital between January 2018 and June 2020 were retrospectively reviewed. Patients with PPOI were assigned to the ileus group, while patients without PPOI (control group) were matched at a 1:1 ratio to the ileus group according to age, American Society of Anesthesiologists physical status score, and type of surgical procedure. The primary outcome was the TPOD between the ileus and control groups. The secondary outcome was risk factors of PPOI.

Results: A total of 267 participants were included in the final analysis. No differences in baseline or operative factors were found between the two groups. The TPOD, intravenous sufentanil dose on postoperative day 1 (POD1), and the use of patient-controlled analgesia with basal infusion were associated with PPOI (P < 0.05). Multivariate logistic regression analysis revealed that an increased TPOD was an independent risk factor for developing PPOI after laparoscopic colorectal procedures (Odd ratio: 1.67, 95% CI [1.03, 2.71], P = 0.04).

Conclusions: The TPOD is an independent risk factor for PPOI after laparoscopic colorectal surgery. We need to explore new strategies of postoperative analgesia to reduce the dosage of TPOD.

Keywords: Case-control studies; Colorectal surgery; Ileus; Nerve block; Opioid-induced constipation; Postoperative pain.

Introduction

Prolonged postoperative ileus (PPOI) is a major complication of colorectal surgery, with a reported prevalence of 10%–30%. PPOI leads to increased morbidity and duration of hospital stay (DoHS), thereby increasing medical costs [1–3]. Determining risk factors for PPOI is one of the key elements for the Enhanced Recovery after Surgery (ERAS) protocol.

Opioid receptors are present throughout the gastrointestinal tract. Activation of μ-receptors located in the enteric nervous system causes increased non-propulsive contrac-
tions and inhibition of water and electrolyte excretion. These actions lead to delayed gastrointestinal transit and hard, infrequent stools [4,5]. An increase in the perioperative opioid dose may be an independent risk factor for PPOI. Although opioids are widely used to attenuate intraoperative stress and represent the cornerstone of pain treatment, anesthesiologists are striving to reduce perioperative opioid consumption to decrease opioid-related gastrointestinal side effects. Minimizing opioid use has been suggested to reduce PPOI risk [6].

Several strategies have been proposed to reduce opioid consumption and improve recovery of bowel function. First, multimodal pain management is recommended whenever possible. Second, a neuraxial or peripheral nerve block [7–9], subcutaneous infiltration of local anesthetics, and use of nonsteroidal anti-inflammatory drugs or acetaminophen have been shown to be effective [10–12]. Patient-controlled analgesia (PCA) without a basal infusion may also be an effective strategy [13].

This study aimed to test the hypothesis that an increased total postoperative opioid dose (TPOD) is associated with increased incidence of PPOI.

**Materials and Methods**

The protocol for this single-center, matched case-control study was approved by the Ethics Review Board of Peking University People’s Hospital in Beijing, China (2021PHB144-001). The requirement for written informed consent was waived due to the retrospective design of the study. The study was conducted according to the STROBE criteria and registered at www.clinicaltrials.gov (NCT05262569).

All consecutive patients who underwent an elective laparoscopic colorectal procedure at the Department of Gastroenterologic Surgery at Peking University People’s Hospital in Beijing, China between January 1, 2018 and June 30, 2020 were included. Patients who met any of the following criteria were excluded: (i) long-term opioid use, (ii) conversion from a laparoscopic to an open procedure, (iii) admission to the intensive care unit (ICU), (iv) opioids other than sufentanil included in the PCA regimen, (v) PCA use for < 48 h, and (vi) missing data on post-surgery opioid consumption.

Patients with PPOI were included in the ileus group. In accordance with the PPOI definition proposed by Vather et al. [14], patients who met ≥ 2 of the following 5 criteria on postoperative day (POD) 4 or later had PPOI: (i) nausea and vomiting over the preceding 12 h, (ii) inability to tolerate a solid or semi-solid diet over the preceding two mealtimes, (iii) abdominal distension, (iv) failure to pass gas or stool for a 24 h period, and (v) radiological evidence of an ileus in the preceding 24 h, without postoperative pain management, returned to operation room before discharge.

The control and ileus groups were matched at a 1:1 ratio for the following: age range (± 5 years), American Society of Anesthesiologists (ASA) physical status score, and type of surgical procedure (colectomy, rectal resection, whole-colon resection, or others).

All patients underwent a standard anesthesia protocol for laparoscopic colorectal procedures at the study center. The opioid administered intraoperatively was sufentanil 0.3–0.5 µg/kg during induction and 0.1 µg/kg before skin incision and/or upon skin closure. Remifentanil 0.1–0.2 µg/kg/min continuous infusion was administered for maintenance of anesthesia. Postoperative pain was managed with patient-controlled intravenous analgesia using sufentanil with or without basal infusion, at the discretion of the anesthesiologist.

Data on baseline factors, operative factors, and analgesia-related risk factors were obtained from electronic medical records. Multiple potential risk factors for PPOI were considered based on a review of the literature.

Baseline factors included age, sex, body mass index, presence of major comorbidities (cardiovascular diseases, cerebral diseases, pulmonary diseases, or diabetes mellitus), ASA physical status scores, and history of abdominal surgery. Operative factors included the type and duration of the surgical procedure, estimated blood loss, total input, time to tolerance of an oral diet, and postoperative DoHS. Analgesia-related protective or risk factors included a transversus abdominis plane (TAP) block, intraoperative opioid consumption (converted into equivalent doses of morphine in mg/kg according to morphine 1 mg = oxycodone 0.5 mg = fentanyl 10 µg = sufentanil 1 µg = remifentanil 10 µg) [15], intravenous opioid dose (sufentanil, µg/kg) on POD1 through PCA, TPOD (sufentanil, µg/kg) through PCA, and basal infusion on PCA.

The primary outcome was the TPOD (sufentanil, µg/kg) between the ileus and control groups. Secondary outcomes included administration of a TAP block, intravenous opioid dose (sufentanil, µg/kg) on POD1, and PCA with basal infusion.

Parametricity was determined using the Shapiro-Wilk test, with normally distributed data expressed as the mean ± standard deviation (SD) and non-parametric data as the median ± interquartile range. Categorical variables are presented as numbers and percentages. Between-group differences were evaluated using the independent t-test or Mann-Whitney U test for continuous variables and Fisher’s exact test for categorical variables. Univariate and multivariate analyses were performed using conditional logistic regression to determine potential risk factors for PPOI. Vari-
ables that were significant ($P < 0.05$) in the univariate analysis were included in the multivariate analysis to determine the independent risk factors for PPOI. The results are presented as odds ratios (ORs) with 95% CIs. Statistical significance was set at $P < 0.05$ for all outcomes. The power of this study was calculated using http://sample-size.net, with the TPOD (sufentanil, $\mu g/kg$) as the primary outcome. All the statistical analyses were performed using SPSS version 23 (IBM Corp.).

**Results**

**Patient population and characteristics**

A total of 596 consecutive cases were reviewed in the initial study, 267 of which were included after applying the exclusion criteria. Of these 267 patients, 15.0% (40/267) met the definition of PPOI according to the study protocol. Thirty-eight patients and controls were matched for age ($\pm$ 5 years), ASA physical status scores, and type of surgical procedure (Fig. 1).

No significant differences in patient characteristics were found between the ileus and control groups (Table 1). The use of a TAP block was significantly lower in the ileus group than in the control group (6 vs. 14, $P = 0.038$). Patients used more sufentanil after surgery ($2.3 \pm 1.0$ vs. $0.7 \pm 1.0 \mu g/kg$, $P < 0.001$) and the sufentanil dose was significantly higher on POD1 ($0.9 \pm 0.4$ vs. $0.4 \pm 0.5 \mu g/kg$, $P < 0.001$) in the ileus group compared to the control group. Additionally, more patients in the ileus group received a PCA pump with a basal infusion (31 vs. 18, $P = 0.002$). The time to tolerance of oral intake (12 [9, 15] vs. 6 [5.75, 7] days) and postoperative DoHS (14 [11, 19.25] vs. 8 [7, 9] days) were significantly longer in the ileus group ($P < 0.001$).

The results of the univariate analysis are presented in Table 2. The TPOD (OR: 1.49, 95% CI [1.21, 1.85], $P < 0.001$), sufentanil dose on POD1 (OR: 2.31, 95% CI [1.37, 3.87], $P = 0.002$), and use of PCA with basal infusion (OR: 2.44, 95% CI [1.08, 5.54], $P = 0.003$) were associated with PPOI. Multivariate logistic regression analysis revealed that an increased TPOD was an independent risk factor for developing a PPOI after a laparoscopic colorectal procedure (OR: 1.67, 95% CI [1.03, 2.71], $P = 0.04$). Each 1 μg/kg increase in the sufentanil dose was associated with a 1.67-fold increase in the risk of PPOI.

**Discussion**

The current study confirmed the hypothesis that an increased TPOD is an independent risk factor for PPOI. The TPOD was significantly higher in the ileus group, which is consistent with a study conducted by Artinyan et al. [16], who demonstrated that
Table 1. Comparison of Baseline Factors between the Groups

<table>
<thead>
<tr>
<th>Baseline factor</th>
<th>Ileus group (n = 38)</th>
<th>Control group (n = 38)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient’s characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>61.3 ± 17.0</td>
<td>60.7 ± 17.0</td>
<td>0.9</td>
</tr>
<tr>
<td>Sex (M)</td>
<td>25 (65.8)</td>
<td>22 (57.9)</td>
<td>0.5</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.0 ± 4.4</td>
<td>23.9 ± 4.4</td>
<td>0.2</td>
</tr>
<tr>
<td>ASA PS (I/II/III)</td>
<td>4/30/4</td>
<td>4/30/4</td>
<td>1.0</td>
</tr>
<tr>
<td>Previous abdominal surgery</td>
<td>4 (10.5)</td>
<td>10 (26.3)</td>
<td>0.076</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>15 (39.5)</td>
<td>16 (42.1)</td>
<td>0.8</td>
</tr>
<tr>
<td>Cerebral diseases</td>
<td>4 (10.5)</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>Pulmonary diseases</td>
<td>1 (2.6)</td>
<td>3 (7.9)</td>
<td>0.3</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>11 (28.9)</td>
<td>5 (13.2)</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Surgical type</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laparoscopic colectomy</td>
<td>19 (50)</td>
<td>19 (50)</td>
<td>1.0</td>
</tr>
<tr>
<td>Rectectomy</td>
<td>18 (47.4)</td>
<td>18 (47.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Whole colon and rectum excision</td>
<td>1 (2.6)</td>
<td>1 (2.6)</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Intraoperative data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAP block</td>
<td>6 (15.9)</td>
<td>14 (36.8)</td>
<td>0.038</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>230.8 ± 89.0</td>
<td>209.1 ± 90.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Duration of surgery &gt; 3 h</td>
<td>29 (76.3)</td>
<td>22 (57.9)</td>
<td>0.087</td>
</tr>
<tr>
<td>Estimated blood loss (ml)</td>
<td>109.5 ± 50.0</td>
<td>91.8 ± 50.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Total input (ml)</td>
<td>2575.0 ± 700.0</td>
<td>2248.7 ± 725.0</td>
<td>0.058</td>
</tr>
<tr>
<td>Intraoperative opioid (mg/kg/h)*</td>
<td>0.78 ± 0.30</td>
<td>0.79 ± 0.38</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Postoperative data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPOD of sufentanil (μg/kg)</td>
<td>2.3 ± 1.0</td>
<td>0.7 ± 1.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sufentanil dose on POD1 (μg/kg)</td>
<td>0.9 ± 0.4</td>
<td>0.4 ± 0.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PCA with a basal infusion</td>
<td>31 (81.6)</td>
<td>18 (47.4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Time to tolerance of an oral diet (day)</td>
<td>12 (9, 15)</td>
<td>6 (5.75, 7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Postoperative DoHS (day)</td>
<td>14 (11, 19.25)</td>
<td>8 (7, 9)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, number (%) or median (Q1, Q3). ASA PS: American Society of Anesthesiologists physical status, TAP: transversus abdominis plane, TPOD: total postoperative opioid dose, PCA: patient-controlled analgesia, POD: postoperative day, DoHS: duration of hospital stay. *Intraoperative opioids were converted to equivalent doses of morphine (mg/kg).

Table 2. Univariate and Multivariate Analysis of Analgesia-related Risk Factors

<table>
<thead>
<tr>
<th>Analgesia-related risk factors</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate analysis of analgesia-related risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total postoperative sufentanil dose (μg/kg)</td>
<td>1.49</td>
<td>1.21, 1.85</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TAP block</td>
<td>0.53</td>
<td>0.22, 1.26</td>
<td>0.1</td>
</tr>
<tr>
<td>Sufentanil dose on POD1 (μg/kg)</td>
<td>2.31</td>
<td>1.37, 3.87</td>
<td>0.002</td>
</tr>
<tr>
<td>PCA with a basal infusion</td>
<td>2.44</td>
<td>1.08, 5.54</td>
<td>0.033</td>
</tr>
<tr>
<td><strong>Multivariate analysis of analgesia-related risk factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total postoperative sufentanil dose (μg/kg)</td>
<td>1.67</td>
<td>1.03, 2.71</td>
<td>0.040</td>
</tr>
</tbody>
</table>


the TPOD is an independent predictor of PPOI. In that study, the mean TPOD of the study population was 2.36 mg/kg of morphine, which was consistent with the value in our ileus group (mean TPOD of sufentanil was 2.3 μg/kg, which is equivalent to 2.3 mg/kg of morphine).

In our study, we controlled for other potential confounders for PPOI by matching the age [17], ASA score [18], and type of surgical procedure [19] between the groups. We excluded the patients whose procedure was converted to open surgery because open procedures involve more bowel handling [20] and patients admitted to the ICU since they receive different postoperative pain management strategies. This resulted in the inclusion of 38 balanced pairs for further analysis. As predicted, the time to tolerance of an oral diet and postoperative DoHS were significantly longer in the ileus group. These data encouraged us to explore...
strategies to minimize the postoperative opioid dose to decrease PPOI occurrence.

Two potential reasons for the association between an increased TPOD and PPOI in this study were postulated. First, fewer patients in the ileus group received a TAP block preoperatively (15.8% vs. 36.8%, P = 0.04), which resulted in significantly higher opioid consumption during the first 24 h in the ileus group (0.9 ± 0.4 vs. 0.4 ± 0.5 μg/kg, P < 0.001). Preoperative TAP blocks have been demonstrated to reduce opioid consumption on POD1 [21]; therefore, the ERAS protocol strongly recommends the use of the TAP block for minimally invasive surgery [22]. We demonstrated that the lower prevalence of TAP blocks in the ileus group was associated with increased opioid consumption on POD1. This may have contributed to the slow recovery of bowel function in the ileus group, resulting in a longer time to tolerate an oral diet and a longer DoHS. Second, more patients in the ileus group received PCA with a basal infusion (81.6% vs. 47.4%, P = 0.002). Zhen et al. [23] previously demonstrated that including a basal infusion on PCA with sufentanil was efficacious and safe [23]. However, whether sufentanil influenced patient recovery (including gastrointestinal function) was not investigated in that study [23]. Sufentanil has recently become the primary opioid used at Peking University People's Hospital postoperatively.

Anesthesiologists usually administer a basal infusion of sufentanil because of its intermediate half-life. However, an increasing number of anesthesiologists are attempting to reduce opioid use to comply with ERAS recommendations. In recent years, one strategy has been to provide PCA without a basal infusion, which resulted in a lower TPOD and PPOI prevalence in the current study.

The primary strength of our study is the matched case-control design to control for confounding factors, thereby focusing on analgesic-related risk factors. However, our study also has three main limitations. First, the protocol for perioperative analgesia according to the ERAS guidelines has changed since this study was conducted [6], which could affect the prevalence of PPOI. Second, patients who were admitted to the ICU postoperatively were excluded as they were deemed to have more comorbidities and to have undergone more complicated procedures. Thus, the results of this study may not be generalizable. Third, our sample size was small; however, using the total postoperative dose of sufentanil as the primary endpoint, the power of our study was calculated to be as high as 100%.

In conclusion, the TPOD was found to be an independent risk factor of PPOI after laparoscopic colorectal procedures. Therefore, we need to explore new strategies of postoperative analgesia to reduce the dosage of TPOD.

**Funding**

None.

**Conflicts of Interest**

No potential conflict of interest relevant to this article was reported.

**Data Availability**

The authors have placed an embargo on the public availability of the data due to ongoing secondary analyses.

**Author Contributions**

Hui Ju (Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Validation; Writing – original draft; Writing – review & editing)

Kai Shen (Data curation; Resources; Supervision)

Jiaxin Li (Formal analysis; Writing – original draft)

Yi Feng (Conceptualization)

**ORCID**

Hui Ju, https://orcid.org/0000-0002-9721-566X

Kai Shen, https://orcid.org/0000-0002-3387-7939

Jiaxin Li, https://orcid.org/0000-0002-1586-4931

Yi Feng, https://orcid.org/0000-0002-3952-1351

**References**


Comparison of dexmedetomidine and opioids as local anesthetic adjuvants in patient controlled epidural analgesia: a meta-analysis

Yafen Gao1,∗, Zhixian Chen2,∗, Yu Huang3,∗, Shujun Sun1,4,†, Dong Yang1,4,†

1Department of Anesthesiology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 2Department of Pathology, Block T, Queen Mary Hospital, Hong Kong, 3Department of Urology, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, 4Department of Pain, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Introduction

Epidural analgesia is a widely practiced analgesic technique commonly used for postoperative analgesia, labor analgesia, and treatment of pain in the late stage of cancer, and has been demonstrated to improve postoperative outcomes and attenuate the physiological response to surgery [1–6]. Patient-controlled epidural analgesia (PCEA) is a common form of epidural analgesia that provides better analgesia, improves patient satisfaction, and reduces clinician workload compared to continuous infusion and intermittent bolus
techniques [7]. Opioids are often used as adjuvants in combination with local anesthetics for epidural analgesia as this provides significant synergistic effects [8]. The combined application prolongs the duration of analgesia, reduces the concentration and dosage of local anesthetics, and increases patient satisfaction [9]. However, the combined use of opioids and local anesthetics increases the incidence of side effects such as itching, urinary retention, nausea and vomiting, and respiratory depression [10–12]. Therefore, the need for a more ideal adjuvant for local anesthesia, with better analgesic effects but fewer adverse effects, is growing. In recent years, several studies on the use of dexmedetomidine (DEX) as an adjuvant to local anesthetics for intravertebral anesthesia and analgesia have provided encouraging results.

DEX is a highly selective Alpha-2 receptor agonist with a variety of pharmacological effects including sedation, analgesia, and anti-sympathetic effects [13,14]. Several meta-analyses have demonstrated that the administration of DEX as an adjuvant in epidural anesthesia is well tolerated, acts synergistically, and provides an improved sedation and analgesic profile [15–18]. Notably, some studies have also shown that administering DEX as a local anesthetic adjuvant in spinal anesthesia [19] and epidural anesthesia [20,21] not only prolongs the duration of anesthesia and improves postoperative analgesia, but also reduces the incidence of itching compared with opioids. However, in the abovementioned studies, the administration of DEX was typically as a single dose with a short duration of action. However, when administering continuous infusions of DEX through the PCEA over a prolonged period, careful consideration of the efficacy of the cumulative dose and possible adverse effects is essential.

Unfortunately, our current understanding of the adverse effects and efficacy of DEX administered to patients in PCEA is limited. In several randomized controlled trials (RCTs), DEX has been compared with opioids as adjuvants to local anesthetics for PCEA; however, the results have been inconsistent and even contradictory. Therefore, a meta-analysis is needed to evaluate the adverse effects and efficacy of DEX versus opioids as adjuvants in PCEA to provide insights into clinical analgesic practices.

**Materials and Methods**

The protocol for this meta-analysis was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the registration number CRD42022307670 on March 10, 2022. This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards [22].

**Search strategy**

Two independent researchers (YFG and ZXC) searched PubMed, Embase, the Cochrane Library, and China Biology Medicine (CBM) for RCTs evaluating DEX as a local anesthetic adjuvant for PCEA from inception until January 10, 2022. The MeSH terms and free texts were used for study retrieval (Supplementary Material 1 for the retrieval strategy). The following terms were combined and used for the literature search: “dexmedetomidine,” “epidural space,” “analgesia, epidural,” “injections, epidural,” and “randomized controlled trial.” Furthermore, a manual search of the references of the included RCTs and systematic reviews in related fields was performed.

**Eligibility criteria**

The eligibility criteria were based on the PICOS framework (participants, intervention, comparison, outcome, and study design) as follows: P: patients receiving PCEA (including postoperative and labor analgesia); I: use of DEX as an adjuvant to local anesthetics in PCEA; C: use of opioids as an adjuvant to local anesthetics in PCEA; O: visual analogue scale (VAS) scores and incidence of adverse effects as the primary outcomes and the number of PCEA bolus doses, total PCEA consumption, Ramsay sedation scale (RSS) scores, and neonatal and maternal outcomes (in labor analgesia) as secondary outcomes; and S: only RCTs were included. Our meta-analysis was divided into two groups for the qualitative synthesis: the DEX group and the opioid group (including but not limited to morphine, fentanyl, sufentanil, and hydromorphone).

Studies with any of the following characteristics were excluded: (1) a single-dose injection of DEX, (2) serious flaws in the study design, (3) incomplete and duplicate publications, (4) un retrievable or unconvertable data; and (5) not written in either English or Chinese.

**Data extraction**

Two evaluators (YFG and YH) independently screened the literature and extracted and cross-checked the data. In cases of disagreement, a third party (SJS) was consulted. During literature screening, the title and abstract were read first. After excluding irrelevant studies, the full texts of the remaining studies were read. Data extraction mainly included relevant information concerning the predefined primary outcomes (i.e., VAS scores and incidence of adverse effects) and secondary outcomes (i.e., RSS scores, number of PCEA bolus doses, PCEA consumption, and neonatal and
maternal outcomes in labor analgesia). When necessary, the data were extracted from graphs or figures. To obtain further information or answers to queries concerning the data, we contacted the authors of the studies listed. When the units used for the outcome indicators differed across the included studies, we converted them to the same units; for example, we consistently converted hours to minutes.

Assessment of risk of bias

Two evaluators (YFG and SJS) assessed the risk of bias in the included studies using the Cochrane Handbook version 5.0.2. For each included RCT, the adequacy of sequence generation, concealment of allocation, blind design, incomplete outcome data, selective reporting, and other risks of bias were assessed. Each item was classified as having “low deviation risk,” “high deviation risk,” or “unclear deviation risk.” Any discrepancies were resolved through discussion, and if necessary, a third researcher (DY) was consulted to resolve disagreements.

Quality of evidence

Two evaluators (ZXC and SJS) used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to evaluate the quality of evidence. The evidence was rated as high, moderate, low, or very low according to the risk of bias, inconsistency, indirectness, imprecision, and publication bias. Disagreements were resolved through discussion or by referring to a third evaluator (DY).

Statistical analysis

The meta-analysis was performed using the RevMan 5.4 software (Nordic Cochrane Center). The binary outcomes are expressed using odds ratios (ORs) with 95% CIs and continuous outcomes are expressed as mean differences (MDs) or standardized mean differences (SMDs) with 95% CIs. The I² test was used to examine the heterogeneity of the pooled results. When no statistical heterogeneity was present among the RCTs (I² < 50%), a fixed-effects model was used to combine effect sizes. If statistical heterogeneity was present among the results (I² ≥ 50%), further sensitivity analyses and subgroup analyses were performed to evaluate the robustness of the synthesized results and to determine the source of heterogeneity. If heterogeneity could not be ruled out, a random effects model was used for the meta-analysis. The planned subgroup analysis assessed the use of PCEA for labor or postoperative analgesia. For the data expressed using the median and range, we obtained the corresponding means and standard deviations (SDs) using an online calculator (http://www.math.hkbu.edu.hk/~tongt/papers/median2mean.html, last accessed on June 26, 2022) [23,24]. For data that were provided only as histograms, we obtained the specific means and SDs using a webplot digitizer (https://apps.automeris.io/wpd/index.zh_CN.html, last accessed on June 26, 2022).

As the observation indicators in the included studies were not completely consistent and the data results required to integrate the indicators were not included in some studies, the primary and secondary outcome results of our meta-analysis were integrated only for studies that contained data on the corresponding indicators. A brief description of some of the related indicators that were reported in the included studies but could not be integrated owing to insufficient data is provided in the Results section. A table combined with different custom symbols was used to visually display the effects of DEX versus opioids in PCEA based on the results of our meta-analysis.

Results

Characteristics of eligible studies and risk of bias

A flowchart of the study selection is shown in Fig. 1. A total of 636 patients were included in the seven RCTs selected for this study [25–31], including 320 and 316 patients treated with DEX and opioids, respectively. The basic characteristics and interventions are summarized in Table 1. Three studies [25,26,30] were conducted on patients receiving labor analgesia, and the remaining studies [27–29,31] were conducted on patients receiving postoperative analgesia in surgical settings. The surgical procedures included cesarean sections [28], lumbar spine surgery [31], elective lung lobectomy [27], and colonic resections [29]. The risk of bias assessments are shown in Fig. 2. The quality of the meta-evidence on the efficacy and adverse effects of DEX in PCEA was generally low (Table 2).

Primary outcomes

VAS scores for postoperative patients at various time points

Four trials, which included 335 patients, reported postoperative VAS scores at various time points (0–4 h, 4–8 h, 24 h, and 48 h), whereas three trials, which included 268 patients, reported VAS scores 12 h after surgery (Fig. 3). Significant heterogeneity was observed among the studies in the pooled analysis in the 24 h (P < 0.001, I² = 82%) and 48 h (P < 0.001, I² = 91%) groups. Besides the statistically insignificant results for the 0–4 h group (MD: 0.25 (CI: -0.11, 0.61), and I² = 0%)

https://doi.org/10.4097/kja.22730
postoperative patients who received DEX reported lower VAS scores than those who received opioids in the 4–8 h (MD: 0.61, 95% CI [0.45, 0.76], P < 0.001), 12 h (MD: 0.85, 95% CI [0.61, 1.09], P < 0.001), 24 h (MD: 0.59, 95% CI [0.06, 1.12], P = 0.030), and 48 h (MD: 0.54, 95% CI [0.05, 1.02], P = 0.030) groups. These results indicate that DEX can significantly prolong postoperative analgesia and reduce postoperative pain compared to opioids.

**Adverse effects**

In this section, we compare the incidence of adverse effects in postoperative patients, including hypotension, bradycardia, itching, urinary retention, nausea and vomiting, and shivering for DEX vs. opioids. Only one study [31] reported the incidence of dry mouth (DEX vs. fentanyl: 5/30 vs. 0/30).

**Hypotension**: Eight trials, which included 636 patients, reported the incidence of hypotension after the administration of DEX or opioids. A total of 320 patients received DEX for postoperative analgesia and 316 received opioids. Heterogeneity among the studies was significant in the pooled analysis (I² = 58%). The OR was 1.21 (95% CI [0.31, 4.81], P = 0.780), and the incidence of hypotension was comparable between the DEX and opioids.

---

**Table 1. Basic Features of Included Studies**

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Patients</th>
<th>Cases</th>
<th>Epidural catheter</th>
<th>Intervention</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mo 2017 [28]</td>
<td>Cesarean section</td>
<td>40/40</td>
<td>-</td>
<td>DEX 1 µg/kg + 0.15% ropivacaine</td>
<td>Loading dose: 5 ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Morphine 5 mg + 0.15% ropivacaine</td>
<td>Background dose: 2 ml/h; bolus dose: 0.5 ml</td>
</tr>
<tr>
<td>Zeng 2016 [29]</td>
<td>Colonic resection</td>
<td>34/33</td>
<td>T10-11</td>
<td>DEX 80 µg + 0.125% levobupivacaine</td>
<td>Loading dose: 3 ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Morphine 4.5 mg + 0.125% levobupivacaine</td>
<td>Background dose: 3 ml/h</td>
</tr>
<tr>
<td>Yan 2019 [27]</td>
<td>Elective lung lobectomy</td>
<td>64/64</td>
<td>T5-6</td>
<td>DEX 0.5 µg/ml + 0.1% ropivacaine</td>
<td>Loading dose: 4 ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sufentanil 0.5 µg/ml + 0.1% ropivacaine</td>
<td>Background dose: 4 ml/h; bolus dose: 4 ml</td>
</tr>
<tr>
<td>Prashanth 2021 [31]</td>
<td>Spine surgeries</td>
<td>30/30</td>
<td>L2-3/L3-4</td>
<td>DEX 1 µg/kg + 0.2% ropivacaine</td>
<td>Loading dose: 12 ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fentanyl 1 µg/kg + 0.2% ropivacaine</td>
<td>Background dose: 5 ml/h</td>
</tr>
<tr>
<td>Cheng 2019 part1 [25]</td>
<td>Full-term pregnancy</td>
<td>40/40</td>
<td>L3-4</td>
<td>DEX 0.5 µg/ml + 0.125% ropivacaine</td>
<td>Loading dose: 10 ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sufentanil 0.5 µg/ml + 0.125% ropivacaine</td>
<td>Background dose: 8 ml/h; bolus dose: 8 ml</td>
</tr>
<tr>
<td>Cheng 2019 part2 [25]</td>
<td>Full-term pregnancy</td>
<td>40/40</td>
<td>L3-4</td>
<td>DEX 0.5 µg/ml + 0.08% ropivacaine</td>
<td>Loading dose: 10 ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sufentanil 0.5 µg/ml + 0.08% ropivacaine</td>
<td>Background dose: 8 ml/h; bolus dose: 8 ml</td>
</tr>
<tr>
<td>Zhang 2019 [30]</td>
<td>Full-term pregnancy</td>
<td>36/34</td>
<td>L2-3</td>
<td>DEX 0.5 µg/ml + 0.1% ropivacaine</td>
<td>Loading dose: 10 ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sufentanil 0.5 µg/ml + 0.1% ropivacaine</td>
<td>Background dose: 6 ml/h; bolus dose: 6 ml</td>
</tr>
<tr>
<td>Li 2020 [26]</td>
<td>Full-term pregnancy</td>
<td>36/35</td>
<td>L2-3</td>
<td>DEX 0.5 µg/ml + 0.1% ropivacaine</td>
<td>Loading dose: 10 ml</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ropivacaine 0.1% + 0.5 µg/ml sufentanil</td>
<td>Background dose: 7 ml/h; bolus dose: 7 ml</td>
</tr>
</tbody>
</table>

DEX: dexmedetomidine.
opioid groups for postoperative analgesia (Fig. 4A).

**Bradycardia**: Eight trials, which included 636 patients, reported the incidence of bradycardia after the administration of DEX or opioids. A total of 320 patients received DEX for postoperative analgesia and 316 patients received opioids. Heterogeneity among the studies was significant in the pooled analysis ($P = 0.030, I^2 = 63\%$). The OR was 0.35 (95% CI [0.05, 2.25], $P = 0.270$), and the incidence of bradycardia was similar between the DEX and opioid groups for postoperative analgesia (Fig. 4B).

**Itching**: Seven trials, which included 576 patients, reported itching after the administration of DEX or opioids. A total of 290 patients received DEX for postoperative analgesia and 286 received opioids. Heterogeneity among the studies was similar between the DEX and opioid groups for postoperative analgesia (Fig. 4B).

**Urinary retention**: Three trials, which included 231 patients, reported the incidence of urinary retention after the administration of DEX or opioids. A total of 116 patients received DEX for postoperative analgesia and 115 received opioids. No significant heterogeneity was observed among the studies in the pooled analysis ($P = 0.170, I^2 = 43\%$). The OR was 2.02 (95% CI [0.87, 4.71], $P = 0.100$), and the incidence of urinary retention was similar between the DEX and opioid groups for postoperative analgesia (Fig. 4D).

**Nausea and vomiting**: Eight trials, which included 636 patients, reported the incidence of nausea and vomiting after the administration of DEX or opioids. A total of 320 patients received DEX for postoperative analgesia and 316 received opioids. No significant heterogeneity was observed among the studies in the pooled analysis ($P = 0.240, I^2 = 24\%$). The OR was 6.83 (95% CI [3.63, 12.84], $P < 0.001$), and the incidence of nausea and vomiting was significantly lower with DEX compared to opioids for postoperative analgesia (Fig. 4E).
### Table 2. GRADE Evidence Result Summary

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Opioid group Mean (SD)</th>
<th>DEX group Mean (SD)</th>
<th>MD/OR (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS score at 0–4 h</td>
<td>1.63 (1.29)</td>
<td>1.46 (1.10)</td>
<td>MD 0.13 [−0.02, 0.27]</td>
<td>335 (4 studies)</td>
<td>🟢🟢🟢🟢 Low</td>
<td>Most studies had at least one risk of bias domain rated as unclear; I² of 43%; serious imprecision (&lt; 400 sample size in total)</td>
</tr>
<tr>
<td>VAS score at 4–8 h</td>
<td>2.89 (1.60)</td>
<td>2.36 (1.17)</td>
<td>MD 0.61 [0.45, 0.76]</td>
<td>335 (4 studies)</td>
<td>🟢🟢🟢🟢 Low</td>
<td>Most studies had at least one risk of bias domain rated as unclear; I² of 0%; serious imprecision (&lt; 400 sample size in total)</td>
</tr>
<tr>
<td>VAS score at 12 h</td>
<td>4.56 (1.60)</td>
<td>3.70 (1.19)</td>
<td>MD 0.85 [0.61, 1.09]</td>
<td>268 (3 studies)</td>
<td>🟢🟢🟢🟢 Low</td>
<td>Most studies had at least one risk of bias domain rated as unclear; I² of 91%; serious imprecision (&lt; 400 sample size in total)</td>
</tr>
<tr>
<td>VAS score at 24 h</td>
<td>3.67 (2.05)</td>
<td>2.99 (1.52)</td>
<td>MD 0.59 [0.06, 1.12]</td>
<td>335 (4 studies)</td>
<td>🟢🟢🟢🟢 Very low</td>
<td>Most studies had at least one risk of bias domain rated as unclear; I² of 58%; very serious imprecision (&lt; 300 events in total, wide 95% CI encompassing appreciable benefit and harm)</td>
</tr>
<tr>
<td>VAS score at 48 h</td>
<td>3.22 (1.97)</td>
<td>2.62 (1.61)</td>
<td>MD 0.54 [0.05, 1.02]</td>
<td>335 (4 studies)</td>
<td>🟢🟢🟢🟢 Very low</td>
<td>Most studies had at least one risk of bias domain rated as unclear; I² of 91%; serious imprecision (&lt; 300 sample size in total)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>24/316</td>
<td>21/320</td>
<td>OR 1.21 [0.31, 4.81]</td>
<td>636 (7 studies)</td>
<td>🟢🟢🟢🟢 Very low</td>
<td>Most studies had at least one risk of bias domain rated as unclear; I² of 58%; very serious imprecision (&lt; 300 events in total, wide 95% CI encompassing appreciable benefit and harm)</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>12/316</td>
<td>19/320</td>
<td>OR 0.35 [0.05, 2.25]</td>
<td>636 (7 studies)</td>
<td>🟢🟢🟢🟢 Very low</td>
<td>Most studies had at least one risk of bias domain rated as unclear; I² of 63%; very serious imprecision (&lt; 300 events in total, wide 95% CI encompassing appreciable benefit and harm)</td>
</tr>
<tr>
<td>Itching</td>
<td>18/286</td>
<td>7/290</td>
<td>OR 2.86 [1.18, 6.95]</td>
<td>576 (6 studies)</td>
<td>🟢🟢🟢🟢 Low</td>
<td>Most studies had at least one risk of bias domain rated as unclear; I² of 43%; serious imprecision (&lt; 300 events in total)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>17/115</td>
<td>9/116</td>
<td>OR 2.02 [0.87, 4.71]</td>
<td>231 (2 studies)</td>
<td>🟢🟢🟢🟢 Moderate</td>
<td>I² of 43%; serious imprecision (&lt; 300 events in total)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>78/316</td>
<td>26/320</td>
<td>OR 6.83 [3.63, 12.84]</td>
<td>636 (7 studies)</td>
<td>🟢🟢🟢🟢 Low</td>
<td>Most studies had at least one risk of bias domain rated as unclear; I² of 24%; serious imprecision (&lt; 300 events in total)</td>
</tr>
<tr>
<td>Shivering</td>
<td>11/203</td>
<td>7/206</td>
<td>OR 1.57 [0.63, 3.95]</td>
<td>409 (5 studies)</td>
<td>🟢🟢🟢🟢 Very low</td>
<td>Most studies had at least one risk of bias domain rated as unclear; I² of 0%; serious imprecision (&lt; 300 events in total, wide 95% CI encompassing no effect and harm)</td>
</tr>
<tr>
<td>RSS score at 0–2 h</td>
<td>2.26 (0.73)</td>
<td>2.59 (0.71)</td>
<td>MD −0.35 [−0.58, −0.12]</td>
<td>268 (3 studies)</td>
<td>🟢🟢🟢🟢 Very low</td>
<td>Most studies had at least one risk of bias domain rated as unclear; I² of 60%; serious imprecision (&lt; 400 sample size in total)</td>
</tr>
<tr>
<td>RSS score at 2–6 h</td>
<td>2.14 (0.63)</td>
<td>2.37 (0.60)</td>
<td>MD −0.23 [−0.46, −0.00]</td>
<td>268 (3 studies)</td>
<td>🟢🟢🟢🟢 Very low</td>
<td>Most studies had at least one risk of bias domain rated as unclear; I² of 62%; serious imprecision (&lt; 400 sample size in total)</td>
</tr>
<tr>
<td>RSS score at 12 h</td>
<td>2.13 (1.28)</td>
<td>2.88 (1.67)</td>
<td>MD −0.79 [−0.91, −0.67]</td>
<td>268 (3 studies)</td>
<td>🟢🟢🟢🟢 Low</td>
<td>Most studies had at least one risk of bias domain rated as unclear; I² of 0%; serious imprecision (&lt; 400 sample size in total)</td>
</tr>
<tr>
<td>RSS score at 24 h</td>
<td>1.95 (0.86)</td>
<td>2.55 (0.70)</td>
<td>MD −0.60 [−0.96, −0.24]</td>
<td>268 (3 studies)</td>
<td>🟢🟢🟢🟢 Very low</td>
<td>Most studies had at least one risk of bias domain rated as unclear; I² of 83%; serious imprecision (&lt; 400 sample size in total)</td>
</tr>
<tr>
<td>RSS score at 48 h</td>
<td>1.62 (0.83)</td>
<td>1.98 (0.76)</td>
<td>MD −0.32 [−0.66, 0.01]</td>
<td>268 (3 studies)</td>
<td>🟢🟢🟢🟢 Very low</td>
<td>Most studies had at least one risk of bias domain rated as unclear; I² of 85%; serious imprecision (&lt; 400 sample size in total)</td>
</tr>
</tbody>
</table>

SD: standard deviation, MD: mean deviation, OR: odds ratios, GRADE: grading of recommendations assessment, development and evaluation, VAS: visual analogue scale, RSS: Ramsay sedation scale.
Fig. 3. Forest plot of VAS scores for postoperative patients at various time points. VAS scores at (A) 0–4 h, (B) 4–8 h, (C) 12 h, (D) 24 h, and (E) 48 h are shown. DEX: dexmedetomidine, SD: standard deviation, IV: inverse variance, VAS: visual analog scale.
<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>M–H, Random, 95% CI</th>
<th>Odds Ratio</th>
<th>M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prashanth 2021 [31]</td>
<td>2</td>
<td>30</td>
<td>10</td>
<td>30</td>
<td>22.0%</td>
<td>0.14 [0.33, 0.72]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Li 2020 [26]</td>
<td>0</td>
<td>35</td>
<td>1</td>
<td>36</td>
<td>11.5%</td>
<td>0.33 [0.01, 8.46]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yan 2019 [27]</td>
<td>1</td>
<td>64</td>
<td>1</td>
<td>64</td>
<td>13.7%</td>
<td>1.00 [0.06, 16.34]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheng 2019 part 1 [25]</td>
<td>5</td>
<td>40</td>
<td>0</td>
<td>40</td>
<td>13.0%</td>
<td>12.55 [0.67, 235.00]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheng 2019 part 2 [25]</td>
<td>4</td>
<td>40</td>
<td>0</td>
<td>40</td>
<td>12.3%</td>
<td>9.99 [0.52, 191.90]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zhang 2019 [26]</td>
<td>0</td>
<td>34</td>
<td>0</td>
<td>36</td>
<td>Not estimable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zeng 2016 [29]</td>
<td>12</td>
<td>33</td>
<td>9</td>
<td>34</td>
<td>26.8%</td>
<td>1.59 [0.56, 4.49]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mo 2017 [28]</td>
<td>0</td>
<td>40</td>
<td>0</td>
<td>40</td>
<td>Not estimable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>316</td>
<td>320</td>
<td>100.0%</td>
<td>1.21 [0.31, 4.81]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 1.55; Chi² = 11.92, df = 5 (P = 0.04); I² = 58%
Test for overall effect: Z = 0.28 (P = 0.78)

---

**Hypotension**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prashanth 2021 [31]</td>
<td>0</td>
<td>30</td>
<td>6</td>
<td>30</td>
<td>18.4%</td>
<td>0.06 [0.00, 1.15]</td>
</tr>
<tr>
<td>Li 2020 [26]</td>
<td>0</td>
<td>35</td>
<td>1</td>
<td>36</td>
<td>16.7%</td>
<td>0.33 [0.01, 8.46]</td>
</tr>
<tr>
<td>Yan 2019 [27]</td>
<td>0</td>
<td>64</td>
<td>0</td>
<td>64</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Cheng 2019 part 1 [25]</td>
<td>0</td>
<td>40</td>
<td>5</td>
<td>40</td>
<td>18.3%</td>
<td>0.08 [0.00, 1.49]</td>
</tr>
<tr>
<td>Cheng 2019 part 2 [25]</td>
<td>0</td>
<td>40</td>
<td>1</td>
<td>40</td>
<td>16.7%</td>
<td>0.33 [0.01, 8.22]</td>
</tr>
<tr>
<td>Zhang 2019 [30]</td>
<td>0</td>
<td>34</td>
<td>0</td>
<td>36</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Zeng 2016 [29]</td>
<td>12</td>
<td>33</td>
<td>6</td>
<td>34</td>
<td>29.3%</td>
<td>2.67 [0.86, 8.27]</td>
</tr>
<tr>
<td>Mo 2017 [28]</td>
<td>0</td>
<td>40</td>
<td>0</td>
<td>40</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>316</td>
<td>320</td>
<td>100.0%</td>
<td>0.35 [0.05, 2.25]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 2.69; Chi² = 10.84, df = 4 (P = 0.03); I² = 63%
Test for overall effect: Z = 1.11 (P = 0.27)

---

**Bradyarrhythmia**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>M–H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prashanth 2021 [31]</td>
<td>0</td>
<td>30</td>
<td>6</td>
<td>30</td>
<td>18.4%</td>
<td>0.06 [0.00, 1.15]</td>
</tr>
<tr>
<td>Li 2020 [26]</td>
<td>0</td>
<td>35</td>
<td>1</td>
<td>36</td>
<td>16.7%</td>
<td>0.33 [0.01, 8.46]</td>
</tr>
<tr>
<td>Yan 2019 [27]</td>
<td>0</td>
<td>64</td>
<td>0</td>
<td>64</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Cheng 2019 part 1 [25]</td>
<td>0</td>
<td>40</td>
<td>5</td>
<td>40</td>
<td>18.3%</td>
<td>0.08 [0.00, 1.49]</td>
</tr>
<tr>
<td>Cheng 2019 part 2 [25]</td>
<td>0</td>
<td>40</td>
<td>1</td>
<td>40</td>
<td>16.7%</td>
<td>0.33 [0.01, 8.22]</td>
</tr>
<tr>
<td>Zhang 2019 [30]</td>
<td>0</td>
<td>34</td>
<td>0</td>
<td>36</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Zeng 2016 [29]</td>
<td>12</td>
<td>33</td>
<td>6</td>
<td>34</td>
<td>29.3%</td>
<td>2.67 [0.86, 8.27]</td>
</tr>
<tr>
<td>Mo 2017 [28]</td>
<td>0</td>
<td>40</td>
<td>0</td>
<td>40</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>286</td>
<td>290</td>
<td>100.0%</td>
<td>2.86 [1.18, 6.95]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 8.00, df = 3 (P = 0.04); I² = 20%
Test for overall effect: Z = 2.32 (P = 0.02)

---

**Itching**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>M–H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li 2020 [26]</td>
<td>5</td>
<td>35</td>
<td>0</td>
<td>36</td>
<td>6.8%</td>
<td>13.16 [0.70, 247.69]</td>
</tr>
<tr>
<td>Yan 2019 [27]</td>
<td>0</td>
<td>64</td>
<td>0</td>
<td>64</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Cheng 2019 part 1 [25]</td>
<td>0</td>
<td>40</td>
<td>1</td>
<td>40</td>
<td>24.2%</td>
<td>0.33 [0.01, 8.22]</td>
</tr>
<tr>
<td>Cheng 2019 part 2 [25]</td>
<td>0</td>
<td>40</td>
<td>0</td>
<td>40</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Zhang 2019 [30]</td>
<td>1</td>
<td>34</td>
<td>0</td>
<td>36</td>
<td>7.6%</td>
<td>3.27 [0.13, 83.03]</td>
</tr>
<tr>
<td>Zeng 2016 [29]</td>
<td>12</td>
<td>33</td>
<td>6</td>
<td>34</td>
<td>61.4%</td>
<td>2.67 [0.86, 8.27]</td>
</tr>
<tr>
<td>Mo 2017 [28]</td>
<td>0</td>
<td>40</td>
<td>0</td>
<td>40</td>
<td>Not estimable</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>286</td>
<td>290</td>
<td>100.0%</td>
<td>2.86 [1.18, 6.95]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 2.80, df = 3 (P = 0.42); I² = 0%
Test for overall effect: Z = 2.32 (P = 0.02)

---

**Urinary Retention**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>M–H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li 2020 [26]</td>
<td>2</td>
<td>35</td>
<td>2</td>
<td>36</td>
<td>23.6%</td>
<td>1.03 [0.14, 7.75]</td>
</tr>
<tr>
<td>Cheng 2019 part 1 [25]</td>
<td>8</td>
<td>40</td>
<td>7</td>
<td>40</td>
<td>71.2%</td>
<td>1.18 [0.38, 3.63]</td>
</tr>
<tr>
<td>Cheng 2019 part 2 [25]</td>
<td>7</td>
<td>40</td>
<td>0</td>
<td>40</td>
<td>5.2%</td>
<td>18.13 [1.00, 329.27]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>115</td>
<td>116</td>
<td>100.0%</td>
<td>2.02 [0.87, 4.71]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 3.52, df = 2 (P = 0.17); I² = 43%
Test for overall effect: Z = 1.63 (P = 0.10)
Fig. 4. (Continued from the previous page) Forest plot comparing adverse effects between the DEX and opioid groups. (A) Hypotension, (B) bradycardia, (C) itching, (D) urinary retention, (E) nausea and vomiting, and (F) shivering. DEX: dexmedetomidine, M-H: Mantel-Haenszel.

**Shivering:** Five trials, which included 409 patients, reported shivering after the administration of DEX or opioids. A total of 206 patients received DEX for postoperative analgesia and 203 received opioids. Heterogeneity among the studies was not significant in the pooled analysis (P = 0.810, I² = 0%). The OR was 1.57 (95% CI [0.63, 3.95], P = 0.34), and the incidence of shivering was comparable between the DEX and opioid groups for postoperative analgesia (Fig. 4F).

**Secondary outcomes**

**Number of PCEA bolus doses**

Two trials, which included 199 patients, reported the number of PCEA bolus doses administered after the administration of DEX or opioids. A total of 99 patients received opioids and 100 received DEX. Heterogeneity among the studies was significant in the pooled analysis (P = 0.060, I² = 73%). The MD was 3.40 (95% CI [1.61, 5.19], P < 0.001), and the number of PCEA bolus doses was dramatically lower with DEX compared with opioids (Fig. 5A).

**Consumption of analgesics in PCEA**

Three trials, which included 269 patients, reported the consumption of analgesics in PCEA after the administration of DEX or opioids. A total of 133 patients received opioids and 136 received DEX. Heterogeneity among the studies was significant in the pooled analysis (P < 0.001, I² = 93%). The MD was 14.85 (95% CI [3.99, 25.71], P = 0.007), and the consumption of analgesics in PCEA was significantly lower with DEX than with opioids (Fig. 5B).

**RSS for postoperative patients at various time points**

Three trials, which included 268 postoperative patients, reported RSS scores at various time points after surgery (0–2 h, 2–6 h, 12 h, 24 h, and 48 h) (Fig. 6). Heterogeneity was observed among the studies in the pooled analysis of the 2–6 h (P = 0.070, I² = 62%), 24 h (P = 0.001, I² = 85%), and 48 h (P = 0.001, I² = 85%) groups. Statistically significant differences in the RSS scores were found between the postoperative patients who received opioids and those who received DEX in the 0–2 h (MD: −0.35, 95% CI [−0.58, −0.12], P = 0.003), 2–6 h (MD: −0.23, 95% CI [−0.46, −0.00], P = 0.050), 12 h (MD: −0.79, 95% CI [−0.91, −0.67], P <
The number of PCEA bolus

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li 2020 [26]</td>
<td>2.8</td>
<td>0.92</td>
<td>35</td>
<td>0.1</td>
<td>0.31</td>
<td>36</td>
<td>63.0%</td>
<td>2.70 [2.38, 3.05]</td>
<td></td>
</tr>
<tr>
<td>Yan 2019 [27]</td>
<td>7.65</td>
<td>6.83</td>
<td>64</td>
<td>3.06</td>
<td>3.79</td>
<td>64</td>
<td>37.0%</td>
<td>4.59 [2.68, 6.50]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>99</td>
<td>100</td>
<td>100.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.40 [1.61, 5.19]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 1.30; Chi² = 3.64, df = 1 (P = 0.06); I² = 73%
Test for overall effect: Z = 3.73 (P = 0.0002)

The consumption of analgesics in PCEA

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Li 2020 [26]</td>
<td>65.44</td>
<td>5.64</td>
<td>35</td>
<td>42.6</td>
<td>6.44</td>
<td>36</td>
<td>35.4%</td>
<td>22.84 [20.03, 25.65]</td>
<td></td>
</tr>
<tr>
<td>Yan 2019 [27]</td>
<td>228.4</td>
<td>21.5</td>
<td>64</td>
<td>213.8</td>
<td>19.6</td>
<td>64</td>
<td>31.3%</td>
<td>14.60 [7.47, 21.73]</td>
<td></td>
</tr>
<tr>
<td>Zhang 2019 [30]</td>
<td>78.1</td>
<td>10.5</td>
<td>34</td>
<td>71.5</td>
<td>12.2</td>
<td>36</td>
<td>33.3%</td>
<td>6.60 [1.28, 11.92]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>133</td>
<td>136</td>
<td>100.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14.85 [3.99, 25.71]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 84.73; Chi² = 29.43, df = 2 (P < 0.00001); I² = 93%
Test for overall effect: Z = 2.68 (P = 0.007)

Fig. 5. (A) Forest plot comparing the number of PCEA bolus doses and consumption of analgesics in PCEA between the DEX and opioid groups, (B) forest plot comparing the consumption of analgesics in PCEA between the DEX and opioid groups. DEX: dexmedetomidine, PCEA: patient-controlled epidural analgesia, IV: inverse variance.

0.001), and 24 h (MD: −0.60, 95% CI [−0.96, −0.24], P = 0.001) groups. In the 48 h group (MD: −0.32, 95% CI [−0.66, 0.01], P = 0.060), no significant difference in the RSS scores were found between the postoperative patients who received DEX compared to those who received opioids. Overall, our results showed that patients treated with DEX in the early postoperative period had significantly higher levels of sedation than those treated with opioids. However, no significant difference was found at 48 h postoperatively.

Neonatal and maternal outcomes in labor analgesia

Four trials, which included 301 patients, compared the effects of DEX vs. opioids on the duration of each labor stage for labor analgesia. Significant heterogeneity was observed among the studies in the pooled analysis for both labor stages (first labor stage, MD = 0.00 [95% CI [−0.02, 0.02], P = 0.70), and the pH of cord blood was similar between the DEX and opioid groups for labor analgesia (Fig. 7C).

Four trials, which included 301 patients, reported the pH of cord blood after the administration of DEX or opioids for labor analgesia. A total of 152 patients received DEX and 149 received opioids for labor analgesia. Heterogeneity among the studies was not significant in the pooled analysis (P = 0.59, I² = 0%). The MD was 0.00 (95% CI [−0.02, 0.02], P = 0.70), and the pH of neonatal blood was similar between the DEX and opioid groups for labor analgesia (Fig. 7D).

Three trials, which included 230 patients, reported the PaO₂ of cord blood. A total of 116 patients received DEX for labor analgesia and 114 received opioids. Significant heterogeneity was observed among the studies in the pooled analysis (P < 0.001, I² = 99%). The MD was −1.92 (95% CI [−5.84, 1.99], P = 0.34), and the PaO₂ of cord blood was similar between the DEX and opioid groups for labor analgesia (Fig. 7E).

Three trials, which included 230 patients, reported the incidence of fetal heart rate abnormalities after the administration of DEX or opioids for labor analgesia. A total of 116 patients received DEX for labor analgesia and 114 received opioids. No significant heterogeneity was observed among the studies in the pooled analysis (P = 0.59, I² = 0%). The OR was 1.21 (95% CI [0.39, 3.70], P = 0.74) and the incidence of fetal heart rate abnormalities was similar between the DEX and opioid groups for labor...
### Fig. 6

Forest plot of RSS scores for postoperative patients at various time points. RSS scores at (A) 0–2 h, (B) 2–6 h, (C) 12 h, (D) 24 h, and (E) 48 h are shown. RSS: Ramsay sedation scale, DEX: dexmedetomidine, SD: standard deviation, IV: inverse variance.
### The duration of the first labor stage

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Opioids</th>
<th>DEX</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study</td>
<td>Events</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Li 2020 [26]</td>
<td>396.11</td>
<td>14.56</td>
<td>35</td>
<td>347.93</td>
</tr>
<tr>
<td>Cheng 2019 part 1 [25]</td>
<td>118.2</td>
<td>37.2</td>
<td>40</td>
<td>114</td>
</tr>
<tr>
<td>Cheng 2019 part 2 [25]</td>
<td>117</td>
<td>36</td>
<td>40</td>
<td>108.6</td>
</tr>
<tr>
<td>Zhang 2019 [30]</td>
<td>406.5</td>
<td>58.2</td>
<td>34</td>
<td>378.5</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>149</strong></td>
<td>152</td>
<td>100.0%</td>
<td>22.48 [-4.07, 49.04]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 663.63$, $\chi^2 = 46.56$, $df = 3$ ($P < 0.00001$); $I^2 = 94$

Test for overall effect: $Z = 1.66$ ($P = 0.10$)

### The duration of the second labor stage

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Opioids</th>
<th>DEX</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study</td>
<td>Events</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Li 2020 [26]</td>
<td>30.59</td>
<td>7.67</td>
<td>35</td>
<td>52.54</td>
</tr>
<tr>
<td>Cheng 2019 part 1 [25]</td>
<td>52.2</td>
<td>11.4</td>
<td>40</td>
<td>49.2</td>
</tr>
<tr>
<td>Cheng 2019 part 2 [25]</td>
<td>51</td>
<td>10.8</td>
<td>40</td>
<td>47.4</td>
</tr>
<tr>
<td>Zhang 2019 [30]</td>
<td>40.3</td>
<td>6.7</td>
<td>34</td>
<td>38.6</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>149</strong></td>
<td>152</td>
<td>100.0%</td>
<td>-3.45 [-16.10, 9.21]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 163.12$, $\chi^2 = 151.32$, $df = 3$ ($P < 0.00001$); $I^2 = 98$

Test for overall effect: $Z = 0.53$ ($P = 0.59$)

### Mode of delivery

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Opioids</th>
<th>DEX</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study</td>
<td>Events</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Li 2020 [26]</td>
<td>7.21</td>
<td>0.08</td>
<td>35</td>
<td>7.21</td>
</tr>
<tr>
<td>Cheng 2019 part 1 [25]</td>
<td>6.28</td>
<td>0.61</td>
<td>40</td>
<td>6.34</td>
</tr>
<tr>
<td>Cheng 2019 part 2 [25]</td>
<td>6.2</td>
<td>0.59</td>
<td>40</td>
<td>6.19</td>
</tr>
<tr>
<td>Zhang 2019 [30]</td>
<td>7.23</td>
<td>0.07</td>
<td>34</td>
<td>7.22</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>149</strong></td>
<td>152</td>
<td>100.0%</td>
<td>0.00 [-0.02, 0.02]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.33$, $df = 3$ ($P = 0.95$); $I^2 = 0$

Test for overall effect: $Z = 0.78$ ($P = 0.44$)

### PH

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Opioids</th>
<th>DEX</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study</td>
<td>Events</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Cheng 2019 part 1 [25]</td>
<td>19.59</td>
<td>0.21</td>
<td>40</td>
<td>20.17</td>
</tr>
<tr>
<td>Cheng 2019 part 2 [25]</td>
<td>20.12</td>
<td>0.24</td>
<td>40</td>
<td>26.14</td>
</tr>
<tr>
<td>Zhang 2019 [30]</td>
<td>29.7</td>
<td>3.3</td>
<td>34</td>
<td>28.8</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>114</strong></td>
<td>116</td>
<td>100.0%</td>
<td>-1.92 [-5.84, 1.99]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 11.76$, $\chi^2 = 216.69$, $df = 2$ ($P < 0.00001$); $I^2 = 99$

Test for overall effect: $Z = 0.96$ ($P = 0.34$)

### PaO$_2$

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Opioids</th>
<th>DEX</th>
<th>Mean Difference</th>
<th>Mean Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study</td>
<td>Events</td>
<td>Total</td>
<td>Mean</td>
</tr>
<tr>
<td>Cheng 2019 part 1 [25]</td>
<td>19.59</td>
<td>0.21</td>
<td>40</td>
<td>20.17</td>
</tr>
<tr>
<td>Cheng 2019 part 2 [25]</td>
<td>20.12</td>
<td>0.24</td>
<td>40</td>
<td>26.14</td>
</tr>
<tr>
<td>Zhang 2019 [30]</td>
<td>29.7</td>
<td>3.3</td>
<td>34</td>
<td>28.8</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>114</strong></td>
<td>116</td>
<td>100.0%</td>
<td>-1.92 [-5.84, 1.99]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 11.76$, $\chi^2 = 216.69$, $df = 2$ ($P < 0.00001$); $I^2 = 99$

Test for overall effect: $Z = 0.96$ ($P = 0.34$)

Fig. 7. (Continued to the next page)
analgesia (Fig. 7F).

**Sensitivity and subgroup analyses**

Sensitivity and subgroup analyses were performed to minimize and identify the sources of heterogeneity. For some indicators, the heterogeneity was significantly reduced among the remaining studies after one study was removed (Table 3). For the VAS scores at 24 h postoperatively, RSS scores at various postoperative times (0–2 h, 2–6 h, 24 h, and 48 h), duration of the first labor stage, mode of delivery, and sensitivity analysis results using a fixed-effects model for pooling were consistent with previous results.

However, though the incidence of hypotension and bradycardia and the duration of the second labor stage were not significantly different between the opioid and DEX groups before the sensitivity analysis, after minimizing the heterogeneity, we concluded that a relatively higher incidence of bradycardia (OR: 2.27, 95% CI [1.05, 4.91], P = 0.04), lower incidence of hypotension (OR: 0.12, 95% CI [0.03, 0.54], P = 0.005), and relatively shorter second labor stage duration (MD: 2.44, 95% CI [0.39, 4.50], P = 0.02) were found in the DEX group compared with the opioid group. Furthermore, we performed a subgroup analysis of the incidence of hypotension and bradycardia based on whether PCEA was used for labor or postoperative analgesia. The results of this subgroup analysis were consistent with the previous unadjusted results. Therefore, we looked at these results dialectically. Unfortunately, even though we performed sensitivity and subgroup analyses, considerable heterogeneity remained for some of the results (VAS scores for postoperative patients at 48 h, PaO\textsubscript{2} of cord blood, etc.); thus, future high-quality studies with larger sample sizes are needed to further confirm these results. The efficacy of DEX vs. opioids in the PCEA is summarized in Table 4.

**Discussion**

This meta-analysis included seven studies, one of which (Cheng et al. [25]) contained two separate trials. The results of the present meta-analysis showed that DEX was superior to opio-
oids in terms of pain relief and the incidence of nausea and vomiting.

The VAS score is a critical parameter for evaluating the efficacy of potential analgesic therapies. This meta-analysis found that the addition of DEX resulted in lower VAS scores than the addition of opioids at 4–8 h, 12 h, and 48 h after surgery. One curious finding was that DEX was not significantly superior to opioids at reducing VAS scores in patients 0–4 h after surgery, which may be explained by the fact that researchers often administer the first dose of local anesthetics in the epidural space to expand the analgesic plane when linking the PCEA pump, thus masking the synergistic analgesic effect of the adjuvant considerably in the early postoperative period. The analgesic effects of DEX may be explained by several potential mechanisms. DEX opens the K⁺ channel on the cell membrane and strengthens the inhibitory effect of local anesthetics on the Na⁺ channel [32]. However, DEX can also inhibit the secretion of norepinephrine by the spinal cord, activate cholinergic nerves, and synergize with local anesthetics to enhance the analgesic effect [33]. In addition, DEX can induce local vasoconstriction by stimulating the Alpha-2 receptors of blood vessels, thereby delaying the absorption of local anesthetics and prolonging their duration [34]. In the meta-analysis, epidural DEX significantly reduced postoperative pain compared to opioids in terms of the VAS score; however, data on labor analgesia were not included, mainly because the time points for the VAS score evaluations in the included studies on labor analgesia varied and thus could not be integrated. In the study conducted by Zhang et al. [30], the progression of the cervical opening diameter was used as the observation point for the VAS score. Both Li et al. [26] and Cheng et al. [25] recorded VAS scores after anesthesia induction, but the observation time points were inconsistent. However, all included studies showed a tendency toward better pain control with DEX than with opioids for epidural labor analgesia. The results of the study conducted by Li et al. [26] demonstrated that the VAS scores were significantly lower in the DEX group than in the opioid group 10 min after epidural placement. Cheng et al. [25] showed the same results 15 min after anesthesia induction, and Zhang et al. [30] similarly showed lower VAS scores in the DEX group after cervical dilation > 3 cm. In a recently published meta-analysis [17] on epidural labor analgesia, the administration of DEX as a single shot or continuous infusion showed pain relief that was comparable with that of opioids. More high-quality research is needed in the future to draw clear conclusions on epidural labor analgesia.

The greatest concern with DEX administration in the epidural space is the potential for adverse effects, especially when used in PCEA because of its longer duration of action. DEX is associated with side effects such as hypotension, bradycardia, itching, dry mouth, shivering, nausea, and vomiting [35,36]. However, our analysis did not show a significantly higher risk of these side effects in the DEX group compared with the opioid group, except for dry mouth, though this is likely because an insufficient amount of studies reported the incidence of dry mouth. Furthermore, DEX significantly reduced the incidence of itching and nausea and vomiting compared with opioids. However, in our leave-one-out analysis, we found that the incidence of bradycardia was higher in the DEX group, whereas in the subgroup analysis of labor and postoperative analgesia, the incidence of bradycardia did not differ between the two groups. In another meta-analysis comparing DEX and placebo, Zhang et al. [15] found that the heart rate was lower in the DEX group; however, the incidence of bradycardia was not statistically significant. In conclusion, our results suggest that DEX is well-tolerated as an epidural adjuvant in PCEA and is superior to opioids in terms of the incidence of pruritus, nausea, and vomiting.

Our results indicate that DEX, when used as an adjuvant in PCEA, clearly increases the RSS scores in the early postoperative period. In studies comparing DEX with clonidine [37–39], DEX significantly improved the degree of sedation. Relevant studies have demonstrated that DEX can diffuse into the cerebrospinal...
fluid through the dura mater and combine with Alpha-2 adrenergic receptors in the blue nucleus of the brainstem to produce a sedative effect [40]. Moderately increased sedation can help reduce the patient’s stress response, reduce the body’s oxygen consumption, maintain hemodynamic stability, and reduce dependence on analgesics that depress respiration. However, excessive sedation may cause side effects such as hypotension, bradycardia, and respiratory depression. As the use of DEX may be complicated by its higher sedative effect, careful attention by physicians is imperative during its use. Moreover, the addition of DEX reduces the consumption of anesthetics and PCEA bolus doses, reflecting the superiority of its analgesic effect laterally. Furthermore, compared with opioids, epidural analgesia with DEX has no significant impact on the duration of the stages, mode of delivery, umbilical artery pH or PaO₂, or fetal heart rate. These findings are consistent with those of another previous study [17] that demonstrated that using DEX in epidural labor analgesia is safe for the fetus.

Previous meta-analyses have demonstrated that a single-shot injection of DEX into the subarachnoid or epidural space prolongs the duration of analgesia and decreases the requirement for rescue analgesia compared to placebo [15,16,18], opioids [41], or clonidine [42] in different surgical procedures. The most important difference between that study and the current meta-analysis is that the purpose of our study was to assess the safety and efficacy of continuous DEX infusions for epidural analgesia and thus, only studies involving continuous DEX infusions for epidural analgesia were included. Previous meta-analyses [17,41] have demonstrated that a single dose of DEX with epidural anesthesia significantly reduces the incidence of nausea and vomiting compared to opioids, which is consistent with our results. Qian et al. [41] found that, compared with epidural opioid administration, epidural DEX administration significantly reduces the incidence of shivering, though our results showed no significant difference. These authors also found that the incidence of dry mouth in the DEX group was significantly higher than that in the fentanyl group; however, the data from our included studies were insufficient to draw a definitive conclusion. In addition, the incidence of itching was significantly lower in the DEX group than in the opioid group in our study.

This meta-analysis has several limitations. First, data from the included studies were relatively insufficient. The VAS and RSS scores only included the postoperative analgesia population and may not be applicable for labor analgesia. Previous studies have reported that DEX may be associated with adverse effects, such as dry mouth and unstable hemodynamic changes. These results could not be synthesized or analyzed due to insufficient data in the studies included in this meta-analysis. Future studies should focus on these aspects. Second, this meta-analysis included studies using three different types of opioids (morphine, sufentanil, and fentanyl), which may have affected the results on pain relief and adverse events. Third, relatively high heterogeneity was found for some of our results, which may have resulted in bias; therefore, further research is required. The relatively high heterogeneity in this study may be explained by the different puncture segments among studies on epidural analgesia, different doses of DEX, and different PCEA parameter settings. Finally, DEX is a relatively new drug, particularly for epidural analgesia, and its long-term effects on the nervous system and maternal lactation are unknown. Therefore, suitable large-scale controlled trials to confirm these results are still necessary in the future.

In conclusion, the results of this meta-analysis showed that DEX is superior to opioids as a local anesthetic adjuvant in PCEA as DEX is associated with better pain relief and a lower incidence of nausea and vomiting and itching. However, some of the results of our meta-analysis should be interpreted with caution given the heterogeneity of the studies and insufficient data.

Funding

This study was supported by the Wu Jieping Medical Foundation (No. 320.6750.2020-21-12). The sponsor was not involved in the study design; collection, management, analysis, and interpretation of data; writing of the report; or decision to submit the report for publication.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Data Availability

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

Author Contributions

Yafen Gao (Writing – original draft)
Zhixian Chen (Data curation; Software; Supervision)
Yu Huang (Methodology; Validation)
Shujun Sun (Funding acquisition; Project administration)
Dong Yang (Supervision; Writing – review & editing)
Supplementary Material

Supplementary Material 1. Details of search strategy.

ORCID

Yafen Gao, https://orcid.org/0000-0001-5315-2073
Zhixian Chen, https://orcid.org/0000-0001-6998-961X
Yu Huang, https://orcid.org/0000-0003-2560-5674
Shujun Sun, https://orcid.org/0000-0002-4890-8785
Dong Yang, https://orcid.org/0000-0002-7377-5961

References

mean from the sample size, median, mid-range, and/or mid-quartile range. Stat Methods Med Res 2018; 27: 1785-1805.
29. Zeng XZ, Lu ZF, Lv XQ, Guo YP, Cui XG. Epidural co-administration of dexmedetomidine and levobupivacaine improves the gastrointestinal motility function after colonic resection in comparison to co-administration of morphine and levobupivacaine. PloS One 2016; 11: e0146215.
Comparison of the median and intermediate approaches to the ultrasound-guided sacral erector spinae plane block: a cadaveric and radiologic study

Bilge Olgun Keleş¹, Necati Salman², Elvan Tekir Yılmaz¹, Habip Resul Birinci¹, Alparslan Apan¹, Selami İnce³, Ali Faruk Özyaşar⁴, Aysun Uz⁵

¹Department of Anesthesiology and Reanimation, Giresun University Faculty of Medicine, Giresun, ²Department of Anatomy, University of Health Sciences Türkiye, Gülhane Faculty of Medicine, Ankara, ³Department of Radiology, Beytepe Murat Erdi Eker State Hospital, Ankara, ⁴Department of Anatomy, Karadeniz Technical University Faculty of Medicine, Trabzon, ⁵Department of Anatomy, Ankara University Faculty of Medicine, Ankara, Turkey

Background: Erector spinae plane block (ESPB) is a well-established method for managing postoperative and chronic pain. ESPB applications for the sacral area procedures are called sacral ESPBs (SESPBs). This cadaveric study aimed to determine the distribution of local anesthesia using the median and intermediate approaches to the SESPB.

Methods: Four cadavers were categorized into the median and intermediate approach groups. Ultrasound-guided SESPBs were performed using a mixture of radiopaque agents and dye. Following confirmation of the solution distribution through computed tomography (CT), the cadavers were dissected to observe the solution distribution.

Results: CT images of the median group demonstrated subcutaneous pooling of the radiopaque solution between the S1 and S5 horizontal planes. Radiopaque solution also passed from the sacral foramina to the anterior sacrum via the spinal nerves between S2 and S5. In the intermediate group, the solution distribution was observed along the bilateral erector spinae muscle between the L2 and S3 intervertebral levels; no anterior transition was detected. Dissection in the median group revealed blue solution distribution in subcutaneous tissue between horizontal planes S1 and S5, but no distribution in superficial fascia or muscle. In the intermediate group, red solution was detected in the erector spinae muscle between the L2 and S3 intervertebral levels.

Conclusions: Radiologic and anatomic findings revealed the presence of radiopaque dye in the superficial and erector spinae compartments in both the median and intermediate groups. However, anterior transition of the radiopaque dye was detected only in the median group.

Keywords: Cadaver; Conduction anesthesia; Dissection; Nerve block; Pain management; Regional anesthesia; Sacrococcygeal region.

Introduction

Postoperative pain is a common problem that necessitates resolution without complications. The erector spinae plane block (ESPB) is currently used as a perioperative analgesic and postoperative pain management technique. Plane blocks are gaining popularity...
over neuraxial techniques because of the low risk of severe side effects. The ESPB, first described by Forero [1] in 2016, is performed in patients experiencing chronic thoracic pain. Recent studies have demonstrated the effectiveness of ESPB in the thoracic and lumbar surgical areas [2]. ESPB is performed by applying a local anesthetic between the transverse process of the vertebra and the erector spinae muscle [2,3].

ESPB applications are named according to the vertebral level at which they are performed; for instance, blocks performed at the level of the sacral vertebrae are called sacral ESPBs (SESPBs). According to the current literature, the SESPB has been applied using two approaches. First, an intermediate approach was described by Tulgar et al. [4] in 2019 for postoperative analgesia in an adult patient who underwent pilonidal sinus surgery. In this approach, the SESPB technique involves placing the needle bilaterally on the intermediate crest. In the same year, Aksu and Gürkan [5] reported adequate postoperative analgesia in a pediatric patient who underwent hypospadias surgery using the median approach to the SESPB, from the median sacral crest. There are radiological, anatomical, or clinical studies of SESPB in the current literature, but there is no anatomical and radiological study comparing the two methods of SESPB [6–11]. The present cadaveric study aimed to determine the distribution of local anesthesia with the median and intermediate SESPB approaches. Radiological images and dissection results were compared to define the limits of distribution of the radiopaque solution.

Materials and Methods

A two-phase radiological and cadaveric study was performed. Ethics approval of this study was obtained from Karadeniz Technical University Faculty of Medicine with number: 2022/229 and the study protocol was registered on ClinicalTrials.gov (NCT05716061). After implementing the SESPB, the preliminary phase included radiological procedures, and the second phase included cadaveric dissections. Four embalmed cadavers (two female and two male; age at death: 68–89 years) were included in the study. None of the cadavers had a history of trauma or sacral surgery.

The cadavers were categorized into two groups, with one female and one male in each group, and the SESPB was performed by an experienced anesthesiologist using the two different approaches under ultrasound (USG) guidance.

For the median approach, a linear probe covered with a sheath was positioned longitudinally at the midline at the level of the L5 spinous process. The median crest of the sacrum was observed, and the probe was moved caudally to visualize the first and second median sacral crest tips and the erector spinae muscle. As described by Aksu and Gürkan, a 22-Gauge (G), 50-mm needle (Stimuplex Ultra360, B. Braun) was then inserted in the cranio-caudal direction using the in-plane technique until the tip of the needle touched the second sacral crest. After negative aspiration, 2 ml saline was injected, and the localization of the needle tip was confirmed using USG. Finally, 40 ml of a blue solution, including 4 ml methylene blue, 20 ml radiopaque dye (Iohexol, Kopaq 350 mg/1 ml, Koçsel), and 16 ml saline, was injected between the sacral crest and erector spinae muscle (Fig. 1A).

For the intermediate approach, first described by Tulgar et al. [4], the block was performed bilaterally (rather than unilaterally, as in the median approach). After the linear probe was covered with a sheath, the USG probe was placed longitudinally at the location exactly over the middle of the sacrum, and the second median crest was observed. The probe was then moved 1.5–2 cm laterally and placed over the second median crest of the sacrum. A
22-G, 50-mm needle was inserted in the caudocranial direction using the in-plane technique. Following negative aspiration, 2 ml saline was injected. USG confirmed the location of the needle tip, and 20 ml red solution was injected into the area between the median and intermediate crests under the erector spinae muscles (Fig. 1B). The same block was applied to the right side. A total of 40 ml of solution was administered to the cadavers (20 ml on each side). The 20 ml solution contained 2 ml red acrylic dye, 10 ml radiopaque dye (Iohexol, Kopaq 350 mg/1 ml, Koçsel), and 8 ml saline.

A different color dye was used for each technique to distinguish between the two methods of cadaveric imaging. Due to the cadaver’s rigidity, injecting the solution was challenging, and performing the block was more difficult than it had been in vivo. However, the procedure’s difficulty was consistent across both groups, regardless of the cadaver’s sex.

Within 30 min of injection, the cadavers were transferred to the Department of Radiology for computed tomography (CT) imaging. The scout view at 512 mm was used to obtain the scans, using a rotation time of 0.8 s, size collimation of 0.6 mm, 120 kv, and an effective current of 120–480 mA (GE Revolution EVO systems). Axial, coronal, and sagittal reconstructions were performed with 1.25-mm sections to evaluate the distribution of the contrast material. Radiological imaging was completed within 30 minutes of administration. The cadavers were then returned to the Department of Anatomy and dissected by experienced anatomists to examine the distribution of the solution through the tissue planes. In the median group, a superficial subcutaneous area was dissected between the L5 and S5 horizontal planes from the medial to the lateral side in accordance with the radiologic results, and the distribution of the blue solution was observed. In the intermediate group, the subcutaneous area between the horizontal planes of L2 and S2 was dissected in the same way as in the first group. Then, according to the radiologic results, the deep part of the erector spinae muscle group was also dissected, and the distribution of the red solution was observed.

Results

No differences were observed in the solution distribution between the male and female cadavers within each group. An experienced radiologist examined all the radiological results. The CT images were examined from the L1 horizontal level to the coccyx tip.

In the median group, CT images revealed subcutaneous pooling of radiopaque solution between the S1 and S5 horizontal planes. Additionally, passage of the radiopaque solution from the S2 to S5 levels through all the sacral foramina via the spinal nerves to the anterior aspect of the sacrum was observed (Figs. 2A–C). In the intermediate group, radiopaque solution distribution was observed along the bilateral erector spinae muscles between the L2 and S3 horizontal planes, and no anterior transition was detected (Figs. 3A–C).

Anatomic dissections were performed from the superficial to deep tissue planes in both groups. In the median group, the distribution of the blue solution was observed in a 15 (horizontal) × 18.5 (vertical)-cm subcutaneous tissue area between the S1 and S5 horizontal planes (Fig. 4). This area corresponds to the superficial tissue plane located between the skin and deep fascia of the back muscle group. The loose areolar tissue of the superficial compartment enabled the distribution of methylene blue solution over the deep fascia but not under the deep fascia or at the deep fascia covering the muscle plane.

In the intermediate group, as anticipated, the distribution of the red solution was not observed in the loose areolar tissue plane between the skin and deep fascia. After removing the loose areolar tissue, the deep fascia over the erector spinae was dissected. The muscle was then cut deeply in a vertical direction to observe the spread of the red solution. The red solution was detected cranially in the erector spinae muscle at the L2–L3 intervertebral levels but not at the horizontal L2 vertebral level (Fig. 5). Caudally, the red solution was detected in the muscle at the S2–S3 intervertebral levels but not under the horizontal S3 vertebral level. At both levels, the distribution of the red solution was limited within the deep fascia enclosing the anterior portion of the erector spinae. The enclosed area included the arteries, veins, nerve structures of the muscle, and erector spinae.

Dissection revealed that the skin and deep fascia were the two main anatomical structures restricting the spread of the injected radiopaque solution. Consequently, the anatomical dissection results are closely aligned with the radiologic results.

Discussion

The current body of literature includes radiological, anatomical, and clinical studies on SESPBs. In our cadaveric study, anatomical and radiological findings results regarding the distribution patterns of the radiopaque dye for the two SESPB procedures were compared. In this study, we analyzed the SESPB procedures described in the literature, using the highest volume of anesthetic agent reported to provide sufficient analgesia for both approaches to avoid any volume-based deficiency that could affect the distribution. Therefore, we administered a 40 ml radiopaque solution for both approaches.
With the median approach, the radiopaque solution spread only to the subcutaneous tissue, with no evidence of muscle involvement in the sacral region. A previous anatomical study conducted by Nanda et al. [12] also examined the SESPB using the median approach and failed to observe any dye spread in the deep tissue compartments, including the sacral foramina and nerves, similar to our observation.

In our study, this distribution could not be demonstrated anatomically, but the radiological distribution of radiopaque dye to the anterior region was shown, this distribution may be volume-dependent. While Nanda used 20 ml for the block, we used a dose of 40 ml.

In addition, our radiological results revealed that the radiopaque solution passed from the sacral foramen to the anterior sacrum via the spinal nerves between the S2 and S5 levels. Here, the radiopaque dye may have diffused through the superficial tissues and reached the foramen, then traveled via the sacral nerves to the anterior part of the sacrum. Radiological observation of this distribution is important and may explain the findings from studies that have demonstrated adequate analgesia from the median SESPB approach.

In a clinical study conducted by Kukreja et al. [10], postoperative analgesia was provided using the median SESPB approach in a sex reassignment surgery. Additionally, Aksu and Gürkan [5] and Öksüz et al. [7] applied the median approach at the S4 level in pediatric anorectal and urogenital surgeries, respectively, and reported successful postoperative analgesia. Based on our radiological results, we believe that the anterior passage of the radiopaque solution may explain the successful analgesic effect on the sensory field of the pudendal and obturator nerves.

According to the literature, ESPBs are performed bilaterally at all vertebral levels; however, sacral ESPBs have only two approaches. The intermediate SESPB method has also been applied bilaterally, similar to other ESPB approaches [1–4,6,9–11,13–16].
In the intermediate approach, the solution was administered to the erector spinae muscle, approximately 1–2 cm lateral to the median crest at the S2 level. Horizontal distribution of the dye longitudinally from the S3 to L2 level was observed. Similar to our study, previous anatomical and CT studies on thoracic and lumbar ESPBs have shown longitudinal spread of the dye, but not into the anterior passage [3,13,14]. Theoretically, the dorsal ramus of the spinal nerves in the erector spinae muscle compartment at all levels is involved due to vertical spread. However, dorsal ramus involvement alone cannot explain the analgesic efficacy observed in some clinical trials focusing on thoracic and lumbar regions; the involvement of the anterior passage or ventral ramus is also required.

Adhikary et al. [15] conducted a study on cadavers using magnetic resonance imaging after a thoracic ESPB and observed the distribution of the solution into the neural foramen and epidural space, confirming the anterior spread of the local anesthetic. In another cadaveric study evaluating ESPB at the level of the thoracic vertebrae, Bonvici et al. [16] revealed the diffusion of the dye ventrally into the intercostal spaces through the blood vessels connected to the nerve passing through the costotransverse foramen. In these two studies, unlike in our study, the anterior passage of the radiopaque solution in the thoracic region was demonstrated. Notably, the erector spinae muscle group is thinner in the thoracic region than in the sacral region, and it thickens as it descends. We evaluated the differences in the anterior passage of the radiopaque solution between the sacral and thoracic regions depending on the muscle thickness. Our findings suggested that in clinical studies comparing ESPBs, the vertebral level at which the block is applied should also be considered.

Diwan et al. [17] conducted a cadaveric study in which they performed SESPBs using an intermediate approach by placing a catheter and administering a continuous infusion of radiopaque solution. Dissection findings in their study revealed the presence of methylene blue above and below the sacral multifidus muscle. They also observed staining of the sacral foramen and sacral nerves, with methylene blue leaking from the dorsal surface of the sacral foramen into the sacral epidural space. They attributed the diffusion of methylene blue into the ventral and epidural spaces to the injection of a continuous and pressurized volume of solution through the catheter. Our study results differed from this study as we administered a single injection rather than a continuous infusion.
Mistry et al. [11] performed an intermediate-approach SESPB in sacral spine surgery and observed selective sensory loss in the L4–S3 dermatomes postoperatively. Piraccini et al. [8] performed a unilateral, intermediate-approach SESPB, administering 15 ml of radiopaque solution at the S1 level to a patient with radicular pain. The patient’s pain decreased after 20 minutes, according to a numerical rating scale, and he was able to stand and walk. Tulgar et al. [4] reported an intermediate SESPB in pilonidal sinus surgery that provided adequate postoperative analgesia. In another clinical study, Kaya et al. [6] achieved adequate analgesia using an intermediate SESPB in anorectal surgery. We believe that this analgesic efficacy could be attributed to the caudal–cranial spread of the solution between the erector spinae muscles and the involvement of the dorsal ramus of the spinal nerves in this region, as demonstrated in our study. This approach may provide adequate analgesia during surgeries involving the lower lumbar and sacral vertebrae, lumbar pain management, and orthopedic surgical interventions.

Tulgar described the administration of the erector spinae block at the sacral region for the first time in a letter and called it the “sacral erector spinae plane block.” In another letter published in 2020, Hamilton [18] explained that erector spinae muscle fibers are more superficial above the multifidus in the sacral region, and thus, the name should be changed to “sacral multifidus
Data Availability

Since my study is a cadaveric study, the data I have is presented in my article.

Author Contributions

Bilge Olgun Keleş (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing)

Necati Salman (Methodology; Project administration; Software; Visualization; Writing – original draft; Writing – review & editing)

Elvan Tekir Yılmaz (Data curation; Methodology; Project administration; Writing – review & editing)

Habip Resul Birinci (Data curation; Methodology; Resources)

Alparslan Apan (Methodology; Project administration; Writing – original draft; Writing – review & editing)

Selami İnce (Data curation; Methodology; Project administration; Writing – review & editing)

Ali Faruk Özyaşar (Data curation; Methodology; Project administration; Visualization)

Aysun Uz (Data curation; Methodology; Project administration)

ORCID

Bilge Olgun Keleş, https://orcid.org/0000-0002-8912-6317

Necati Salman, https://orcid.org/0000-0003-3927-8010

Elvan Tekir Yılmaz, https://orcid.org/0000-0001-8631-2520

Habip Resul Birinci, https://orcid.org/0000-0002-9221-4350

Alparslan Apan, https://orcid.org/0000-0001-9660-3276

Selami İnce, https://orcid.org/0000-0002-6611-4962

Ali Faruk Özyaşar, https://orcid.org/0000-0002-5396-9486

Aysun Uz, https://orcid.org/0000-0002-4005-5466

Funding

None.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

References


45: 640-4.
Comment on “Single-shot regional anesthesia for laparoscopic cholecystectomies: a systematic review and network meta-analysis”

Dear Editor,

I read with great interest the recently published systematic review and network meta-analysis [1] that assessed the efficacy of the single-shot regional anesthesia technique in laparoscopic cholecystectomy (LC). I greatly appreciate the authors’ efforts and wish to present my reflections on this article.

In the Introduction section, De Cassai et al. [1] state that “many meta-analyses evaluated different regional techniques for postoperative pain and analgesia requirements in LC” and cite a few references. However, one of the referenced studies (reference #12 of De Cassai et al. [1]) did not evaluate any regional techniques or postoperative pain. This study, which was conducted by Sedaghat et al. [2], only evaluated maternal and fetal complications in LC versus open cholecystectomies.

My primary concern, however, is that the number of studies included for each regional technique (i.e., the breakup) is not provided. Moreover, even for the primary outcome (postoperative opioid consumption), only 46 of the 84 eligible studies could be included. Because the breakup was not available and, as a consequence, the number of patients included for each regional technique may be highly variable, it is not clear whether a definitive conclusion can be drawn.

The different components of pain involved in LC are also not fully clarified in this study. De Cassai et al. [1] state in the Discussion section that both visceral and somatic components of pain may occur with LC, and the postoperative analgesia should be chosen accordingly. While I agree with this, De Cassai et al. [1] subsequently contradict this statement, suggesting that, based on previous studies, visceral pain is the most important contributor, and the results of this study regarding the rectus sheath block are therefore not surprising. However, if the unfavorable results are applicable to the rectus sheath block, then how the favorable results regarding the transverse abdominis plane block can be explained that also covers only the somatic pain like the rectus sheath block? The point is further confused given that De Cassai et al. [1] state exactly the opposite in the “Introduction” section, i.e., the “primary source of pain reported for LC is incisional.”

Additionally, I strongly believe that a major limitation of this meta-analysis is that shoulder pain, which is also an important component of pain after LC, was not included as an outcome. This is despite the fact that shoulder pain was assessed by many of the studies included in the meta-analysis. Shoulder pain occurs frequently following LC, with an incidence of 31%–80%. Although the intensity of pain is usually mild and only lasts for 1 to 2 days, in some patients it can cause more discomfort than incisional pain and can last longer, even up to a few weeks [3]. Trocar site infiltration or intraperitoneal instillation significantly reduces shoulder pain compared to controls [4].

In conclusion, I believe that somatic, visceral, and shoulder pain (triad) are important components of pain after LC and the regional technique used should therefore focus on all three factors.

Raghuraman M Sethuraman
Department of Anesthesiology, Sree Balaji Medical College & Hospital, Bharath Institute of Higher Education and Research, Chennai, India

Corresponding author: Raghuraman M Sethuraman, M.D. Department of Anesthesiology, Sree Balaji Medical College & Hospital, Bharath Institute of Higher Education and Research, #7, Works Road, New Colony, Chromepet, Chennai 600044, India
Tel: +91-6379141854 Fax: +91-044-4291 1000
Email: draghuram70@gmail.com; raghuraman.anaesth@bharathuniv.ac.in

Received: February 26, 2023; Revised: August 10, 2023; Accepted: August 13, 2023

Funding: None.

Conflicts of Interest: No potential conflict of interest relevant to this article was reported.

ORCID: Raghuraman M Sethuraman, https://orcid.org/0000-0001-8464-7458

References
Han scale and difficult facemask ventilation: time to add an “R”?

Recommendations for airway management have increasingly focused on the maintenance of oxygenation during airway instrumentation [1,2]. Facemask ventilation (FMV) plays a key role as a method of both routine and rescue ventilation in anesthesia [1,2] and critical care settings.

Various difficult airway management guidelines include FMV as a relevant item and emphasize its role in hypoxemia or other high-risk situations, including preoxygenation when airway access is challenging for physiological reasons. However, in-depth instructions on how to perform this technique properly or which maneuvers or adjuvant tools can be applied for optimization are not provided. Recommendations provided by the Difficult Airway Society (DAS) emphasize the importance of muscle relaxation (MR) for facilitating FMV and other airway-related maneuvers [1]. Additionally, the American Society of Anesthesiologists (ASA) recommendations highlight the importance of documenting the nature of difficulties in airway management to guide future care delivery [2]. Other guidelines for the management of tracheal intubation in critically ill adults also suggest MR be used for facilitating FMV.

No scales or individual risk factor have been shown to have sufficiently reliable capacity to predict difficult FMV, either alone or in combination [4]. However, routine clinical practice still relies on the global assessment of risk factors rather than the use of a specific tool (such as the Mallampati score for predicting difficult laryngoscopy). Moreover, as some of these risk factors, such as age and obesity, are not modifiable (at least in the short term), the actual risk of difficult FMV may be significantly overestimated. Hence, the history of difficult FMV in the patient’s medical record becomes a more powerful predictor of future situations; thus, accurate documentation is essential.

Among the available scales for grading technical difficulty in the clinical setting, the one proposed by Han et al. [5] is the most widely used. The Han scale is simple, reproducible, and practical, with each grade conveniently associated with relevant changes in clinical practice. Although subjective, scores will not underestimate the difficulty associated with, for instance, an inexperienced operator or the avoidance of adjuvant maneuvers. The scales proposed by Warters or by Lim-Nielsen have not gained comparable popularity in routine practice because of their complexity and the need for additional monitoring tools.

The easy adoption of the Han scale can partly be explained by its similarity to other “practical” airway-related scales, such as the Cormack-Lehane scale. The latter has undergone several modifications since it was first described. The most widely accepted modification has been the proposed split of Grade 2 into Grades 2a and 2b, which was suggested by Yentis and Lee in 1998. This modification provides additional information regarding the difficulty of intubation, as Grade 2a is associated with potential visualization of the tube passing through the glottis but Grade 2b is not. Various other proposed modifications have not been widely adopted by practitioners, as many are excessively complex and not sufficiently clinically relevant.

Additionally, no consensus regarding the appropriate timing of MR for FMV has been reached. The evidence does not tend to support the clinical practice of systematically checking for adequate FMV prior or to MR: the available evidence supports non-checkers more than checkers. Some evidence suggests that loss of muscle tone in the upper airway may lead to airway collapse, which could impair the ventilatory efficiency with FMV under MR in up to a quarter of patients [3]. However, the evidence in favor of “non-checkers” is more robust and recent, with data suggesting improvements in ventilatory capacity both in terms of the ability to facilitate vocal cord opening after induction and improvements in compliance. Additionally, the widespread availability of sugammadex has undoubtedly contributed to the increase in the “non-checker” group, as MR can be reversed rapidly and is thus considerably safer.

The widespread use of laryngeal masks may also have contributed to an increase in the proportion of FMV performed without MR, as the liberal use of relaxants is not warranted. Additionally, as no simple scale is available that provides information on the “relaxation condition” during FMV, it may be under-reported: even if muscle relaxants are not administered prior to FMV, MR is a recognized rescue maneuver recommended by clinical practice guidelines and thus its effect should be adequately recorded in the patient’s history if used [2].

Therefore, we would like to propose the use of a modified Han scale [5] or the “Han-R” scale (Fig. 1). For this proposed scale, the letter “R” is included immediately after the Han grade if ventilation was performed under MR. Consecutive reporting of the Han score in the absence and presence of MR is a simple way to report changes in facilitation of FMV when a state of adequate relaxation is reached. Therefore, a Han 3-2R score would represent a one-grade improvement in FMV difficulty once the muscle relaxant achieves a clinically relevant effect and a Han 2-2R score would represent no change in difficulty after MR. Additionally, a Han 2 score would mean that FMV was conducted without MR, while a Han 2R score would mean that FMV was conducted with MR. The proposed change is a simple way to include valuable information without complicating the format or information provided by the original scale. Splitting the intermediate grades could facilitate early decision-making regarding the use of adjuvants or inclusion of a second operator in subsequent airway approaches, especially in clinical situations with few resources. Furthermore, the proposal does not preclude the use of other scales that would provide information about the quality of the FMV. Finally, no additional effort in routine practice or specific monitoring tools are
required for the Han-R scale, making the potential adoption of this scale in day-to-day clinical practice simple and immediate.

In summary, specifying the relaxation status during FMV and any changes in difficulty using the modified Han or “Han-R” scale is a simple way to add important information analogous to specifying the use of BURP or other adjuvant maneuvers alongside the Cormack-Lehane grade in the patient’s medical record.

David Lopez-Lopez1, Adrian Garcia-Romar1, Patricia Neira-Somoza2, Pablo Casas-Reza1, Rocio Mato-Bua1

1Department of Anesthesiology, Perioperative Care and Pain Medicine, A Coruña University Hospital, 2Surgical and Perianesthesia Nursing, A Coruña University Hospital, A Coruña, Spain

Corresponding author: David Lopez-Lopez, M.D. Department of Anesthesiology, Perioperative Care and Pain Medicine, A Coruña University Hospital, As Xubias 84, 15006, A Coruña, Spain Tel: +34-981178000 Fax: +34-981178001 Email: david.lopez.lopez@sergas.es

Received: June 24, 2023; Revised: August 22, 2023 [1st]; October 5, 2023 [2nd]; October 19, 2023 [3rd]; Accepted: November 20, 2023

Funding: None.

Conflicts of Interest: No potential conflict of interest relevant to this article was reported.

Author Contributions: David Lopez-Lopez (Conceptualization; Investigation; Methodology; Validation; Writing – original draft; Writing – review & editing); Adrian Garcia-Romar (Conceptualization; Visualization; Writing – review & editing); Patricia Neira Somoza (Conceptualization; Methodology; Writing – review & editing); Pablo Casas-Reza (Supervision; Writing – review & editing); Rocio Mato-Bua (Conceptualization; Supervision)

ORCID: David Lopez-Lopez, https://orcid.org/0000-0003-4258-4510; Adrian Garcia-Romar, https://orcid.org/0000-0001-6875-013X; Patricia Neira-Somoza, https://orcid.org/0000-0003-0453-3691; Pablo Casas-Reza, https://orcid.org/0000-0002-2799-8523; Rocio Mato-Bua, https://orcid.org/0000-0002-0971-6991

References


Serratus posterior superior intercostal plane block: novel block for minimal invasive cardiac surgery - A report of three cases-

Median sternotomy is the standard approach for cardiac surgery (CS). However, conventional CS has some disadvantages such as severe pain, a long hospital stay, and cosmetic concerns. Minimally invasive cardiac surgery (MICS) is not associated with these disadvantages [1]. MICS facilitates earlier mobilization and faster postoperative recovery. Incision types for MICS include upper/lower hemisternotomy and right/left anterior minithoracotomy. An incision is made at the level of the second, third, or fourth intercostal space, with the
The serratus posterior superior intercostal plane block (SPSIPB) is a novel block that is performed between the serratus posterior superior (SPSm) and the intercostal (ICm) muscles [5]. As an example for thoracic analgesia, the SPSIPB has been used to provide analgesia after breast surgery [5]. Our aim here is to report on our experience with administering SPSIPBs for left-sided MICS in three patients. Written informed consent was obtained from all the patients.

The demographics of the patients were as follows: male aged 50 years (Patient 1), female aged 53 years (Patient 2), and female aged 47 years (Patient 3). The height/weight of the patients were 172 cm/75 kg, 168 cm/80 kg, and 160 cm/70 kg, respectively. At the end of surgery, each patient underwent an SPSIPB in the lateral decubitus position. A linear probe was placed near the medial border of the scapula and a 22-G, 80-mm block needle (Stimuplex Ultra 360°, B-Braun) was inserted between the third rib and the SPSm (Fig. 1). After correction, 30 ml of 0.25% bupivacaine was administered. Ibuprofen 400 mg and tramadol 100 mg were administered intravenously at the end of surgery. All patients were transferred to the cardiovascular intensive care unit (CVICU) after surgery and were attached to a patient-controlled analgesia (PCA) device containing tramadol (2 mg/ml, 10-mg bolus, 7 mg/h infusion, 20-min lockout, and 4 h). Patients were extubated 2 h after admission to the CVICU. 400 mg of ibuprofen was administered intravenously every 8 h. Pain was evaluated using the numerical rating scale (NRS) and the sedation level was assessed using a 4-point sedation scale during the NRS evaluation. The sedation level of all the patients was zero during assessments. The NRS scores at 2, 4, 8, 16, and 24 h were 1/1/3/2/0 for Patient 1, 1/1/2/1/0 for Patient 2, and 1/2/3/2/1 for Patients 3, respectively. The blockade lasted a maximum of 8 h. The posteroanterolateral dermatomal coverage (pin-prick test) was between C5-T8, C5-T7, and C6-T8 for each patient, respectively. The PCA dose administered to each patient was a 20-mg bolus.

The use of SAPBs in cardiothoracic surgery is a safe and effective option for postoperative pain [2]. The SAPB targets the lateral branches of the intercostal nerves. As these nerves receive sensory innervation from the anterolateral thorax, the SAPB only provides anterolateral hemithoracic analgesia. In contrast, the SPSIPB provides anteroposterior thoracic analgesia, as a recent report shows dye spreading from the C7 to the T7 ICm and nerves [5]. Based on the spread pattern, the SPSIPB may be a better choice than the SAPB for CS. However, the patient must be moved to the lateral decubitus position for the SPSIPB, while the SAPB can be performed after MICS without any positional changes. This can be a significant limitation for the use of SPSIPB in MICS. This position makes the paravertebral block (PVB) easier to perform than the SPSIPB. The PVB, however, is associated with a high risk of complications such as pneumothorax and vascular injury; thus the SPSIPB is safer than the PVB. The ESPB is effective for analgesia after CS. However, it was recently reported that ESPB was not associated with a significant reduction in pain after CS [3]. The TTMPB, which is performed between the transverse thoracic muscle and the ICm, provides effective analgesia management following CS; however, the area of block coverage is close to the blood vessels and pleura [4]. The PIFPB is performed between the pectoralis major muscle and the ICm [4]. However, the PIFPB fails to cover the T6 level. Both the TTMPB and PIFPB are close to the surgical area, and their effectiveness may be affected by the type of surgery.

In conclusion, we evaluated the efficacy of SPSIPB in patients who underwent MICS. SPSIPB provides effective analgesia management after MICS. A randomized controlled trial would be better suited to accurately judge the feasibility of the SPSIPB, rather than a case report.

Bora Bilal¹, Bahadir Ciftci², Selcuk Alver³, Ali Ahiskalioglu³, Serkan Tulgar⁴

---

*Fig. 1. Sonoanatomy and needle direction during serratus posterior superior intercostal plane block. The trapezius, rhomboid major, and serratus posterior superior muscles; second and third ribs; and the pleura are visible as anatomical landmarks. The needle is facing the cranio-caudal direction. The needle tip is visible just over the third rib.*
Comment on “The novel diagonal suprascapular canal block for shoulder surgery analgesia: a comprehensive technical report”

Dear Editor,

I read with keen interest a technical report published recently in the *Korean Journal of Anesthesiology* describing the “diagonal suprascapular canal (DiSC)” approach for the suprascapular nerve (SSN) block [1] and wish to present my reflections.

I believe strongly that a few points need to be considered before this technique is adopted for perioperative analgesia. First, providing the SSN block at the midpoint between the suprascapular and spinoglenoid notches to selectively target the lateral trunk of the SSN might be a better option for patients with chronic pain, as suggested previously by Tran et al. [2]. However, applying the same technique for “shoulder surgery analgesia,” as per the title of this technical report [1], might not be adequate because the medial trunk of the SSN, which provides sensory coverage predominantly to the anterior region of the shoulder [3], also contributes to pain in surgical procedures. Furthermore, a previous cadaveric study found anatomical variations such that the “posterior region received innervation from the proximal branch of the medial trunk in half of the specimens” [3].

The author states that for patients with respiratory compromise, the sub-omohyoid SSN block may not be considered because of the risk of phrenic nerve involvement as well as significant associated sensory and motor block of the upper limb [1]. However, this statement contradicts a point based on two published articles made earlier in the article that “the main advantage of this combined shoulder block compared with other techniques, such as the interscalene block, is the reduction in the motor and sensory block of the upper limbs and minimal phrenic paralysis” [1]. In addition, the sub-omohyoid approach was not used in the cadaveric study cited for phrenic nerve staining (Ref #5 of the technical report [1]); thus, the statement is not supported by that study. Indeed, that study [2] describes the SSN block at the midpoint between the suprascapular and spinoglenoid notches, similar to the technique described in this report [1]. Moreover, many clinical studies have shown that the sub-omohyoid SSN block does not compromise respiratory function, unlike the interscalene block, while the analgesic efficacy is similar. Because of the restriction of number of references, I will discuss two studies that specifically focus on this point [4,5]. Lim et al. [4] observed a significant reduction of forced vital capacity and diaphragmatic excursion in the interscalene block group when compared to the anterior and posterior SSN blocks. Notably, that study also found that pain relief was better with the anterior approach (sub-omohyoid plane at the supracla-

References

For the insights made by Almeida [1] on our previous article. The Diagonal Suprascapular Canal (DiSC) block has been described as a novel individualized anterior suprascapular nerve (SSN) block [1]. This tailored block is performed from a completely novel anterior entry point in the supine position. It is a step-forward block that allows the SSN to be blocked proximally at the level of the suprascapular notch, at the emergence of the medial and lateral trunk (midpoint of the suprascapular canal [SSC]), or even laterally at the level of the spinoglenoid notch. Anatomical variations in the divisions of the SSN should be considered whenever the block is performed distally (laterally [distally]) in the SSC. However, in most cases, the target of the DiSC block in the perioperative setting is the entry of the SSC. The block may also be administered at the SSC midpoint (or laterally/posteriorly) in specific cases such as isolated infraspinatus tendon rupture or infraspinatus fracture [1].

Siegenthaler et al. [2] evaluated the spread of local anesthetics after performing a supraclavicular SSN block using a sub-omohyoid approach. To the best of my knowledge, this is the only study of local anesthetic spread using the sub-omohyoid SSN block. The authors concluded that as the proximity of the SSN to both the brachial plexus in the sub-omohyoid region and to the pleura need to be critically considered, the sub-omohyoid approach should be regarded as an alternative to rather than a replacement for the classic posterior approach.

Further clinical studies, despite not observing the local anesthetic spread, have compared the sub-omohyoid SSN block with the interscalene nerve block or posterior SSN approach [3,4]. The sub-omohyoid SSN block results in a diminished forced vital capacity compared to baseline, though the impact is lower than with the interscalene block [4]. In contrast, another clinical study showed that in comparison to the posterior SSN block, the sub-omohyoid SSN
block provides an additional block of the axillary nerve, suggesting that for the sub-omohyoid approach, the local anesthetic may reach at least the superior or intermediate trunk or the posterior division of the brachial plexus, which confirms the results reported by Siegenthaler et al. [2].

Concerns regarding the novelty of the DiSC block are disconcerting. The DiSC block is a novel, potentially safer and simpler anterior approach that involves a diagonal view of the SSC through which the SSN travels [1]. The approach proposed by Tran et al. [5] cannot be performed using an anterior approach because the clavicle conflicts with the ultrasound beam, preventing correct visualization of the SSC during the puncture; thus, the needle is inserted at a posterior entry point in the anterior medial direction using ultrasound visualization that is completely different from that with the DiSC block.

To date, the sub-omohyoid SSN block has either been referred to as an anterior or supraclavicular SSN block. Given the introduction of this novel anterior approach, the term “anterior SSN block” cannot be used as a synonym for the sub-omohyoid SSN. Although anterior SSN block approaches have clear advantages, the sub-omohyoid SSN block is a less selective “anterior SSN block” than the DiSC block [3,4] and may be riskier. Therefore, although the sub-omohyoid SSN block may be the first option in most patients, it must be avoided in high-risk respiratory patients [3]. In conclusion the diagonal suprascapular block is a simple, more selective in some scenarios and a safer anterior SSN block.

Carlos Rodrigues Almeida
Department of Anesthesiology, Tondela-Viseu Hospital Center, Viseu, Portugal

Corresponding author: Carlos Rodrigues Almeida, M.D., D.E.S.A.
Department of Anesthesiology, Tondela-Viseu Hospital Center, Avenida Rei Dom Duarte, S/N, Viseu 3500-401, Portugal
Tel: +351-916851385 Fax: +351-232420500
Email: 6769@hstviseu.min-saude.pt

Received: September 22, 2023; Accepted: October 24, 2023

Funding: None.

Conflicts of Interest: No potential conflict of interest relevant to this article was reported.

ORCID: Carlos Rodrigues Almeida, https://orcid.org/0000-0001-6980-841X

References

https://doi.org/10.4097/kja.23700

Lipophilicity of drugs, including local anesthetics, and its association with lipid emulsion resuscitation

Local anesthetics are commonly used to provide pain relief during the peri-operative period. However, there is a risk of local anesthetic systemic toxicity (LAST) when these anesthetics are accidentally injected into the bloodstream or administered in excessive amounts. This can lead to cardiovascular depression and central nervous system symptoms, such as seizures. Currently, a treatment approach for LAST involves the use of lipid emulsion [1]. Lipid emulsion has also shown effectiveness in mitigating the cardiovascular depression caused by a toxic dose of non-local anesthetic drugs that have high lipid solubility [1]. The underlying mechanism associated with the use of lipid emulsion for treating drug toxicity is known as the ‘lipid shuttle’ [1]. This concept suggests that the lipid and surfactant components of the emulsion interact with drugs with high lipid solubility (defined by a log P value greater than 2) [1]. Subsequently, the lipid emulsion containing these lipid-soluble drugs, such as bupivacaine, is transported to the liver, muscle, and adipose tissue for detoxification and storage [1]. Furthermore, lipid emulsion can also alleviate severe vasodilation induced by a toxic dose of aminoamide local anesthetics, and the extent of this effect is dependent on the lipid solubility of the specific local anesthetic used (with bupivacaine having a higher log P value than ropivacaine and mepivacaine) [2]. Currently, the log P (or log P<sub>ow</sub>) value is widely used to indicate the lipophilicity of drugs, such as local anesthetics (log P [PubChem] values: bupivacaine = 3.41; ropivacaine = 2.9; lidocaine = 2.44; and mepivacaine = 1.95). Moreover, the octanol/water (o/w) partition coefficient is only a surrogate indicator regarding lipophilicity of drugs including local anesthetics that may be used as one of several factors to predict whether intractable cardiovascular collapse induced by a toxic dose of a drug
Table 1. Physiochemical Properties of Local Anesthetics

<table>
<thead>
<tr>
<th>Local anesthetic</th>
<th>Log P*</th>
<th>pKₐ †</th>
<th>Estimated log D[°] at pH 7.4</th>
<th>Estimated log D[°] at pH 7.1</th>
<th>Non-ionized fraction[°] (%) at pH 7.4</th>
<th>Non-ionized fraction[°] (%) at pH 7.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupivacaine</td>
<td>3.41</td>
<td>8.1</td>
<td>2.63</td>
<td>2.37</td>
<td>16.6</td>
<td>9.1</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>2.9</td>
<td>8.1</td>
<td>2.12</td>
<td>1.86</td>
<td>16.6</td>
<td>9.1</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>2.44</td>
<td>7.8</td>
<td>1.89</td>
<td>1.66</td>
<td>28.5</td>
<td>16.6</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td>1.95</td>
<td>7.9</td>
<td>1.47</td>
<td>1.25</td>
<td>33.4</td>
<td>20.1</td>
</tr>
<tr>
<td>Levobupivacaine</td>
<td>3.6</td>
<td>8.1</td>
<td>2.82</td>
<td>2.56</td>
<td>16.6</td>
<td>9.1</td>
</tr>
</tbody>
</table>


is well responsive to lipid emulsion resuscitation. However, the o/w partition coefficient is not the best indicator regarding lipophilicity for drugs undergoing lipid emulsion resuscitation because of following reasons: First, the o/w partition coefficient is a distribution ratio of the non-ionized form of drugs in the octanol and water phase [3]. However, since drugs, including local anesthetics, exist in both ionized and non-ionized forms in vivo, the use of the distribution coefficient (log D) becomes clinically more relevant for assessing the lipophilicity than log P [3]. Log D indicates the distribution ratio of both forms (ionized and non-ionized) of drugs between the octanol and water phases [3]. Log D is dependent on the acid dissociation constant (Kₐ) and the pH value of the surrounding medium [4]. Moreover, as a patient with severe hemodynamic depression or cardiac arrest due to LAST or drug toxicity of non-local anesthetics shows acidosis, which can affect the distribution coefficient [4]. Thus, the log D of weak bases such as local anesthetics (pKₐ 7.7 to 8.1) is estimated using the following equation: log D = log K₀ + log Kₐ – log (Kₐ + 10⁻P) where K₀ is the logarithm of the o/w distribution ratio of the compound, and log Kₐ is the logarithm of the acid dissociation constant (Kₐ) of the compound. The pKₐ is the negative logarithm of the acid dissociation constant (Kₐ) when the ionized and non-ionized forms of the drug exist in the solution at equal amounts (50%). For example, the non-ionized form of bupivacaine at pH 7.4 is only 16.6% of the total concentration of bupivacaine, calculated using the Henderson-Hasselbalch equation: pH = pKₐ + log([A⁻]/[HA]), where A⁻ is the concentration of the conjugate base and HA the concentration of the acidic form of the compound. Therefore, the log P is not a good indicator to evaluate the lipophilicity of local anesthetics because the log P value considers the distribution ratio of only 16.6% non-ionized form of bupivacaine in the octanol and water phase (Table 1). Furthermore, acidosis at pH 7.1 that is commonly observed in patients undergoing lipid emulsion resuscitation for LAST or drug toxicity of non-local anesthetics further reduces the non-ionized form of bupivacaine to 9.1% (Table 1). The log D of local anesthetics is lower than log P because the ionized molecules of the local anesthetics are mainly distributed in the water phase (Table 1) [3]. The order of log P of local anesthetics is similar to that of log D of local anesthetics (Table 1). However, log P of bupivacaine that reflects only the non-ionized form of bupivacaine is 3.41 (Table 1), but the (calculated) estimated log D of bupivacaine that reflects all forms (ionized and non-ionized) of bupivacaine is decreased to 2.63 (Table 1). Second, in the clinical practice using lipid emulsion resuscitation for LAST or drug toxicity, the lipid to water distribution ratio of drugs including local anesthetics that indicates the distribution ratio of both forms (ionized and non-ionized forms of local anesthetics) in the lipid and water phase has more clinical relevance than octanol to water distribution ratio because octanol is different from lipid. Thus, although the order of log P in the local anesthetics is similar to that of log D, further studies to compare the distribution ratio of drugs including local anesthetics in lipid and water phases with that in octanol and water phase are needed [5].

Susanne K Wiedmer¹, Ju-Tae Sohn²,3

¹Department of Chemistry, University of Helsinki, Helsinki, Finland
²Department of Anesthesiology and Pain Medicine, Gyegosang National University Hospital, Gyegosang National University College of Medicine, ³Institute of Medical Science, Gyegosang National University, Jinju, Korea

Corresponding author: Ju-Tae Sohn, M.D.
Department of Anesthesiology and Pain Medicine, Gyegosang National University Hospital, 79 Gangnam-ro, Jinju 52727, Korea
Tel: +82-55-750-8586 Fax: +82-55-750-8142
Email: jtsohn@gnu.ac.kr

Received: November 11, 2023; Revised: November 29, 2023; Accepted: November 29, 2023

Funding: None.
Conflicts of Interest: No potential conflict of interest relevant to this article was reported.
Author Contributions: Susanne K Wiedmer (Conceptualization; Data curation; Validation; Writing – review & editing); Ju-Tae Sohn (Conceptualization; Data curation; Project administration; Writing – original draft; Writing – review & editing)
ORCID: Susanne K Wiedmer, https://orcid.org/0000-0002-3097-6165;
References


Korean J Anesthesiol 2024;77(1):170-172
https://doi.org/10.4097/kja.23825

Online access in http://ekja.org
Notice

The Korean Society of Anesthesiologists
Editorial Board / Tel: +82-2-792-5128 / Fax: +82-2-792-4089 / Email: journal@anesthesia.or.kr

1. On-line manuscript review process

1) All proposed manuscripts for publication in the Korean Journal of Anesthesiology will be processed exclusively online. Please use the "Questions and Answers” section of our website (http://www.editorialmanager.com/kja) for any concerns you may have vis-à-vis problems, questions, or suggestions for improvement. You may also direct them to the attention of the electronic manuscripts processing manager (editorial manager) (M2PI, +82-2-6966-4930).

2) Processing publication-related inquiries for newly submitted manuscripts through the main number of the KJA would cause undue burden for the KJA in its general duties. As such, these inquiries should be made entirely online in the “Questions & Answers” section of the website. Requests and orders - including the expected date of publication and the status of manuscript under review - should be made online, and responses shall be provided without delay upon confirmation.

2. Information and regulation for submitting manuscripts

1) The corresponding author will be notified by e-mail whenever there is any change in the status of a submitted manuscript. Authors could also obtain this information directly through the website. The KJA will respond to all review inquiries. However, the expected Volume and Number cannot be provided, if it has not yet been confirmed; as such, we would not be able to entertain inquiries on this matter.

2) Doctoral and Master’s dissertations should abide by the manuscript submission guidelines of the KJA and should accompany a scanned file of the thesis title and the signature(s) of the examiner(s). This information should be entered in the “Paper Information” section during the online submission process.

3) The corresponding author should be a faculty. The corresponding author will be notified by e-mail whenever there is any change in the status of a submitted manuscript, and any resubmission can only be made by the corresponding author.

4) A manuscript needs to be resubmitted if there is a change in the makeup of the manuscript authorship; thus, special care should be taken when registering authors.

5) Manuscript review is terminated after two reviews, but a member of the review committee may request for a 3rd review.
Author’s checklist

Before submitting your manuscript to KJA, please read in detail the part of manuscript preparation of author information in journal homepage to make sure that your manuscript is correctly described based upon the journal style.

Title page
☐ Please check that author names and affiliations are correct. Also, corresponding author details (including email address) should be included in the title page.

Abstract
☐ Please make sure that the results shown in the abstract are the same in the results section of the manuscript and in the table or figure.
☐ Please check the number of keywords. Six or more keywords are recommended.

Main text
☐ Please ensure that the aim or hypothesis of this manuscript is described in the introduction section.
☐ Please check the description about written informed consent and IRB approval for a clinical human study in the methods section.
☐ Please check that primary and secondary outcome measurements are properly described in the methods section.
☐ Please check that there is a description about sample size calculation in the methods section.
☐ Please ensure that appropriate statistical analysis is used for comparison of variables.
☐ Please draw a CONSORT diagram in a randomized controlled study as you can as possible.
☐ Please ensure that the number of patients included in the statistical analysis is the same in the results section of the manuscript.
☐ Please check that the table contents are identically described in the results section of the manuscript.
☐ Please check that the conclusions of the manuscript are appropriately described based upon results.
☐ Please check that references cited are appropriate and correctly formatted as the KJA style.

Tables and figures
☐ Please describe p value with three decimal places and express the unit corresponding to the variable in tables.
☐ Please supply high-resolution figures suitable for print production.
☐ Please check that there are explanations about abbreviations and marks in table and figure legends.

Online access in http://ekja.org
Instructions to authors

Enacted March 24, 1995
Recently revised (28th) December 1, 2023

The Korean Journal of Anesthesiology (KJA) is an international, English-language, open-access, and peer-reviewed journal for anesthesiology, critical care, and pain medicine. As an official scientific journal of the Korean Society of Anesthesiologists (KSA), the KJA published monthly until 2014 and now publish bimonthly in 2015 (on the first day of February, April, June, August, October, and December). Its abbreviated title is “Korean J Anesthesiol.” The KJA publishes definitive articles that can improve clinical care or guide further research in the field of anesthesiology. Additionally, KJA gladly reviews and publishes negative results for which publication will benefit clinical practice and promote further research activity. Manuscripts for submission to the KJA should be written according to the following policies. The KJA follows the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication, available at: www.icmje.org/, if otherwise not described below.

Editorial Policy

The Editor assumes that all authors listed in a manuscript have agreed with the following policy of the KJA on submission of manuscript. Except for the negotiated secondary publication, manuscript submitted to the KJA must be previously unpublished and not be under consideration for publication elsewhere. Under any circumstances, the identities of the referees will not be revealed. If a new author should be added or an author should be deleted after the submission, it is the responsibility of the corresponding author to ensure that the author concerned are aware of and agree to the change in authorship. The KJA has no responsibility for such changes. Minimum publication charges and additional fee for reprints will due on every manuscript. Color illustrations are charged to the authors. All published manuscripts become the permanent property of the KSA and may not be published elsewhere without written permission.

General information

1. Publication types
   The KJA focuses on Original articles (Clinical trial/Experimental research, Meta-analysis), Case reports, Reviews, Letters to the editor, Statistical round, and Editorials.

2. Language
   Manuscripts submitted to the KJA should be compiled in English. Spellings should abide by American spellings. Medical terminology should be written based on the most recent edition of Dorland’s Illustrated Medical Dictionary. Accepted manuscripts are requested to be proofread by professional English editors.

3. Submission of manuscript
   In addition to members of the KSA, any researcher throughout the world can submit a manuscript if the scope of the manuscript is appropriate. Authors are requested to submit their papers electronically by using the online manuscript submission system, available at: https://www.editorialmanager.com/kja/default.aspx. Authors, reviewers, and editors send and receive all correspondences through this system.

4. Peer review process
   Under any circumstances, the identities of the reviewers will not be revealed and the reviewers will be blinded to the names of the authors and the institutions from which the manuscripts have been sent. Submitted manuscripts will be reviewed by 2 or more experts in the corresponding field. The Editorial Board may request authors to revise the manuscripts according to the reviewer's opinion. After revising the manuscript, the author should upload the revised files with a reply to each item of the reviewer's opinion. The author's revisions should be completed within 30 days after the request. If it is not received by the due date, the Editorial Board will not consider it for publication again. To extend the revision period to more than 30 days, the author should negotiate with the Editorial Board. The manuscript review process should be finished the second review. If the authors wish further review, the Editorial Board may consider it. The Editorial Board will make a final decision on the approval for publication of the submitted manuscripts and can request any further corrections, revisions, and deletions of the article text if necessary. Statistical editing is also performed if the data need professional statistical review by a statistician. The review and publication processes that are not described in the Instructions for Authors will be incorporated into the Editorial Policy Statements approved by the Council of Science Ed-

Online access in http://ekja.org
5. Article processing charge and publication fee
There is no charge for submitting and processing a paper until policy change. But, the KJA charges a publication fee for each printed page of KRW. Publication fees are waived if the affiliation of corresponding author is outside Korea.

6. Copyrights
Copyrights of all published materials are owned by the KSA. On behalf of co-author(s), corresponding author must complete and submit the journal’s copyright transfer agreement, which includes a section on the disclosure of potential conflicts of interest based on the recommendations of the International Committee of Medical Journal Editors, “Uniform Requirements for Manuscripts Submitted to Biomedical Journals” (http://www.icmje.org/recommendations/). A copy of the form (https://ekja.org/authors/copyright_transfer_agreement.php) is made available to the submitting author within the Editorial Manager submission process.

7. Open access
KJA is an open access journal. Accepted peer-reviewed articles are freely available on the journal website for any user, worldwide, immediately upon publication without additional charge. Articles are distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0/) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited. To use the tables or figures of KJA in other periodicals, books or media for scholarly, educational purposes, the process of permission request to the publisher of KJA is not necessary. This is in accordance with the Budapest Open Access Initiative definition of open access. It also follows the open access policy of PubMed Central at United States National Library of Medicine (http://www.ncbi.nlm.nih.gov/pmc/). All the content of the journal is available immediately upon publication without embargo period.

Research and publication ethics
For the policies on research and publication ethics that are not stated in these instructions, the Good Publication Practice Guidelines for Medical Journals, available at: https://www.camje.or.kr/board/view?b_name=bo_publication&bo_id=13, or the Guide-lines on Good Publication, available at: publicationethics.org/, can be applied.

1. Conflict-of-interest statement
Conflict of interest exists when an author or the author’s institution, reviewer, or editor has financial or personal relationships that inappropriately influence or bias his or her actions. Such relationships are also known as dual commitments, competing interests, or competing loyalties. These relationships vary from being negligible to having a great potential for influencing judgment. Not all relationships represent true conflict of interest. On the other hand, the potential for conflict of interest can exist regardless of whether an individual believes that the relationship affects his or her scientific judgment. Financial relationships such as employment, consultancies, stock ownership, honoraria, and paid expert testimony are the most easily identifiable conflicts of interest and the most likely to undermine the credibility of the journal, the authors, or of the science itself. Conflicts can occur for other reasons as well, such as personal relationships, academic competition, and intellectual passion (http://www.icmje.org/conflicts-of-interest/). If there are any conflicts of interest, authors should disclose them in the manuscript. The conflicts of interest may occur during the research process as well; however, it is important to provide disclosure. If there is a disclosure, editors, reviewers, and reader can approach the manuscript after understanding the situation and the background of the completed research.

2. Statement of informed consent and Institutional Review Board approval
If the study in the article is on human subjects or human-originated material, informed consent for the study and the Institutional Review Board (IRB) approval number needs to be provided. Copies of written informed consents and IRB approval for clinical research should be kept. If necessary, the editor or reviewers may request copies of these documents to make potential ethical issues clear.

3. Statement of human and animal right
Clinical research should be done in accordance of the Ethical Principles for Medical Research Involving Human Subjects, outlined in the Helsinki Declaration of 1975 (revised 2013) (available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). Authors should indicate whether the procedures were conducted in accordance with the Helsinki Declaration-2013 in the Text. Clinical studies that do not meet
the Helsinki Declaration will not be considered for publication. Human subjects should not be identifiable, such that patients’ names, initials, hospital numbers, dates of birth, or other protected healthcare information should not be disclosed. For animal subjects, research should be performed based on the National or Institutional Guide for the Care and Use of Laboratory Animals, and the ethical treatment of all experimental animals should be maintained.

4. Registration of the clinical trial research
Any researches that deals with clinical trial should be registered with the primary national clinical trial registration site such as Korea Clinical Research Information Service (cris.nih.go.kr/) or other sites accredited by WHO or International Committee of Medical Journal Editor such as ClinicalTrials.gov (clinicaltrials.gov/).

5. Reporting guidelines
The KJA recommends a submitted manuscript to follow reporting guidelines appropriate for various study types. Good sources for reporting guidelines are the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Network (www.equator-network.org/) and the U.S. National Library of Medicine's (NLM's) Research Reporting Guidelines and Initiatives (www.nlm.nih.gov/services/research_report_guide.html). The appropriate checklist (and flow diagram, if applicable) must be included with each submission.

6. Authorship
Authorship credit should be based on: 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; AND 2) drafting the article or revising it critically for important intellectual content; AND 3) final approval of the version to be published; AND 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet these 4 conditions. If the number of authors is equal to or greater than 2, there should be a list of each author’s role in the submitted paper. Authors are obliged to participate in peer review process. All others who contributed to the work who are not authors should be named in the Acknowledgements section. KJA has a strict policy on changes to authorship after acceptance of the article and will only consider changes in the most extraordinary situations once the article is accepted.

7. Plagiarism and duplicate publication
Plagiarism is the use of previously published material without attribution. The KJA editorial office screens all submitted manuscripts for plagiarism, using a sophisticated software program, prior to peer review. When plagiarism is detected at any time before publication, the KJA editorial office will take appropriate action as directed by the standards set forth by the Committee on Publication Ethics (COPE). For additional information, please visit http://www.publicationethics.org. It is mandatory for all authors to resolve any copyright issues when citing a figure or table from a different journal that is not open access.

8. Secondary publication
It is possible to republish manuscripts if the manuscripts satisfy the condition of secondary publication of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, available at: www.icmje.org/.

9. Feedback after publication
If the authors or readers find any errors, or contents that should be revised, it can be requested from the Editorial Board. The Editorial Board may consider erratum, corrigendum or a retraction. If there are any revisions to the article, there will be a CrossMark description to announce the final draft. If there is a reader’s opinion on the published article with the form of Letter to the editor, it will be forwarded to the authors. The authors can reply to the reader’s letter. Letter to the editor and the author’s reply may be also published.

9-1. Process to manage the research and publication misconduct
When the Journal faces suspected cases of research and publication misconduct such as a redundant (duplicate) publication, plagiarism, fabricated data, changes in authorship, undisclosed conflicts of interest, an ethical problem discovered with the submitted manuscript, a reviewer who has appropriated an author’s idea or data, complaints against editors, and other issues, the resolving process will follow the flowchart provided by the Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts). The Editorial Board of KJA will discuss the suspected cases and reach a decision. KJA will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

9-2. Policy of Article withdrawal, retraction, and replacement
1) Article withdrawal
Articles in Press (articles that have been accepted for publication but which have not been formally published and will not yet have the complete volume/issue/page information) that include errors, or are discovered to be accidental duplicates of
other published article(s), or are determined to violate our journal publishing ethics guidelines in the view of the editors (such as multiple submission, bogus claims of authorship, plagiarism, fraudulent use of data or the like), may be “Withdrawn”.  
2) Article retraction  
Errors serious enough to invalidate a paper’s results and conclusions (Infringements of professional ethical codes, such as multiple submission, bogus claims of authorship, plagiarism, fraudulent use of data or the like) may require retraction.  
3) Article replacement  
Replacement (retraction with republication) can be considered in cases where honest error (e.g., a misclassification or miscalculation) leads to a major change in the direction or significance of the results, interpretations, and conclusions. If the error is judged to be unintentional, the underlying science appears valid, and the changed version of the paper survives further review and editorial scrutiny, then replacement of the changed paper, with an explanation, allows full correction of the scientific literature.  
See also the National Library of Medicine’s policy on retractions and the recommendations of the International Committee of Medical Journal Editors (ICMJE) concerning corrections and retractions, or https://publicationethics.org/resources/guidelines.  
9-3. Appeals and complaints  
KJA adheres to COPE guidelines regarding appeals to editorial decisions and complaints. For additional information, please visit https://publicationethics.org/core-practices.  

Data sharing statement  

Submitting manuscripts in preprint archives  
A preprint is a preliminary version of a scientific article that is posted online at publicly accessible repositories before undergoing a formal peer review in a traditional academic journal.  
Authors are encouraged to submit the final versions of their preprints to KJA without treating them as duplicate submissions or publications. During the manuscript submission process, authors should disclose the preprint’s DOI to exclude it from the estimation of the similarity index for the final manuscript. We will conceal the preprint’s DOI to blind peer reviewers to the authors’ list. Any differences between the authors’ list of the final manuscript submitted to KJA and the preprint should be minimal and will require a thorough explanation. After acceptance for publication, authors will be asked to update the meta-information of the preprint to point to the DOI of the final published article in KJA.  
Articles published without peer review, including preprints, abstracts of conferences, and American Society of Anesthesiologists (ASA) refresher course lectures, may not be included in the references.  

Manuscript preparation  
1. Word processors and format of manuscript  
A manuscript must be written in proper and clear English. The manuscript, including tables and their footnotes, and figure legends, must be typed in one double space. Materials should be prepared with a standard 12-point typeface or greater (Times New Roman typeface is preferred). The manuscript should be in the following sequence: cover letter (optional), title page file, manuscript (title and running title, abstract and keywords, introduction, materials and methods, results, discussion, references, tables, and figure legends), figures, other submission elements. All pages should be numbered consecutively starting from the title page. All numbers should be written in Arabic numerals throughout the manuscripts. Our preferred file format is DOCX or DOC. A single PDF file that contains all materials in a file including figures and figure legends is acceptable. In that case, authors should add line numbers throughout the document. Manuscript containing anything in headers and footers, except of page numbers, will be returned to authors. If your PDF submission is accepted, you will be asked to upload your final document file in DOCX or DOC format as well. Make sure to update your PDF file with the most recent version of your manuscript.  

2. Abbreviation of terminology  
Abbreviations should be avoided as much as possible. When they are used, full expression of the abbreviations following the abbreviated word in parentheses should be given at the first use. Common abbreviations, however, may be used, such as DNA. Abbreviation can be used if it is listed as a MeSH subject heading (http://www.ncbi.nlm.nih.gov/mesh).
3. **Word-spacing**

1) Leave 1 space for each side, using arithmetic marks as +, −, ×, etc.
Leave no space for hyphen between words.
2) Leave 1 space after “,” and “;”. Leave 2 spaces after “.” and “;”.
3) Using parentheses, leave 1 space each side.
4) Brackets in parentheses, apply square brackets.

4. **Citations**

1) If a citation has 2 authors, write as “Hirota and Lambert.” If there are more than 3 authors, apply ‘et al.’ at the end of the first author’s surname. Ex) Kim et al. [1].
2) Citation should be applied after the last word or author’s surname.
3) Apply citation before a comma or period.
4) Identify reference by several or coupled Arabic numbers, enclosed in square brackets on the line as [1,3,5].

5. **Arrangement of manuscript**

All articles should be arranged in the following order.

- Cover letter (optional)
- Title Page file, uploaded separately
- Manuscript, as a single file in word processing format (eg, .doc), consisting of Title and running title, Abstract (if required for the article type; see relevant section), Body Text, Referenc-es, Tables, Figure Legends, if any (in numerical order, on the same page); be sure to number all pages of the manuscript file
- Figures (each Figure should be a separate file in figure file format)
- Other submission elements (Supplemental Digital Content, etc.)

Each new section’s title should begin on a new page. The conclusion should be included in the discussion section. Number pages consecutively, beginning with the first page. Page numbers should be placed at the middle of the bottom of page. For survey-based clinical studies, the original survey document does not need to be included in the body of the manuscript but may be supplemented in an appendix.

6. **Statistical Analysis**

1) Describe the statistical tests employed in the study with enough detail so that readers can reproduce the same results if the original data are available. The name and version of the statistical package should be provided.
2) Authors should describe the objective of the study and hypo-thesis appropriately. The primary/secondary endpoints are predetermined sensibly according to the objective of the study.
3) The characteristics of measured variables should determine the use of a parametric or nonparametric statistical method. When a parametric method is used, the authors should de-scribe whether the basic statistical assumptions are met.2,3
4) For an analysis of a continuous variable, the normality of data should be examined. Describe the name and result of the particular method to test normality.
5) When analyzing a categorical variable, if the number of events and sample is small, exact test or asymptotic method with appropriate adjustments should be used. The standard chi-squared test or difference-in-proportions test may be performed only when the sample size and number of events are sufficiently large.
6) The Korean Journal of Anesthesiology (KJA) strongly en-courages authors to show confidence intervals. It is not rec-ommended to present the P value without showing the confi-dence interval. In addition, the uncertainty of estimated values, such as the confidence interval, should be described consistently in figures and tables.4
7) Except for study designs that require a one-tailed test, for example, non-inferiority trials, the P values should be two-tailed. A P value should be expressed up to three decimal places (not as “P < 0.05”). If the value is less than 0.001, it should be described as “P < 0.001” but never as “P = 0.000.” For large P value greater than 0.1, the values can be rounded off to one decimal place, for example, P = 0.1, P = 0.9.
8) A priori sample size calculation should be described in de-tail.5 Sample size calculation must aim at preventing false negative results pertaining to the primary, instead of secondary, endpoint. Usually, the mean difference and standard deviation (SD) are typical parameters in estimating the effect size. The power must be equal to or greater than 80 percent.

---

In the case of multiple comparisons, an adjusted level of significance is acceptable.6  
9) It is recommended using mean ± SD or median (Q1, Q3) format to present representative values of continuous variables. Results must be written in significant figures. The measured and derived numbers should be rounded off to reflect the original degree of precision. Calculated or estimated numbers (such as mean and SD) should be expressed in no more than one significant digit beyond the measured accuracy. Therefore, the mean ± SD of body weight in patients measured on a scale that is accurate to 0.1 kg should be expressed as 65.45 ± 2.52 kg.  
10) Except when otherwise stated herein, authors should conform to the most recent edition of the American Medical Association Manual of Style.7  

7. Organization of manuscript  
1) Clinical or Experimental research  
(1) Title page  
① Title  
Title should be concise and precise. For the title, only the first letter of the first word should be capitalized.  
② Author information  
First name, middle initial, and last name of each author, with their highest academic degree(s) (M.D., Ph.D., etc.), and institutional affiliations; make sure the names of and the order of authors as they appear on the Title Page and entered in the system match exactly.  
③ Running title  
A running title of no more than 40 characters, including letters and spaces, should be described. If inappropriate, the editorial board may revise it.  
④ Corresponding Author  
Name, mailing address, phone number, and e-mail address of the corresponding author  
⑤ Previous presentation in conferences  
Title of the conference, date of presentation, and the location of the conference may be described.  
⑥ Conflict of interest  
It should be disclosed here according to the statement in the Research and publication ethics regardless of existence of conflict of interest. If the authors have nothing to disclose, please state: “No potential conflict of interest relevant to this article was reported.”  
⑦ Funding  
Funding to the research should be provided here. Providing a FundRef ID is recommended including the name of the funding agency, country and if available, the number of the grant provided by the funding agency. If the funding agency does not have a FundRef ID, please ask that agency to contact the FundRef registry (e-mail: fundref.registry@crossref.org). Additional detailed policy of FundRef description is available from http://www.crossref.org/fundref/.  
⑧ Acknowledgments  
Any persons that contributed to the study or the manuscript, but not meeting the requirements of an authorship could be placed here. For mentioning any persons or any organizations in this section, there should be a written permission from them.  
⑨ IRB number  
⑩ Clinical trial registration number  

If any of these elements are not applicable to your submission, write “not applicable” after the number and topic; for example, “Prior Presentations: Not applicable.”  

(2) Manuscript  
① Title and Running title  
② Abstract  
All manuscripts should contain a structured abstract that is written only in English. Provide an abstract of no more than 250 words. It should contain 4 subsections: Background, Methods, Results, and Conclusions. Quotation of references is not available in the abstract. A list of keywords, with a minimum of 6 and maximum of 10 items, should be included at the end of the abstract. The selection of keywords should be from MeSH (http://www.ncbi.nlm.nih.gov/mesh) and should be written in small alphabetic letters with the first letter in capital letter. Separate each word by a semicomma (,), and mark a period (.) at the end of the last word.  
③ Introduction  
The introduction should address the purpose of the article concisely and include background reports that are relevant to the purpose of the paper.  
④ Materials and Methods  
- The materials and methods section should include sufficient details of the design, subjects, and methods of the article in order, as well as the data analysis methods and con-  

6Lee S and Lee DK. What is the proper way to apply the multiple comparison test? Korean J Anesthesiol 2018; 71: 353-60.  
7http://www.amamanualofstyle.com/
trol of bias in the study. Sufficient details need to be addressed in the methodology section of an experimental study so that it can be further replicated by others.

- When reporting experiments with human or animal subjects, the authors should indicate whether they received approval from the IRB for the study and the IRB approval number needs to be provided. When reporting experiments with animal subjects, the authors should indicate whether the handling of the animals was supervised by Institutional Board for the Care and Use of Laboratory Animals. "American Society of Anesthesiologists physical status classification" should not be abbreviated. As a rule, subsection titles are not recommended.

- Clearly describe the selection of observational or experimental participants. Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). For additional information, please visit http://www.icmje.org/about-icmje/faqs/icmje-recommendations/.

- Reports of randomized trials must conform to the revised CONSORT guidelines and should be submitted with the CONSORT flow diagram. The CONSORT checklist should be submitted as a separate file along with the manuscript. The CONSORT statement, checklist, and flow diagram can be found at http://www.consort-statement.org or EQUATOR Network (https://www.equator-network.org/home/)

- Units
Laboratory information should be reported in International System of Units [SI]. Please refer to A Guide for Biological and Medical Editors and Authors, 6th Edn. Baron DN and Clarke HM, ed. (2008), CRC Press. or visit http://www.icmje.org/about-icmje/faqs/icmje-recommendations/

- Exceptions
A. The unit for volume is "L", others in “dl, ml, μl”.
B. The units for pressure are mmHg or cmH₂O.
C. Use Celsius for temperature
D. Units for concentration are M, mM, μM.
E. When more than 2 items are presented, diagonal slashes are acceptable for simple units. Negative exponents should not be used.
F. Leave 1 space between number and units.

- Drug Names
Use generic names. If a brand name must be used, insert it in parentheses after the generic name. Provide ® or ™ as a superscript and the manufacturer's name.

- Ions
Ex) Na⁺ [O], Mg²⁺ [O], Mg⁺⁺ [X], Mg⁺⁺⁺ [X]

- Statistics
Statistical methods must be described with enough detail so that readers can reproduce the same results if the original data available. The KJA strongly encourages authors to show confidence intervals. It is not recommended to present the P value without showing the confidence interval. A sample size calculation should be described in detail. Sample size calculation must aim at preventing false negative results pertaining to the primary, instead of secondary, endpoint.

- Results
Results should be presented in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat all of the data in the tables or illustrations in the text; emphasize or summarize only the most important observations. Results can be sectioned by subsection titles but should not be numbered. Citation of tables and figures should be provided as Table 1 and Fig. 1.

- Discussion
The discussion should be described to emphasize the new and important aspects of the study, including the conclusions. Do not repeat the results in detail or other information that is given in the Introduction or the Results section. Describe the conclusions according to the purpose of the study but avoid unqualified statements that are not adequately supported by the data. Conclusions may be stated briefly in the last paragraph of the Discussion section.

- References
References should be obviously related to documents and should not exceed 50. For exceeding the number of references, it should be negotiated with the Editorial Board. References should be numbered consecutively in the order in which they are first mentioned in the text. Provide footnotes in the body text section. All of the references should be stated in English, including author, title, name of journal, etc.

- If necessary, the editorial board may request original documents of the references.
- Six authors can be listed. If more than 6 authors are listed, only list 6 names with ‘et al.’
- Provide the start and final page numbers of the cited reference.
- Abstracts of conferences are not allowed to be included in the references. The American Society of Anesthesiologists (ASA) refresher course lecture is not acceptable as a reference.
- Description format
  A. Regular journal
  Author name. Title of journal Name of journal published year; volume: start page-final page.
  B. Monographs
  - If reference page is only 1 page, mark ‘p’.
  - Mark if it is beyond the 2nd edition.

C. Chapter

D. Electronic documents

E. Online journal article

F. Papers that have been submitted and accepted for publication should be included in the list, with the phrase ‘in press’ replacing volume and page number. Authors should be prepared to give the volume and page number at the time of proof correction.

Table
- Type or print each table on a separate sheet of paper.
- Number tables consecutively in the order of their first citation in the text.
- Supply a brief title
- Tables should be more than 4 rows and should not be over 1 page.
- Except for titles and first letters, all of the text in the tables should be written in small alphabetic letters.
- In demographic data, sex would be provided as M/F, and age in yr. Data of year, weight, height, and any other units would be provided with 1 decimal place.
- “±” sign in the upper column of table should be lined up with the lower column.
- Footnotes should be provided consecutively in order of the cited tables or statistics.
- Marks for footnote should be given in order of *, †, ‡, §, ¶, **, ††, ‡‡... When marks are used to explain items of the table, indicate them with superscripts.
- Define all abbreviations except those approved by the International System of Units. Define all abbreviations every
time they are repeated.

3 Legends for figures and photographs
   • All of the figures and photographs should be described in the text separately.
   • The description order is the same as in the footnotes in tables and should be in recognizable sentences.
   • Define all abbreviations every time they are repeated.

(3) Figures and illustrations
   ① The KJA publishes in full color, and encourages authors to use color to increase the clarity of figures. Please note that color figures are used without charge for online reading. However, since it will be charged upon the publication, authors may choose to use colors only for online reading.
   ② Standard colors should be used (black, red, green, blue, cyan, magenta, orange, and gray). Avoid colors that are difficult to see on the printed page (e.g., yellow) or are visually distracting (e.g., pink). Figure backgrounds and plot areas should be white, not gray. Axis lines and ticks should be black and thick enough to clearly frame the image. Axis labels should be large enough to be easily readable, and printed in black.
   ③ Figures should be uploaded as separate tif, jpg, pdf, gif, ppt files. Width of figure should be 84 mm (one column). Contrast of photos or graphs should be at least 600 dpi. Contrast of line drawings should be at least 1,200 dpi. Number figures as “Fig. (Arabic numeral)” in the order of their citation. (ex. Fig. 1).
   ④ Photographs should be submitted individually. If Figure 1 is divided into A, B, C and D, do not combine it into 1, but submit each of them separately. Authors should submit line drawings in black and white.
   ⑤ In horizontal and vertical legends, the letter of the first English word should be capitalized.
   ⑥ Connections between numbers should be denoted by “-“, not “-“. Do not space the numbers (ex. 2–4).
   ⑦ Figures (line drawings) should be clearly printed in black and white.
   ⑧ Figures should be explained briefly in the footnotes. The format is the same as the table format.
   ⑨ An individual should not be recognizable in the photographs or X-ray films unless written consent of the subject has been obtained and is provided at the time of submission.
   ⑩ Pathological samples should be pictured with a measuring stick.

(4) Other submission elements (Video submission)
The KJA publishes supplemental video (movie) clip(s) that will be available online. Not only recording of the abstract, text, audio or video files, but also data files should be added here.

Each video clip should clearly illustrate the primary findings within an adequate amount of viewing time and be discussed in the text. Authors should provide appropriate labeling (e.g., arrows, abbreviations of anatomic structures, etc.) in the video clips. However, all identifying information, including patient name and/or ID number, hospital name, and date of the procedure, should be removed.

Video clips should contain succinct teaching points that must be supported by the current literature or standard reference texts, preferably those most accessible to the general reader. The adequacy of the teaching points will be evaluated during the review process and finally confirmed by the editorial board at the end of the review process.

Video clips are uploaded as the last file(s) at the time of manuscript submission and should be marked as supplementary video files.

① The video clip(s) should have simple file names (e.g., Video 1***, Video 2****) and include the appropriate extension (e.g., .mov, .mpg).
② The maximum number of video clips is 20.
③ The video clip(s) should be playable on both Windows and MAC computers. The video clip(s) should be tested for playback before submission, preferably on computers not used for their creation, to check for any compatibility issues.
④ Individual video files should be a minimum of 480 x 320 pixels (smaller clips will not be accepted) and a maximum of 2 GB. Files of < 15 MB will be rejected outright unless special arrangements have been made with the editorial board prior to submission. Approval of files of > 2 GB will be made at the end of the review process.
⑤ Supplemental still images that correspond to the respective video clip(s) should be, but are not always required to be, accompanied by legends. The video clip file name(s) should refer to the corresponding figure number(s).

2) Systematic review and meta-analysis
Systematic reviews are systematic, critical assessments of literature and data sources in order to answer a specific question, and/or includes a statistical technique leading to a quantitative summary of results and examining sources of differences in results among studies, if any. The subtitile should include the phrase “A systematic review” and/or “A Meta-analysis.”

Organization of systematic review and meta-analysis: Same as clinical and experimental studies, except:
   • All systematic reviews and meta-analyses should be regis-
tered at an appropriate online public registry (e.g., PROSPERO; http://www.crd.york.ac.uk/PROSPERO/), and registration information should be included with the submission.

- Authors of reports of meta-analyses of clinical trials should submit the PRISMA flow diagram. The PRISMA checklist should be submitted as a separate file along with the manuscript. For information regarding PRISMA guidelines, please visit http://www.prisma-statement.org or EQUATOR Network (https://www.equator-network.org/home/). Systematic reviews and meta-analyses of observational studies in epidemiology should be reported according to MOOSE guidelines. For more information regarding MOOSE guidelines, please visit http://www.equator-network.org/reporting-guidelines/meta-analysis-of-observational-studies-in-epidemiology-a-proposal-for-reporting-meta-analysis-of-observational-studies-in-epidemiology-moose-group/.

- No limitation the number of the references.

3) Case Reports

A case report is almost never a suitable means to describe the efficacy of a treatment or a drug; instead, an adequately powered and well-controlled clinical trial should be performed to demonstrate such efficacy. The only context in which a case report can be used to describe efficacy is in a clinical scenario, or population, that is so unusual that a clinical trial is not feasible.

Case reports of humans must state in the text that informed consent to publication was obtained from the patient or guardian. Authors should submit copies of written informed consents by using the online manuscript submission system. If it is unavailable, the IRB approval should be needed. Copy of IRB approval should be kept. If necessary, the editor or reviewers may request copies of these documents. Rarity of a disease condition is itself not an acceptable justification for a case report.

(1) Title page: Same as clinical and experimental studies.

(2) Manuscript

① Title and Running title.

② Abstract: All case reports should contain a structured abstract that is written only in English. Provide an abstract of no more than 150 words. It should contain 3 subsections: Background, Case, and Conclusions. A list of keywords, with a minimum of 6 and maximum of 10 items, should be included at the end of the abstract. The selection of keywords should be from MeSH (http://www.ncbi.nlm.nih.gov/mesh) and should be written in small alphabetic letters with the first letter in capital letter. Separate each word by a semicolon (;), and mark a period (.) at the end of the last word.

③ Introduction: Should not be separately divided. Briefly describe the case and background without a title.

④ Case report: Describe only the clinical statement that is directly related to diagnosis and anesthetic management.

⑤ Discussion: Briefly discuss the case, and state conclusions at the end of the case. Do not structure the conclusion section separately.

⑥ References: Do not exceed 15 references. For exceeding the number of references, it should be negotiated with the Editorial Board.

⑦ Tables and figures: Proportional to clinical and experimental studies.

4) Reviews

Review articles synthesize previously published material into an integrated presentation of our current understanding of a topic. Review articles should describe aspects of a topic in which scientific consensus exists, as well as aspects that remain controversial and are the subject of ongoing scientific disagreement and research. Review articles should include unstructured abstracts equal to or less than 250 words in English. Figures and tables should be provided in English. References should be obviously related to documents and should not be exceed 100. For exceeding the number of references, it should be negotiated with the Editorial Board. Body text should not exceed 30 A4 pages, and the number of figures and tables should be equal to or less than 6.

5) Letters to the Editor

Letters to the Editor also should include brief constructive comments on the articles published in KJA and interesting cases. Book reviews as well as news of scientific societies and scientific meeting dates in Korea or abroad can be included. Letters to the editor of humans must state in the text that informed consent to publication was obtained from the patient or guardian. Authors should submit copies of written informed consents by using the online manuscript submission system. If it is unavailable, the IRB approval should be needed. Copy of IRB approval should be kept. If necessary, the editor or reviewers may request copies of these documents. Letters to the Editor cover individual articles not described by any of the above categories. The short manuscripts with a constructive note on the Journal or the anesthesiology at large are welcome.

Cover pages should be formatted as those of clinical research papers. The body text should not exceed 1,000 words and should have no more than 5 references. For exceeding the number of references, it should be negotiated with the Editorial Board. A figure or a table may be used. A maximum of five au-
thors is allowable. Letter may be edited by the Editorial Board and if necessary, responses of the author of the subject paper may be provided.

6) Statistical Round
A Statistical Round is a narrative review of the application of contemporary quantitative sciences to issues of concern to anesthesia researchers. A Statistical Round involves a focused discussion on one or more unique or interesting statistical analysis methods that has previously been published in this journal or expresses the general policies or opinions of the Statistical Round Board. They are solicited by the Statistical Round Board and reviewed by the Statistical Editor. There are no word limits to or rules regarding the structure of a Statistical Round. They should have an unstructured abstract of no more than 250 words in English. All articles in a Statistical Round will be published in English and translated into Korean for the convenience of Korean readers. The Korean version of the Statistical Round will be published only on the Web page of the Journal (https://ekja.org). The inclusion of sample datasets as Web (Supplemental) content is encouraged.

8. Recently revised instructions for authors are applied from December 2023 submissions.