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Okcheon plant
47, Uiryodanji-gil, Okcheon-eup, Okcheon-gun, Chungcheongbuk-do, Korea
① +82.43.730.2800  ⑥ +82.43.730.2890
Aims and Scope

The Korean Journal of Anesthesiology (Korean J Anesthesiol; KJA) is an international, English-language, and Peer-reviewed journal for anesthesiology, critical care, and pain medicine. As an official journal of the Korean Society of Anesthesiologists, KJA was founded in 1968 and published monthly until 2014 and will now publish bimonthly in 2015.

KJA aims to publish high-quality clinical and scientific materials on all aspects of anesthesiology, critical care, and pain medicine. In addition to publishing original articles, KJA features reviews, editorials, case reports, and letters to the editor. The major consideration for publication includes clarity, uniqueness, and advancement in design, performance, and knowledge. KJA also features Statistical Round to provide educational fundamentals and practical implications for clinical and experimental statistics to its readers. Additionally, KJA gladly reviews and publishes negative results for which publication will benefit clinical practice and promote further research activity.

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101-3503, Lotte Castle President, 109 Mapo-daero, Mapo-gu, Seoul 04146, Korea
Tel: +82-2-795-5129 Fax: +82-2-792-4089 Email: anesthesia@kams.or.kr journal@anesthesia.or.kr

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Studies show: Patients were randomly assigned to receive suugammadex (0.6, 1.2, or 2.4 mg/kg) or placebo intravenously over 30 minutes. The primary endpoint was the time to recovery of the TOF ratio to 0.9. The secondary endpoint was the time to recovery of the TOF ratio to 0.5. The safety and efficacy of suugammadex were compared with placebo using non-parametric analysis of variance (ANOVA) with adjustments for within-subject correlation.

Results: All doses of suugammadex significantly reduced the time to recovery of the TOF ratio to 0.9 compared with placebo. The time to recovery of the TOF ratio to 0.9 was significantly shorter in the suugammadex 0.6 mg/kg group compared with the placebo group (p < 0.05). The time to recovery of the TOF ratio to 0.5 was also significantly shorter in the suugammadex 0.6 mg/kg group compared with the placebo group (p < 0.05). There were no significant differences in adverse events between the suugammadex and placebo groups.

* Information presented above is based on the full prescribing information.
Sex/gender and additional equity characteristics of providers and patients in perioperative anesthesia trials: a cross-sectional analysis of the literature

Nicole Etherington¹, Michael Wu², Sylvain Boet¹,³

¹Clinical Epidemiology Program, Ottawa Hospital Research Institute, ²Faculty of Medicine, University of Ottawa, ³Department of Anesthesiology and Pain Medicine, The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada

Keywords: Anesthesiology; Cross-sectional studies; Gender identity; Review; Sex; Social class.
Postoperative neurocognitive disorders

Setayesh Reza Tasbihgou, Anthony Ray Absalom

Department of Anesthesiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

인지 기능의 저하는 대수술의 합병증으로 빈번히 발생한다. 술후 인지장애는 일반적으로 단기 장애인 술후 섬망과 장기 장애인 술후 인지기능 장애(postoperative cognitive dysfunction, POCD)로 구분된다. 장기 장애는 진단하기에 까다로우며 간과되는 경우가 많다. 장기 장애의 진단을 위해 신경심리학적 검사를 통한 객관적 평가가 필요하다. 많은 연구들이 지난 수십 년 동안 POCD를 다루었지만, 일부 환자가 수술 전의 인지 기능 수준으로 회복하지 않는 이유에 대해 여전히 보고된 바가 없다. 수술과 마취 모두 POCD 발생에 중요한 역할을 하는 것으로 알려져 있으며, 고령 및 낮은 수준의 술후 인지기능과 같은 환자 관련 특정 요인들이 술후 인지 저하를 예측하는 것으로 연구들을 통해 지속적으로 보고되고 있다. 본 논문은 POCD의 개요와 그 원인을 제시하고 가능한 예방적 전략을 권장사항으로 제공한다.

Keywords: Aged; Delirium; Frail elderly; Inflammation; Neurocognitive disorders; Perioperative care; Postoperative cognitive complications.
General considerations for sample size estimation in animal study

동물실험에서 표본 크기 추정을 위한 일반적 고려사항

Mun Jung Ko, Chi-Yeon Lim

Department of Biostatistics, Dongguk University College of Medicine, Goyang, Korea

이 논문의 목적은 동물실험에서 표본 크기 계산을 위한 기본적인 개념과 방법을 소개하는 것이다. 임상연구 계획 단계에서 표본 크기를 계산하는 것은 연구의 타당도, 정확도, 신뢰도를 보여주기 위한 매우 중요한 과정이다. 그러나 모든 연구에서 표본 크기를 계산해야 하는 것은 아니다. 연구하기에 앞서 자신이 하고자 하는 연구의 목적의 예비 연구 및 탐색적 연구인지, 혹은 가설 검정이 목적이 되는지 식별하는 것이 중요하다. 대부분의 동물실험은 예비 연구 및 탐색적 연구이기 때문에 표본 크기 추정보다는 과학적 수준 및 질적인 수준을 유지하면서 실험을 실시하기 위한 다른 고려사항을 생각해 보는 것이 더 적절할 수도 있다. 동물실험에서 표본 크기는 다양한 상황과 연구의 목적에 따라 계산될 수 있고, 정밀도 분석(precision analysis), 검정력 분석(power analysis) 등의 방법으로 추정할 수 있다. 이러한 경우에는 정규성 가정이 만족되지 않아서 비모수적 방법으로 표본 크기를 계산할 수도 있고, 소표본 연구만 가능한 경우도 있다.

Keywords: Animal study; Exploratory study; Nonparametric sample size; Parametric sample size; Pilot study; Power analysis; Precision analysis.
Demographic and clinical factors associated with same-day discharge and unplanned readmission following shoulder arthroplasty: a retrospective cohort study


Department of Anesthesiology and Perioperative Medicine, University of California Los Angeles, Los Angeles, CA, Department of Anesthesiology, University of California San Diego, La Jolla, CA, Department of Biological Sciences, University of California San Diego, La Jolla, CA, School of Medicine, University of California San Diego, La Jolla, CA, Department of Radiology, University of California Davis, Sacramento, CA, Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, TX, Department of Medicine, Division of Biomedical Informatics, University of California San Diego, La Jolla, CA, USA

Keywords: Ambulatory; Discharge planning; Health care quality; Optimization; Outpatient; Rehabilitation.
Risk factors associated with hypotensive bradycardic events during open shoulder surgery in the beach chair position

Ji Won Choi, Duk Kyung Kim, Hee Joon Jeong, Young Ri Kim, Yoon Joo Chung, Yong Hun Son

Department of Anesthesiology and Pain Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Keywords: Aged; Brachial plexus block; Bradycardia; Hypotension; Reflex; Shoulder arthroplasty; Sitting position.
Evaluation of the relationship between lactacidemia and postoperative complications after surgery for peritoneal carcinomatosis

Marta Soriano Hervás, Rosa Játiva-Porcar, Daniel Robles-Hernández, Anna Serra Rubert, Blanca Segarra, Cristina Oliva, Javier Escrig, José Antonio Llueca

Departments of 1 Anesthesiology, 2 Obstetrics and Gynecology, 3 General Surgery, University General Hospital of Castellon, Castellón de la Plana, Spain

배경: 세포감퇴수술(cytoreduction surgery)은 복막 암종증의 치료법으로 개발되었다. 그러나 이 수술은 중요한 합병증과 관련이 있다. 본 연구는 세포감퇴수술을 받은 환자를 대상으로 중환자실(intensive care unit, ICU)에서 수술 직후 기간에 수술과 관련된 합병증의 발생 비율과 젖산혈증 사이의 관계를 평가하는 것을 목표로 하였다.

방법: 본 연구는 후향적 관찰 연구로 수행되었으며, 총 57명의 세포감퇴수술을 받은 환자를 대상으로 하였다. 모든 환자는 세포감퇴수술 직후 ICU에 입원했다. ICU 입원 및 퇴원시 혼중 젖산농도를 측정했다. ICU 입원 기간 동안 발생한 술후 합병증은, 합병증으로 인한 사망률 분석(failure-to-rescue analysis) 방법에 따라 기록되었으며, 그 중증도는 Clavien-Dindo 분류에 의해 축이(stratified) 되었다.

결과: ICU 입원 시 젖산농도는 누적 합계 곡선 그래프를 통해 도출된 젖산혈증 역치에 대해, 합병증이 발생한 환자에서 합병증이 발생하지 않은 환자보다 비보정 상대 위험도는 거의 3배로(2.9, 95% CI: 1.6, 5.3) 유의하게 높았다. 교란 요인들의 보정 후 상대 위험도는 더욱 높아졌다(3.1, 95% CI: 1.8, 3.6). 젖산농도는 ICU에서 퇴원할 때에도 합병증 발생군에서 여전히 유의하게 높았다.

결론: 혈청 젖산농도는 복막 암종증에 대한 세포감퇴수술을 받은 환자에서 술후 합병증의 위험 요소이다. 본 연구의 결과는 ICU 입원 시 젖산농도가 2.5 mmol/L 이상이면 중증의 합병증이 발생할 위험도가 거의 3배로 증가함을 시사한다.

Keywords: Cytoreduction surgical procedures; Intensive care units; Lactic acid; Mortality; Peritoneal neoplasms; Postoperative complications.
The effect of interscalene brachial plexus block with propofol sedation on preventing perioperative hypothermia during arthroscopic shoulder surgery

Ji Hye Lee, Hyun Joo Heo, Yu Yil Kim, Seung Min Baek, Ki Man Kim, Da Wa Jung

Department of Anesthesiology and Pain Medicine, Presbyterian Medical Center, Jeonju, Korea

Keywords: Arthroscopy; Body temperature; Brachial plexus block; Interscalene; Sedation; Shoulder.
Prevention of epidural catheter migration: a comparative evaluation of two tunneling techniques

Sujeet Gautam¹, Anil Agarwal¹, Pravin Kumar Das², Sandeep Khuba¹, Sanjay Kumar¹

Department of Anesthesiology, ¹Sanjay Gandhi Post Graduate Institute of Medical Sciences, ²Dr Ram Manohar Lohia Institute of Medical Sciences, Uttar Pradesh, Lucknow, India

배경: 경막외 제통의 실패는 카테터 이동을 감소시키는 고정 기술을 사용하여 그 비율을 줄일 수 있다. 본 임상 연구에서 경막외 카테터 이동 방지를 위한 두 가지 경막외 카테터 터널링 기술의 역할을 비교했다.

방법: 복부 수술을 받은 환자들을 경막외 카테터 고정 방법에 따라 각각 50명의 환자로 구성된 3개 그룹으로 무작위 배정했다. 대조군(CG)에서는 경막외 카테터가 터널링 없이 고정되었고, 터널링 그룹 1과 2 (TG1 및 TG2)는 각각 카테터 루프가 있거나 없는 터널링으로 정의되었다. 1차 평가변수는 경막외 카테터의 이동이었고, 2차 평가변수는 진통의 적절성과 염증 징후였다. 모든 환자에 대해 수술 후 경막외 카테터가 제거될 때까지 1일 2회 급성 통증 의료팀이 추적관찰을 수행했다. 연구 결과는 일원 분산분석(ANOVA), 카이제곱 검정 및 Fisher의 정확검정을 사용하여 분석되었다. P값의 유의 수준은 P < 0.05로 설정되었다.

결과: 세 그룹은 환자들 특성 면에서 유사했다. 카테터 이동은 다른 두 그룹, 즉 TG1 (8명 환자) (P = 0.045) 및 CG (17명 환자) (P = 0.001)에 비해, TG2 (2명 환자)에서 유의하게 감소했다. 진통의 적절성 및 카테터 부위 염증에서는 세 그룹 간에 차이가 확인되지 않았다 (P > 0.05).

결론: 다른 두 그룹에 비해, 카테터 이동은 TG2에서 카테터 루프가 없는 터널링 방법에 의해 현저하게 감소했다. 이에 본 연구의 결과를 통해 실제 통증 조절의 임상현장에서 카테터 루프 도입 없이 터널링을 일반적으로 사용할 것을 제안하고, 향후 연구를 더 큰 표본 크기로 수행할 것을 기대한다.

Keywords: Catheter associated infection; Catheter migration; Epidural analgesia; Epidural catheter tunneling; Epidural injection; Postoperative pain.
Clinical usefulness of ultrasound as an early diagnostic tool for neuroleukemiossis - a case report -

Neuroleukemiossis의 조기 진단 도구로서 초음파의 임상적 유용성

Soon Ju Baek, Jung Woong Lee, Sukyung Chung, Shu Chung Choi, Jin Young Chon

Department of Anesthesiology and Pain Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

배경: Neuroleukemiossis는 백혈병에서 드물게 발생하는 합병증이다. 그것은 비특이적 증상 및 특별한 진단 방식이 필요하기 때문에 진단이 지연될 수 있다.

증례: 6년 전에 급성 골수성 백혈병 판정을 받은 70세 남성이 좌측 대퇴부 후방부위의 전격통 및 방사통을 주소로 방문했다. 요추 MRI 영상에서 L2-3의 경미한 디스크 돌출을 보였는데, 이것으로는 환자의 증상을 설명하기에 불충분했다. 요추 경막외 차단 및 이상근 주사에 대한 통증 반응이 불충분한 상태에서, 초음파를 사용하여 양쪽 좌골 신경을 비교하여 검사를 시행했다. 왼쪽 좌골 신경부위에서 hypoechoic mass가 비대해진 것을 확인했다. 이후 전신 마취 하에 종괴 생검 결과, 조직검사 결과에서 neuroleukemiossis로 확인되었다.

결론: 초음파는 neuroleukemiossis의 선별 진단 도구로서 비용적으로 저렴하고, 비침습적이며, 사용법이 간단하기 때문에 빠른 진단 방식으로 사용될 수 있다.

Keywords: Complications; Diagnosis; Extramedullary myeloid cell tumor; Leukemia; Neoplastic; Ultrasonography.
Intraoperative refractory status epilepticus caused by propofol -a case report-

Abhyuday Kumar¹, Amarjeet Kumar², Neeraj Kumar², Ajeet Kumar¹

Departments of ¹Anesthesiology, ²Trauma & Emergency, All India Institute of Medical Sciences Patna, Bihar, India

Case Report

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https://doi.org/10.4097/kja.20162
pISSN 2005–6419 • eISSN 2005–7563

Keywords: Anesthesia; Intraoperative complications; Myoclonus; Propofol; Status epilepticus; Tonic-clonic seizure.

배경: 두 가지 항간질제를 투여했음에도 불구하고 지속되는 간질지속증은 난치성 간질지속증(refractory status epilepticus, RSE)이라고 한다. 프로포폴(propofol)에 의한 발작과 유사한 증상의 발현은 선행 연구에 널리 보고되어 있다. 그러나 프로포폴로 인한 RSE는 드물며 진단에 뒤지마가 발생한다.

증례: 44세 남성 환자가 수술 중 RSE를 보였으며, 프로포폴 주입으로 전신마취 상태에 있었다. 발작은 벤조디아제핀(benzodiazepines)과 페니토인(phenytoin)에 대해 내성이 있었다. 그 후, 프로포폴 주입 중단 후 발작이 가라앉았고, 환자의 마취 유지를 위해 펜타닐(fentanyl)과 덱스메데토미딘(dexmedetomidine) 주입으로 바꾸었다. 숭후 추적관찰에서 특이사항은 발견되지 않았다.

결론: 본 논문은 수술 중 난치성 발작의 치료를 집중적으로 다루며, 프로포폴로 인한 발작 특성에 대한 탐색의 필요성을 강조하여 보고한다.

The Korean Society of Anesthesiologists, 2021
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Online access in http://ekja.org
A journal article is a comprehensive account of a theoretical argument or proof of reproducible experimental results and statistical analyses conducted in accordance with the appropriate procedure and form. However, no matter how well written the article is, its value cannot be gauged without a reader (who peruses it), and other subsequent researchers who cite it (to maintain and protract its lifespan).

Journal editors should solicit papers of excellent quality to improve the academic level, enhance national and international recognition, and maintain the reputation of their journals by increasing the frequency of citations. Moreover, they should endeavor to publish high-quality journals through thorough management of all processes related to thesis publication. It is important to establish a framework to facilitate the submission of excellent papers by frequently managing objective indicators to evaluate the quality of journals and notifying readers. We would like to periodically disseminate the production and citation indicators of this journal to achieve this goal.

Productivity review of KJA

Korean Journal of Anesthesiology (KJA) was founded in 1968 as an official journal of the Korean Society of Anesthesiologists. It was published monthly until 2014 and bimonthly since 2015. KJA aims to publish high-quality clinical and scientific reports of all aspects of anesthesiology, critical care, and pain medicine.

In 2020, KJA received 690 articles (all types of submissions). Since 2018, the number of submissions has increased by 37% annually. KJA has published a total of 99 articles, which consisted of 8 editorials, 14 reviews, 4 statistical rounds, 26 clinical research articles, 4 experimental research articles, 13 case reports, 25 letters to the editor, and 5 articles belonging to other categories.

KJA has adopted a rapid review system since 2014, which ensures that the editorial team provides their final decision within 7 days. In the previous year, 65% of all submissions were rapidly rejected by this system. Finally, the acceptance rate was 12.1%, and the rejection rate was 86.2%. The 4-year (2017–2020) average acceptance rate was 15.0% and the rejection rate was 83.5%. The average duration between the date of receiving the manuscript and the first decision was 13.4 days. This statistic is an indication of the duration required for key activities in the process. We are immensely proud of our rapid review system and relatively fast decision time, since it gives authors more choices.

Bibliometric analysis

Bibliometric analyses were performed using the Bibliometrix (ver 3.0, an R-tool for comprehensive science mapping analysis) package program [1]. For production analysis,
all paper published in KJA in 2020 were assessed using the source data collected from SCOPUS (http://www.scopus.com).

In 2020, the average number of citations per document was 1.303. The total number of authors was 364, authors per document was 4.28, and collaboration index was 4.17. The most productive authors are presented in Table 1. We appreciate their contributions toward KJA through this editorial. Table 2 depicts the countries of the 12 corresponding authors in 2020. The country-based frequency of publication was as follows: South Korea (40.0%), India (19.0%), the United States of America (15.8%), Singapore (5.3%), Italy (4.2%), and others. Table 3 contains the most frequently used keywords in 2020, which consisted of the keywords used by authors, Keywords-Plus, and words in the title. Keywords-Plus, which is available on the Web of Science platform, automatically extracts information from the metadata of a particular research field, because indexing terms also assist in the determination of the knowledge structure, although it may be less comprehensive in revealing the intrinsic aim of a study. It seems that KJA tends to focus primarily on subjects such as regional anesthesia, postoperative pain/analgesia, nerve blocks, and COVID-19 in 2020 based on the results of the author's keywords.

Table 1. Top 10 Most Productive Authors in 2020

<table>
<thead>
<tr>
<th>Authors</th>
<th>Articles</th>
<th>Articles Fractionalized</th>
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<td>In J</td>
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<td>Kumar R</td>
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Table 2. Corresponding Author’s Countries in 2020

<table>
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<th>SCP</th>
<th>MCP</th>
<th>MCP_Ratio</th>
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<td>0</td>
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<tr>
<td>Singapore</td>
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<td>4</td>
<td>1</td>
<td>0.2</td>
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<tr>
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<td>3</td>
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</tbody>
</table>

Freq: frequency, SCP: single country publication, MCP: multiple country publications

Table 3. Top 20 Most Frequent Keywords and Frequency in 2020

<table>
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<th>Author's keywords</th>
<th>Keywords-Plus</th>
<th>Words in title</th>
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<td>Regional anesthesia</td>
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<td>Patients</td>
</tr>
<tr>
<td>Postoperative pain</td>
<td>Article</td>
<td>Block</td>
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<td>General anesthesia</td>
<td>Adult</td>
<td>Anesthesia</td>
</tr>
<tr>
<td>Nerve block</td>
<td>Female</td>
<td>Case</td>
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<tr>
<td>Analgesia</td>
<td>Male</td>
<td>Analgesia</td>
</tr>
<tr>
<td>Acute pain</td>
<td>Case report</td>
<td>Postoperative</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>Clinical article</td>
<td>Randomized</td>
</tr>
<tr>
<td>Pain</td>
<td>Letter</td>
<td>Pain</td>
</tr>
<tr>
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<td>Postoperative pain</td>
<td>Effects</td>
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<td>Anesthesia</td>
<td>Patient</td>
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<td>Controlled study</td>
<td>Surgery</td>
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<td>General anesthesia</td>
<td>Trial</td>
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<td>Humans</td>
<td>Ventilation</td>
</tr>
<tr>
<td>Ultrasonography</td>
<td>Major clinical study</td>
<td>Controlled</td>
</tr>
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<td>Artificial intelligence</td>
<td>Middle aged</td>
<td>COVID</td>
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<tr>
<td>Artificial respiration</td>
<td>Aged</td>
<td>Plane</td>
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<tr>
<td>Brachial plexus block</td>
<td>Artificial ventilation</td>
<td>Study</td>
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<td>Cesarean section</td>
<td>Endotracheal intubation</td>
<td>Ultrasound-guided</td>
</tr>
<tr>
<td>Child</td>
<td>Propofol</td>
<td>Versus</td>
</tr>
<tr>
<td>Coronavirus infections</td>
<td>Review</td>
<td>Airway</td>
</tr>
</tbody>
</table>
ence database (Web of Science Core Collection database maintained by Clarivate Analytics. Access date: January 11, 2021) for citation analysis. Table 4 contains the most relevant sources that cited the reports published in KJA as references during 2020. Table 5 lists the 7 most cited papers published in KJA in 2020. The two most cited papers were a case report of an emergency cesarean section in a patient with COVID-19 and an anesthesia recommendation editorial for COVID-19 patients [2,3]. Last year, most journals mass produced COVID-19 related literature, and the citation of such studies has also increased. The next two most cited studies were two reports of ultrasound-guided regional blocks [4,5]. The surge in the interest in multimodal analgesia is thought to have had a synergistic effect on interest in the literature on various regional blocks.

Journals are competing endlessly for the attention of readers, considering that numerous papers are published every day. KJA will endeavor to strive to provide more useful information to its readers, as one of the journals that continues to grow in its field.

### Acknowledgements

I sincerely appreciate not only all the authors who submitted the great works to KJA, but also all the editors and reviewers for their hard work throughout the year.

### Conflicts of Interest

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

### References


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<table>
<thead>
<tr>
<th>Table 4. Top 20 Most Relevant Sources That Cited KJA Articles in 2020</th>
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<tbody>
<tr>
<td><strong>Sources</strong></td>
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<tr>
<td>Journal of Anesthesia</td>
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<td>Journal of Perinatology</td>
</tr>
<tr>
<td>Anaesthesia</td>
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<tr>
<td>Journal of Clinical Anesthesia</td>
</tr>
<tr>
<td>Journal of Clinical Medicine</td>
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<tr>
<td>Anesthesiology</td>
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<tr>
<td>Canadian Journal of Anesthesia</td>
</tr>
<tr>
<td>Head and Neck Journal for the Sciences and Specialties of the Head And Neck</td>
</tr>
<tr>
<td>International Journal of Environmental Research and Public Health</td>
</tr>
<tr>
<td>Prenatal Diagnosis</td>
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<tr>
<td>Regional Anesthesia and Pain Medicine</td>
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<tr>
<td>Acta Obstetricia Et Gynecologica Scandinavica</td>
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<td>Anesthesia and Analgesia</td>
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<td>Angle Orthodontist</td>
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<td>Annals of Plastic Surgery</td>
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<td>Annals of the New York Academy of Sciences</td>
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<td>Archives of Gynecology and Obstetrics</td>
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<td>Biomed Research International</td>
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<tr>
<td>BMC Anesthesiology</td>
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<td>British Journal of Anaesthesia</td>
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</table>

<table>
<thead>
<tr>
<th>Table 5. Top Seven Most Cited Manuscripts Published in 2020</th>
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<tbody>
<tr>
<td><strong>Paper</strong></td>
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<tr>
<td>Lee DH, 2020</td>
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<tr>
<td>Kim HJ, 2020</td>
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<td>Salama ER, 2020</td>
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<td>Gabriel RA, 2020</td>
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<td>Kmen K, 2020</td>
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<td>Boscolo A, 2020</td>
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<td>Bak H, 2020</td>
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</table>
Emerging safety concerns in elderly patients undergoing shoulder surgery

Won-Jung Shin

Department Anesthesiology and Pain Medicine, Laboratory for Cardiovascular Dynamics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Recently, shoulder surgery, including open and arthroscopic total shoulder arthroplasty, has been increasingly performed [1]. In the United States, the number of patients undergoing total shoulder arthroplasty has more than doubled between 2005 and 2013 [2]. With an increasing elderly population, the prevalence of degenerative shoulder diseases has also increased, which may contribute to the rising number of shoulder surgery performed. Considering that elderly patients have various comorbidities, complications and problems related to anesthesia and surgery emerge together.

Traditionally, shoulder surgery was performed as an inpatient procedure for elderly patients due to comorbidities associated with aging and postoperative pain control. As enhanced recovery protocol has been introduced for various types of orthopedic surgery, shoulder surgery is now performed in the outpatient setting [3]. The shift toward ambulatory surgery has resulted in cost saving and patient convenience. However, the issue of safety and adverse events related to ambulatory shoulder surgery is unresolved. In the first issue of 2021 Korean Journal of Anesthesiology, Burton et al. [4] investigated the demographic and clinical factors that were associated with same-day discharge and unplanned readmission after shoulder arthroplasty. They found that factors such as old age, comorbidities (such as diabetes and congestive heart failure), and poor functional status were associated with a lower odds of discharge on the same day and a higher risk of unplanned readmission.

Perioperative complications associated with arthroscopic shoulder surgery, such as cerebral desaturation and hypotensive ischemia, postoperative dyspnea, neurologic injuries, and inadvertent hypothermia, are unconquerable [5]. In particular, there is the possibility of a serious side effects of compromised cerebral perfusion in the beach chair position by which improves intra-articular visualization during arthroscopic surgery. Choi et al. [6] showed that symptomatic hypotensive bradycardia occurred in 60% of all shoulder surgeries with the beach chair position and that preoperative interscalene brachial plexus block and old age were risk factors for symptomatic hypotensive bradycardia. During shoulder arthroscopy, hypothermia is common and can be contributed by the irrigation of the shoulder joint, impaired thermoregulation, and vasodilation due to anesthesia. Prevention of hypothermia is meaningful as it plays an important role in adverse events such as blood loss, cardiac morbidity, and wound problem [7]. Lee et al. [8] found that perioperative hypothermia was more prevalent in general anesthesia than in interscalene brachial plexus block combined with propofol sedation. They also showed that there was no difference in the incidence of hypothermia between the elderly and younger patient groups.

From these retrospective studies [4,6,8], it is thought that elderly patients with comorbidities are unlikely to be discharged on the same day and are at an increased risk of readmission in the setting of ambulatory shoulder surgery. Old age may also be associated with a high risk of hypotensive bradycardia, particularly in the beach chair position. In
elderly patients, interscalene brachial plexus block combined with propofol sedation could prevent inadvertent intraoperative hypothermia, which is more likely with general anesthesia. Interscalene block, however, may induce symptomatic hypotensive bradycardia associated with the beach chair position. In conclusion, the risk of perioperative complications in elderly patients undergoing shoulder surgery depends on the surgical position, anesthetic techniques, and presence of significant comorbidities. Therefore, further studies are needed to identify perioperative strategies to ensure the safety of elderly patients undergoing shoulder surgery.

**Conflicts of Interest**

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

**References**

Sex/gender and additional equity characteristics of providers and patients in perioperative anesthesia trials: a cross-sectional analysis of the literature

Nicole Etherington¹, Michael Wu², Sylvain Boet¹,³

¹Clinical Epidemiology Program, Ottawa Hospital Research Institute, ²Faculty of Medicine, University of Ottawa, ³Department of Anesthesiology and Pain Medicine, The Ottawa Hospital, University of Ottawa, Ottawa, ON, Canada

Sex and gender, among other equity-related characteristics, influence the process of care and patients’ outcomes. Currently, the extent to which these characteristics are considered in the anesthesia literature remains unknown. This study assesses their incorporation in randomized controlled trials (RCTs) on anesthesia-related interventions, for both patients and healthcare providers. This is a cross-sectional analysis using an existing dataset derived from the anesthesia literature. The dataset originated from a scoping review searching MEDLINE, Embase, CINAHL, CENTRAL, and the Cochrane Database of Systematic reviews. RCTs investigating the effect of anesthesia-related interventions on mortality for adults undergoing surgery were included. Equity outcome measures were recorded for both patients and providers and assessed for inclusion in the study design, reporting of results, and analysis of intervention effects. Three-hundred sixty-one RCTs (n = 144,674) were included. Most RCTs (91%) reported patient sex/gender, with 58% of patients identified as male. There were 139 studies (39%), where 70% or more of the sample was male, compared to just 14 studies (4%), where 70% or more of the sample was female. Only 10 studies (3%) analyzed results by patient sex/gender, with one reporting a significant effect. There was substantial variation in how age was reported, although nearly all studies (98%) reported some measure of age. For healthcare providers, equity-related information was never available. Better consideration of sex/gender and additional health equity parameters for both patients and providers in RCTs is needed to improve evidence quality, and ultimately, patient care and outcome.

Keywords: Anesthesiology; Cross-sectional studies; Gender identity; Review; Sex; Social class.

Introduction

Clinical evidence based on randomized controlled trials (RCTs) often guides healthcare decisions in many countries around the world [1,2]. Although RCTs provide evidence on the impact of healthcare interventions, potential differences within and between population subgroups tend to be overlooked in the design, conduct, and analysis of RCTs [3–5]. For example, the Guidelines to the Practice of Clinical Hyperbaric Medicine and Provision of Hyperbaric Oxygen Treatment from the Canadian Undersea and Hyperbaric Medical Association recommend treating severe carbon monoxide (CO) poisoning with
hyperbaric oxygen therapy regardless of any health equity-related characteristics (e.g., sex, gender, education, and ethnicity) [6]. However, a recent study from Huijun et al. [7] recruited couples treated for CO poisoning and analyzed patient outcome according to sex and females’ pre- or post-menopausal status. The authors demonstrated that ‘sex is an important prognostic indicator in CO poisoning,’ as severity of poisoning and subsequent outcome was worse for males relative to their female spouses. Thus, male patients may actually require a different course of treatment, highlighting the importance of considering health equity-related characteristics in optimizing patient care.

Without attention to health equity-related characteristics, the generalizability and applicability of RCT results can be reduced [3,5,8,9]. Continued implementation of some interventions based on previous RCT results can also generate further health inequities between groups [10]. Thus, consideration of health equity-related characteristics is important to optimize patient outcome, avoid research waste, advance health research and policy, and ultimately reduce population health inequities.

Health-related equity characteristics are increasingly being investigated in perioperative care [11–17]. These characteristics may be particularly relevant in anesthesia. Evidence suggests, for example, that patient sex impacts some aspects of care and outcomes. Specifically, patient sex and/or gender interacts with emergence and recovery from general anesthesia [18], postoperative complications [18], remifentanil dosing for laryngeal mask airway insertion [19], prescription of analgesics [20], and hypnotic and muscle relaxant effects of anesthetic drugs [21]. Though the impact of anesthesiologist sex and gender on practice and patient outcome is unknown, recent evidence suggest these factors influence surgical practice patterns, postoperative complications, and mortality [12,22,23]. There is limited work on additional equity characteristics, but some evidence suggests that racial-ethnic disparities in pain management and use of neuraxial anesthesia, and that both patient and provider factors are involved [12]. Based on these and other findings [24–27], it is necessary to assess the state of the anesthesia literature for incorporation of equity characteristics in RCTs. This can inform the design, analysis, and reporting of future RCTs as well as meta-analyses of existing trials.

If patient outcome after anesthesia care varies by sex and gender or any equity characteristic, then anesthesia trials must account for these variables in study design, reporting, and analysis. Similarly, if anesthesia practice varies by provider sex and/or gender and/or additional equity characteristics, interventions to improve practice must account for these factors. Currently, the extent to which sex, gender, and other health equity categories are considered in the anesthesia literature remains unknown. It is important to determine this information given the potential to improve patient outcomes, provider training, research, and knowledge translation.

This study aims to assess the extent to which sex/gender and other health equity variables are considered in the design, analysis, and reporting of RCTs investigating the impact of anesthesia-related interventions on adult surgical patient mortality. Health equity categories, including sex/gender, will be assessed for both patients and providers. We hypothesize that female patients are under-represented in anesthesia RCTs and that data are most often not reported or analyzed according to patient sex/gender. We also expect anesthesiologist sex/gender to be uncommonly reported and analyzed. Finally, we anticipate limited reporting and analysis of all additional health equity characteristics including age and ethnicity, for both patients and providers.

Materials and Methods

This study conducted a cross-sectional secondary analysis of the original data set of 369 RCTs from our previously completed scoping review of anesthesia-related interventions that impact surgical patient mortality [28]. Details can be found elsewhere [28], in supplementary data. In brief, RCTs were retrieved from the following electronic databases: MEDLINE, Embase, CINAHL, CENTRAL, and the Cochrane Database of Systematic Reviews. The original search strategy was developed by the research team with an information specialist and reviewed by another information specialist (PRESS) [29]. Language restrictions were not applied to the literature search; however, data were extracted only from studies published in English or French. All databases were searched from inception to March 2015.

RCTs were included in this data set if they involved an anesthesia-related intervention (i.e., an intervention during the perioperative period performed or organized by a healthcare provider trained in anesthesia) administered to an adult patient (older than 16 years old) and assessed mortality as an outcome. Mortality was selected as a criterion for inclusion based on its clinical importance and feasibility considerations. RCTs were not included if they focused only on comparing different surgical techniques or if they involved procedures using local anesthesia alone. Relevant studies and their data were previously identified and extracted in duplicate by pairs of independent reviewers for our aforementioned scoping review.

For the purposes of this study, an additional level of screening and data extraction was conducted by one reviewer and verified by a second reviewer using DistillerSR (Evidence Partners, Ottawa, Canada). Conflicts were resolved through consensus or in-
volvement of a third reviewer as needed. Eight studies were subsequently excluded due to patient sex/gender as an inclusion or exclusion criteria. These studies involved gynecologic procedures, mastectomies, orthopedic and cardiac surgeries performed on female patients only, and prostatectomies performed on male patients only. Thus, the final data set for this study included 361 RCTs (n = 144,674), that investigated anesthesia-related interventions impacting surgical patient mortality.

Ethical approval was not required for this study as all information was publicly available. This manuscript was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement [30].

We defined the population for this study as adult patients undergoing a surgical procedure with general anesthesia, and healthcare providers with training in anesthesia who are involved in RCTs investigating the impact of anesthesia-related interventions on surgical patient mortality.

Health equity variables were extracted according to the categories outlined by the PROGRESS-Plus framework that is the gold standard set out by the Cochrane Equity Methods Group [31]. Categories include: Place of residence, Race/ethnicity/culture/language, Occupation, Gender/sex, Religion, Education, Socioeconomic status, Social capital, as well as the ‘Plus’ categories of age, disability, and sexual orientation.

We assessed the design, reporting of results, and analysis of each RCT:

1. Design: Consideration of PROGRESS-Plus categories in study design through sample representation of respective groups

2. Reporting: Results disaggregated (i.e., reported separately) by PROGRESS-Plus categories

3. Analysis: Differences in effect of intervention statistically tested by patient and provider PROGRESS-Plus categories

Equity outcome measures were recorded for both patients and providers.

For the race/ethnicity variable, participants were grouped into two categories, Caucasian and non-Caucasian, due to heterogeneity in the non-Caucasian groups reported by included studies. Descriptive statistics and absolute values and percentages were used for both number of studies and participants.

DistillerSR (Evidence Partners, Canada) and Microsoft Excel (Microsoft Corp., United States) were used for extraction and analysis, respectively.

**Results**

Results are shown in Table 1. Full details of included studies are available in Supplemental Table 1. Seven studies (2%) did not incorporate any of the equity categories (865 patients [0.6%]). These studies are not included in Table 1.

Three hundred thirty studies (91%) considered patient sex/gender, with 83,784 (62%) patients identified as male and 51,925 (38%) identified as female. There were 139 studies (42%) where 70% or more of the sample was male compared to just 14 studies (4%) where 70% or more of the sample was female.

Three hundred fifty-two studies (98%) considered patient age (n = 146,682 [99%]). There was substantial variation in how age

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<th>PROGRESS-Plus category</th>
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<td>Patients; studies</td>
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<tr>
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<td>11538 (8); 12 (3)*</td>
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<td>Age</td>
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<td>13933 (9); 22 (6)*</td>
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<td>343 (0.2); 1 (0.3)*</td>
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<td>Residence</td>
<td>2313 (1.6); 2 (0.6)*</td>
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Values are presented as number of participants (%); number of studies (%). *It indicate categories with reported results. NR: not reported.

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was reported from overall population means and standard deviations to broad age ranges (e.g., under 65 years, over 65 years) to medians per control and intervention group. Twenty-two studies (6.1%) considered patient race/ethnicity (n = 22,956 [15%]). Of these patients, 20,510 (89%) were Caucasian and 2,446 (11%) were non-Caucasian (Supplemental Table 2).

One study (0.3%, 343 patients [0.2%]) assigned patients a lifestyle score that took employment status into account, but did not indicate the distribution of patients per employment category [31]. Two studies (0.6%, 2,313 patients [1.7%]) looked at residence or living situation. Hempenius et al. [32] included the categories alone-independent, with others-independent, protected housing-dependent, home for the elderly-dependent, and nursing home-dependent. Most patients (n = 126) lived independently, either alone (n = 59) or with others (n = 66). Carson et al. [33] considered whether patients lived in the United States (n = 1,222) or Canada (n = 794) as well as whether the patient lived in their own home or a retirement home (n = 1,778), nursing home (n = 214), and some other residence (n = 31).

Most studies (339 studies [94%], 134,589 patients [91%]) did not disaggregate results by any equity characteristic. The remaining 22 disaggregated results by sex/gender and/or age.

Twelve (3%) studies (11,538 patients [8%]) reported results separately by patient sex/gender (Supplemental Table 3). Twenty-two (6%) studies (13,933 patients [9%]) reported results separately by patient age (Supplemental Table 4). Of these studies, 9 also disaggregated results by sex/gender.

Ten studies (3%) tested for a significant difference in the effect of the intervention by patient sex/gender (n = 11,395 [8%]). One study (n = 762) involving cardiac surgery and a device-related intervention reported male sex increases the risk of mortality [35].

Of the 22 studies that presented results by age tested for significant differences, most studies (15 [68%]) reported no significant difference in the effect of the intervention by patient age, although 7 (32%) reported age to play a significant role, either increasing or decreasing risk of mortality.

Sex/gender, age, race/ethnicity, and any other equity category never appeared in any study for healthcare providers. This remains true for design, reporting, and analysis.

Discussion

This study examined the integration of health equity characteristics for both providers and patients in the design, analysis, and reporting of RCTs investigating the impact of anesthesia-related interventions on adult surgical patient mortality. Although patients’ sex/gender is generally included in the design of anesthesia RCTs, it is rarely considered in reporting of results and analysis. This is also true of age. Other patients’ health equity characteristics are rarely included in the design, reporting of results, or analysis. Health equity characteristics of providers are never considered.

Reporting of patient sex/gender appears to be more common in the anesthesia literature than in surgery-specific clinical research, with only 2% of studies failing to provide any sex/gender-related data compared to nearly 20% in surgical studies [34]. This is certainly an encouraging practice, although more adequate incorporation into the study design should be promoted to permit sufficiently powered sub-group analyses. When sex/gender is not considered in trial design, it is impossible to ensure statistical power to any further analyses accounting for this factor. Not surprisingly, only 12 of the reviewed studies disaggregated results by patient sex/gender, 10 tested for significant differences, and only one reported a significant difference in mortality between male and female patients. Of course, we recognize that it is not always feasible to conduct sub-group analyses. However, even when studies are underpowered, or when sex/gender analyses may not be relevant, data should still be reported by sex/gender to facilitate future meta-analyses and to inform sample size calculations for future studies [35]. Reporting of this information can also improve the replicability of a study.

Overall, there was an over-representation of male patients, with males comprising 70% or more of the sample in 139 (39%) of the included studies. This may be the result of most studies involving cardiac procedures, where trials have historically focused on male patients. However, the number of female patients undergoing cardiac surgery every year is increasing and heart disease remains a leading cause of death for women [36]. Further, in the last 20 years, the prevalence of myocardial infarctions has increased in midlife among women aged 35–54 years while simultaneously declining in men of the same age [37]. Heart disease and differences in its clinical presentation have traditionally been under-recognized in women, resulting in ‘less aggressive treatment strategies and a lower representation of women in clinical trials’ [37]. This is problematic, especially considering that women have poorer survival rates following many types of cardiac procedures [38]. Our findings underscore the need to recruit, report, and analyze according to sex/gender, particularly when assessing anesthesia interventions in cardiac surgery. With the majority of surgical procedures in the United States performed on female patients [39], it is critical to understand the implications of anesthesia-related interventions for both female and male patients, and how effects may differ between them. When data on male and female participants is aggregated, there is a risk of masking important sex/gender differences.
nder differences and lead to adverse effects for patients in clinical practice [40]. For example, inadequate consideration of sex differences in pharmacokinetics and pharmacodynamics resulted in 10 drugs being withdrawn from the market, with eight posing greater health risks for women than for men [40, 41]. Accordingly, trials investigating pharmaceutical interventions in anesthesia should consider these variables. Even if trials cannot analyze their data based on health-equity characteristics (e.g., because of small sample size), we believe that all trials should at least report their data based on health-equity characteristics. This way, future systematic reviews may be able to further explore the impact of health-equity characteristics on patient outcome in perioperative medicine.

Beyond sex/gender, few studies reported on additional health equity characteristics. One exception is age that was reported by all but one study. Like sex/gender, a much lower number of studies disaggregated and analyzed results by age. Though age was often included, it was reported in various ways. More standardized reporting of age (e.g., mean/SD or median/IQR for each group and participants overall) is needed as well as consideration of how it intersects with sex/gender given the importance of these two characteristics together for health. Again, standardized and disaggregated reporting would make future meta-analyses possible.

Race/ethnicity, another key health-related characteristic that can also interact with sex/gender and age, was reported in only 6% of the examined trials. Within these trials, nearly 90% of patients were Caucasian. Patients from other racial/ethnic groups were clearly under-represented, preventing understanding of the role patient race/ethnicity has in anesthesia-related interventions. Without this type of information, it is not possible to identify heterogeneity among patients, potentially augmenting the risks of particular interventions and certainly reducing the effectiveness of knowledge translation [42]. Research may wish to assess the role of race/ethnicity when considering the effectiveness of anesthesia interventions during metabolic and vitreoretinal procedures in particular, given recent findings of racial/ethnic differences in clinical presentation and outcomes [15, 16].

Failure to examine differences in the effect of an intervention on clinical outcomes by sex/gender and additional health equity characteristics misses an opportunity to optimize patient care and may even pose significant risk to patient safety (e.g., different side effects, reactions to treatments, and biological and social factors influencing outcomes of a treatment). When equity characteristics remain absent from RCT analysis and interpretation, as found in reviews of other clinical trials [5, 42], the external validity of the study remains limited [35]. When we wish to conclude patients are more or less likely to experience morbidity and/or mortality as a result of an intervention, it is important for results either to be appropriately generalizable to the broader patient population or to limit the results to a specific clearly defined sub-group based on certain equity characteristics. It is noteworthy, for example, that our study found pharmacotherapy trials and trials involving cardiac surgery to be based on mostly male and Caucasian samples, when some evidence suggests that these patient characteristics can be critical modifiers in these instances [21, 43, 44]. For example, female patients undergoing cardiac surgery often have different risk factors than male patients (e.g., older, higher body mass index), and higher hospital and early mortality has been found for those who undergo coronary artery bypass grafting [44]. This again emphasizes the need to study sex/gender and other equity characteristics when anesthesia interventions involve pharmacotherapy or cardiac surgery.

Because health equity characteristics are known determinants of health that can modify the relationship between healthcare interventions and outcomes of interest, their inclusion or exclusion in clinical trials also has implications for knowledge translation. We recognize that this type of data collection may not always be possible within the requirements of some Research Ethics Boards (REB) and this may have affected the ability of some of the included studies to collect adequate patient information. However, it is important for REBs to consider the benefits of collecting equity data in clinical trials, provided participant confidentiality is maintained. With emerging evidence that sex/gender and additional characteristics are relevant to how individuals respond to particular healthcare interventions, ‘there is an ethical and scientific imperative to report to whom research results apply’ [35]. When evidence is moved into practice, it must be determined whether it will improve outcomes for some or all patients. Part of advancing evidence-based practice in anesthesiology and other disciplines includes attention to the equitable representation of patients within the evidence base. If the evidence base exhibits sex/gender or any other type of bias, this limitation should be acknowledged in practice. For example, if women and non-Caucasians continue to be under-represented in anesthesia research, they may experience an increased likelihood of adverse events compared to male and Caucasian patients as a result of certain interventions. This has certainly been the case in other clinical areas such as infectious disease management [45]. Future anesthesia research can integrate these concerns into trial design and data analysis in order to enhance its value.

Integration of providers’ equity-related parameters throughout all RCT elements (design, reporting, and analysis) appears to be non-existent. In the assessed anesthesia literature, no study reported provider sex/gender or any additional characteristic. Yet, these may be important in identifying differences in practice pat-
terns and areas for improvement. For example, a recent study reports lower mortality and readmission rates for female internists compared to male internists [46]. Research also demonstrates that male physicians tend to undermanage female patients (e.g., less extensive investigation, providing less medication and at lower doses) but finds no difference in the treatment of male or female patients when the physician is a woman [47,48]. Sex/gender representation of anesthesia providers who deliver patient interventions in RCTs are currently unclear. Future research may examine if trends found among patients (e.g., more men than women; more Caucasians than non-Caucasians) are similar for providers. This may help to determine whether RCT findings are generalizable to all providers, or if patient intervention effectiveness varies by provider characteristic. Reporting of provider sex/gender, along with other equity characteristics, may help to determine representation of diverse provider groups in research trials. It would also allow future knowledge syntheses to assess the potential clinical effects of practice differences among various anesthetic provider groups.

Research has started to consider sex/gender for surgeons, finding implications for practice and patient outcome [12,22,23,49]. With an increasing number of women entering medical school every year, it is time for anesthesiology to do the same and to consider the implications of additional equity-related characteristics. For example, recent research suggests that when female anesthesiologists make an incorrect clinical decision, they are challenged more often than their male colleagues [50]. Sex/gender may therefore be important for interventions addressing leadership, communication, and overall teamwork in the operating room. Similarly, male and female anesthesia providers may benefit from different approaches to training, as demonstrated in surgery [49]. This may be especially needed if the sex/gender of anesthesia providers influences the patient outcome, similar to what emerging evidence shows for surgeons [12,23]. With the incorporation of equity-related parameters for anesthesia providers in research, knowledge translation interventions to improve practice may become optimally effective.

There are some limitations to generalizing the conclusions drawn from this review. It is not inclusive of all anesthesia-related papers and included only RCTs that assessed mortality as an outcome. In addition, because this review includes only studies published up until 2015, it may not reflect changes taking place within the literature in recent years. Other types of data sets may influence results. However, three recent studies of sex/gender reporting in medical research [5,42,51] found similar results to what we have reported here, suggesting our observed trends may apply to additional areas of anesthesia as well as other medical fields. Although it is possible that reporting of sex/gender and other equity characteristics has improved over the last decades, recent publication in the Lancet by Sugimoto et al. [42] suggests reporting has not significantly increased in recent years despite more attention being paid to sex/gender in research. For example, from 1980 to 2016, reporting of patient sex only increased by 8% in clinical medicine. In biomedical research, only 31% of papers published in 2016 reported the sex of patients [42]. Accordingly, while our data set represents a subset of the anesthesia literature, it is likely to still be representative of current reporting trends. Given that no equity measures were ever integrated for providers, it may also be reasonable to assume that these findings are consistent across anesthesia domains. It is possible that consideration of sex/gender and additional equity characteristics in anesthesia trials will improve over the next decade given evolving requirements of journals and funding agencies.

It should also be acknowledged that most studies in this dataset reported mortality as a secondary outcome. Still, this does not detract from the need to improve reporting of sex/gender and additional equity data regardless of the outcome assessed. Where it is not possible to analyze outcomes by certain equity parameters, reporting this data can still allow for future meta-analyses to evaluate potential differences.

A final possible limitation is that relevant studies may have not been included, despite conducting a rigorous and standardized search of the literature [28]. If mortality terms were not mentioned in the title or abstract of a study, they would not have been included due to the literature search and screening process. Nevertheless, as previously mentioned, this dataset is still likely to be representative of trends in the broader anesthesia literature.

There is a need for better integration of sex/gender and additional health equity parameters for both patients and providers in the design, reporting, and analysis of anesthesia RCTs in order to improve evidence quality and ultimately patient care and outcome.

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Liza Begunova, Liberal Arts and Sciences Program, Dartmouth
College, Hanover, NH, United States
Susan Bragg, MD, Department of Anesthesia, University of Toronto, Toronto, ON, Canada
Ian D. Carrigan, B.Sc., Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada
José De Wit, MD, Department of Anesthesia, University of Ottawa, Ottawa, ON, Canada
Sarah Larrigan, Biomedical Sciences, University of Ottawa, Ottawa, ON, Canada
Cassandra T. Mendonca, MD, Department of Anesthesia, University of Ottawa, Ottawa, ON, Canada
Isaac Miao, MD, Department of Anaesthesia, University of Ottawa, Ottawa, ON, Canada
Karim Mohamed, MD, Department of Anesthesia, University of Ottawa, Ottawa, ON, Canada
David Nicola, MD, B.Sc. (Hons.), Family Medicine, McGill University, Montreal, Quebec, Canada
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Conflicts of Interest

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

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Author Contributions

Nicole Etherington (Conceptualization; Formal analysis; Investigation; Writing – original draft)
Michael Wu (Formal analysis; Investigation; Writing – review & editing)
Sylvain Boet (Investigation; Supervision; Writing – review & editing)

Supplementary Materials

Supplementary Table 1. PROGRESS-Plus representation of patients in RCTs testing anesthesia-related interventions (n = 361)
Supplementary Table 2. Studies that report race/ethnicity
Supplementary Table 3. Studies that disaggregate by sex/gender
Supplementary Table 4. Studies that disaggregate by age

ORCID

Nicole Etherington, https://orcid.org/0000-0002-7933-4593
Michael Wu, https://orcid.org/0000-0003-0948-8500
Sylvain Boet, https://orcid.org/0000-0002-1679-818X

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Postoperative neurocognitive disorders

Setayesh Reza Tasbihgou, Anthony Ray Absalom

Department of Anesthesiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

A decline in cognitive function is a frequent complication of major surgery. Postoperative cognitive impairments have generally been divided into short- (postoperative delirium) and long-term disturbances (postoperative cognitive dysfunction [POCD]). Long-term impairments are often subtle and overlooked. They need to be objectively assessed using neuropsychological tests to be diagnosed. Although POCD has been the subject of considerable research over the past decades, it remains uncertain why some patients do not return to preoperative levels of cognitive function. Surgery and anesthesia have both been implicated to play a role in POCD development, and certain patient-related factors, such as advanced age and low preoperative baseline cognitive function, have consistently been found to predict postoperative cognitive decline. This article will present an overview of POCD and its etiology and provide advice on possible strategies on its prevention.

Keywords: Aged; Delirium; Frail elderly; Inflammation; Neurocognitive disorders; Perioperative care; Postoperative cognitive complications.

Introduction

It has been over five decades since Bedford observed that surgery in elderly patients was followed by a significant cognitive decline that lasted for an extensive period [1]. Through interviews (with patients and relatives) and subjective assessment, he found that 7% of his (elderly) patients who underwent surgery and received general anesthesia showed signs of cognitive impairment. He published these findings in The Lancet, concluding that “the allegation ‘He’s never been the same since his operation’ is sometimes true, and that an irreversible gross dementia is occasionally the aftermath of surgical operations under general anesthesia [1].”

By the late 1980s, psychometric tests were used to objectively assess cognitive decline after surgery, particularly in patients undergoing cardiac surgery [2]. The studies also consistently documented long-term cognitive disorder in elderly patients, although there were varying incidences and severities [3–5]. As a result, the concept of postoperative cognitive dysfunction (POCD) was developed as a diagnosis based on these objective measurements. Although surgery and anesthesia have improved dramatically since then, the exact understanding of when, how, and why some patients do not return to baseline cognitive function remains elusive. As cognitive dysfunction, in the form of delirium, has been shown to be important for perioperative outcome and mortality [6–8], it is also important to consider the effects of long-term cognitive impairment and its possible risk factors. In this review, we present a brief overview of POCD and its etiology and provide advice on possible strategies on its prevention.
Postoperative cognitive impairment: delirium and POCD

Postoperative cognitive impairments have generally been divided into short-(delirium) and long-term disturbances (POCD) [9]. The former is familiar among many clinicians and well defined according to the Diagnostic and Statistical Manual of Medical Disorders (DSM)-5 [10]. It states that delirium consists of impairments in attention, awareness, and cognition. Cognition is considered to be a dynamic state, involving multiple domains, such as memory, orientation, language, visuospatial ability, and perception [11]. It fluctuates throughout the day and is affected by both endogenous and exogenous factors [12]. The incidence of postoperative delirium is between 20% and 45% in older adult patients undergoing surgery [13,14].

In contrast, the term POCD has been used to refer to any signs of new cognitive impairment that exceeds the expected length of time needed to recover from the acute effects of surgery and anesthesia [9,15,16]. Unlike delirium, which is a relatively simple and recognizable syndrome, POCD is clinically far less apparent as it often only manifests as mild cognitive decline in one or more cognitive domains [9,17,18]. Furthermore, the DSM-5 does not list POCD as a diagnosis. In 2018, this prompted an expert panel of scientists and clinicians, The International Perioperative Cognition Nomenclature Working Group, to address, clarify, and give structure to POCD and other perioperative cognitive impairments, while proposing new nomenclature to be used in relation to these terms [5].

This working group stated that all cognitive changes associated with surgery and anesthesia should be summarized under the term “perioperative neurocognitive disorders,” thus aligning these impairments with the clinical diagnostic criteria for “neurocognitive disorders (NCDs)” already applied in the DSM-5 [5,10]. The working group recommended POCD assessment at least 30 days postoperatively, at which point most patients are expected to have recovered, physically, psychologically, and emotionally from surgery and hospitalization [5]. If assessment is performed too early, the effects of POCD may be overshadowed by acute postoperative delirium or other cognitive complications that may arise from immobility, sleep deprivation, and ongoing pharmacological interventions [2]. When cognitive impairment manifests itself beyond 12 months postoperatively, mild or major (e.g., dementia) NCDs should be considered over POCD [5].

The term “delayed neurocognitive recovery” may be used to describe a cognitive disorder that is detected within 30 days after surgery when delirium has been excluded. Table 1 summarizes the recommendations offered by the working group [5,12].

**POCD assessment**

Unlike delirium, the diagnosis of POCD has primarily been confined to research. Its diagnosis relies on objectively measurable cognitive decline assessed with neuropsychological tests [15,16,19]. Subjective reports of cognitive changes by patients or proxies are also relevant; however, most studies comparing cognitive complaints and neuropsychological test results were unable to find a significant correlation [16,20]. Certain cognitive functions may be less relevant to a patient’s daily life, and as such, any dysfunction may be overlooked by the patient. There is no agreed upon definition for POCD, but it generally refers to impairment of memory, learning, concentration, attention, or psychomotor performance [5,15]. Neuropsychological tests are often specific to one of these cognitive domains.

Neuropsychological tests that were used in a key international multicenter study on POCD (International Study of Post-Operative Cognitive Dysfunction [ISPOCD] I) are described in Table 2. There are a wide variety of neuropsychological tests, which all have different levels of sensitivity and reliability. The ISPOCD mostly used written tests. However, our research group favors computerized tests, such as the Cogstate Computerized Cognitive Test Battery®, because of its ease of use, versatility, and availability of age-matched control group test data.

Certain tests are more vulnerable to the effects of practice and have a poor test-retest reliability [12,16,19]. Others notoriously have floor and ceiling effects resulting from tests being either too difficult or too easy to detect subtle changes [16]. The method

---

**Table 1.** A Summary of the Recommendations for the New Nomenclature of Perioperative Disorders, from the International Perioperative Cognition Nomenclature Working Group [5]

<table>
<thead>
<tr>
<th>Terms</th>
<th>Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurocognitive disorder (mild or major [e.g., dementia])</td>
<td>Preexisting/preoperative cognitive impairment or cognitive impairment developing after 12 months of surgery.</td>
</tr>
<tr>
<td>Emergence delirium</td>
<td>Delirium diagnosed within minutes or hours after surgery.</td>
</tr>
<tr>
<td>Postoperative delirium</td>
<td>Delirium diagnosed within days after surgery, up to 1 week or until discharge.</td>
</tr>
<tr>
<td>Delayed neurocognitive recovery</td>
<td>Cognitive decline up to 30 days postoperatively.</td>
</tr>
<tr>
<td>Postoperative (neuro)cognitive dysfunction</td>
<td>Cognitive impairment detected between 30 days and 12 months postoperatively.</td>
</tr>
</tbody>
</table>

https://doi.org/10.4097/kja.20294
with which these test results are interpreted also varies throughout the literature [2]. Test batteries, consisting of multiple tests, are able to assess various cognitive domains and are recommended as they are able to describe brain functions in more detail and with increased sensitivity [2,16]. To measure cognitive decline, investigators should determine the change between baseline preoperative and postoperative cognitive functions. To correct for age-related test-retest variability, determining the change in cognitive function with the use of a reliable change index is recommended, as it calculates this change with reference to the expected change found within an age-matched control group [16].

### Incidence of POCD

The incidence of POCD ranges from 20% to 50% in older patients 3 months after cardiac surgery and 5% to 55% in those undergoing major noncardiac surgeries [15,21–25]. This large variation is the result of the methodological differences between studies, making data comparison often difficult. In addition to the various types of test that may be administered for measuring cognitive change, the degree of change and cutoffs necessary for determining POCD have also varied throughout literature. Generally, POCD is divided into mild or major neurocognitive decline, if testing exhibits a decline of > 1 or > 2 standard deviations of cognitive function compared to preoperative cognitive performance, respectively. As described above, the timing of tests is also a known source of variability; the later the cognitive assessment is conducted and the more stringent the statistical criteria for identifying POCD, the lower the reported incidence [16].

This point is illustrated by the large multicenter ISPOCD study conducted in 1998, which observed 1000 patients (age > 60 years) undergoing various noncardiac surgeries [15]. A comprehensive neuropsychological test battery was administered with a strict criterion for POCD. This study found that 25.8% (95% CI: 23.1, 28.5) of patients showed signs of cognitive dysfunction 1 week postoperatively. Cognitive dysfunction at 3 months postoperatively was 9.9% (95% CI: 8.1, 12.0). A later study by Monk et al. found similar incidences of POCD in 365 patients undergoing noncardiac surgery: 41.4% (95% CI: 36.2, 46.7) at discharge and 12.7% (95% CI: 8.9, 16.4) at 3 months [25]. A recent systematic review of 24 studies found that the incidence of POCD at 3 months was 11.7% (95% CI: 10.9, 12.5), although they concluded that major differences in methodology and definitions accounted for variations in the results [26].

### Pathogenesis of POCD

Despite a growing volume of research concerning POCD, the exact etiology for cognitive decline after surgery and anesthesia is still not well understood. Surgery-, anesthesia-, and patient-related factors have all been implicated in playing a role in POCD development, and support for various hypotheses has changed markedly over the years. Historically, a poor cognitive outcome after surgery was often regarded as a consequence of cerebral hypoperfusion and hypoxemia [2,17]. Indeed, inadequate cerebral oxygenation will result in brain damage and cognitive decline. Although intuitively compelling, no strong evidence has been found in favor of POCD being the direct consequence of impaired cerebral hemodynamics and oxygenation [2,24,27]. This was also confirmed by the ISPOCD, which monitored perioperative blood pressure and oxygenation and showed that POCD developed in the absence of perioperative hypoxemia or hypotension [15].

Factors such as the type and duration of surgery and anesthesia have also often been presumed to be associated with the incidence of POCD. However, this has not yet been conclusive. A comprehensive study by Evered et al. [21] compared the incidence of

Table 2. Neuropsychological Tests Used in the International Study of Post-Operative Cognitive Dysfunction 1 (ISPOCD 1)

<table>
<thead>
<tr>
<th>Tests</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini-mental state examination (MMSE) [70]</td>
<td>A commonly used assessment, initially developed to evaluate dementia. It assesses multiple cognitive domains, including attention, memory, and orientation.</td>
</tr>
<tr>
<td>Visual verbal learning test [71]</td>
<td>Based on Rey’s auditory recall test. It assesses verbal memory by asking patients to recall a list of words that they were presented with earlier.</td>
</tr>
<tr>
<td>Concept shifting test (trail-making test) [72]</td>
<td>Also known as trail-making tests A and B. It is used to assess executive function and attention by asking subjects to connect a series of consecutive numbers, letters, or both as quickly as possible.</td>
</tr>
<tr>
<td>Stroop color word interference test [73]</td>
<td>This test evaluates the ability to inhibit cognitive interference from multiple congruent and incongruent stimuli.</td>
</tr>
<tr>
<td>Letter-digit coding test (symbol-digit substitution task) [74]</td>
<td>Used to assess executive function. Patients are presented with a series of digits and letters that are paired and another list of only digits. Then, they are asked to write the corresponding letter as fast as possible.</td>
</tr>
<tr>
<td>Four boxes test [75]</td>
<td>This test is computer based. It is used to measure reaction time by asking patients to select a black circle in one of four boxes on a screen as quickly as possible.</td>
</tr>
</tbody>
</table>
POCD after coronary angiography under sedation, total hip replacement, and coronary artery bypass graft under general anesthesia. Interestingly, the incidence of POCD was similar and thus independent of the nature of surgery or type of anesthesia administered. Furthermore, evidence on whether the use of volatile or intravenous anesthetics may be related to POCD has also been controversial and conflicting [38]. Moreover, other studies have not found any correlation between regional or general anesthesia and incidence of POCD, which further supports the argument that the type of anesthesia appears to be unrelated to POCD development [29,30]. Therefore, it is unlikely that POCD is solely caused by anesthesia or surgery.

A recurring theme and current rationale for the pathogenesis of cognitive dysfunction encompass the role of an inflammatory response to surgery and anesthesia [2,17,27]. It is commonly known that inflammatory processes, such as those associated with pneumonia or urinary tract infection, are regularly accompanied by cognitive decline, particularly in the elderly population [31,32]. Extending this model to POCD, it is thought that the release of proinflammatory mediators, triggered by peripheral surgical stress or trauma, may result in an exaggerated systemic inflammatory response, leading to neuroinflammation in vulnerable individuals [17,27,33]. The release of inflammatory cytokines is known to lead to endothelial dysfunction and also disruption of tight junctions, which results in an increased blood-brain-barrier (BBB) permeability [27,34]. Consequently, systemic inflammatory cytokines will penetrate the BBB, triggering neuroinflammation and activation of the neuronal immune system, including microglia and astrocytes [27,33,35]. Inflammatory mediators are also produced within the brain, as a result of peripheral-to-central signaling via humoral and neuronal pathways [36]. The consequences of this immune response are healing, but if excessive, it may also result in further (cerebral) tissue damage in the form of increased synaptic dysfunction, inhibition of neurogenesis, and neuronal death [27].

In mouse models, surgery caused hippocampal-dependent memory impairment that was associated with increased expression of plasma cytokines and reactive microgliosis and interleukin (IL)-1β transcription and expression in the hippocampus [37,38]. By inhibiting IL-1β, these neuroinflammatory changes were mitigated. Another study showed that tumor necrosis factor (TNF)-α inhibition was also able to limit the release of IL-1 and prevent neuroinflammation and cognitive decline in mice [39]. Thus, peripheral surgical injury can result in inflammation and neuroinflammation. However, interpreting and determining the significance of an inflammatory marker is challenging, as inflammation is a normal physiological response to injury [27].

Generally, inflammation is only harmful when proinflammatory responses outweigh the anti-inflammatory response. Certain patient-related factors are known to exacerbate proinflammatory responses or increase the vulnerability of some patients to the effects of inflammation. Advanced age has been consistently associated with POCD throughout the literature [2,12]. Structural cerebral changes, such as a reduction in gray matter volume and myelinated axon length, are normal changes that occur with aging [27,40]. The normal decline in cognitive function in the elderly population might possibly be further exacerbated by the loss of neuronal dendrite spines and alterations in synaptic transmission and receptors [41]. Furthermore, BBB dysfunction has also been found in older patients even in the absence of surgery [42]. Thus, this decline in “cognitive reserve” may explain how elderly patients are more susceptible to effects of inflammation and therefore neuronal injury. A low preoperative cognitive function and lower education level have also been frequently associated with POCD, also suggesting the vulnerability of a reduced “cognitive reserve” [2,15,25,43].

Predisposing patient factors may also exaggerate an inflammatory response, as a result of “immune priming” [27]. For instance, normal aging without any comorbidities has been associated with a low-grade inflammatory activity and increased plasma TNF-α and IL-6 levels compared to younger patients [44]. Elderly patients are also more susceptible to sepsis [45]. It is unsurprising that patients of advanced age may be more likely to develop an exaggerated inflammatory response as a consequence of surgery. The immune system activation caused by atherosclerosis or neurodegenerative disorders, such as Alzheimer’s and Parkinson’s diseases, may also prime individuals to develop an excessive inflammatory response [46,47]. The presence of Alzheimer’s dementia biomarkers in the cerebrospinal fluid has been shown to be associated with POCD at 3 months, which has also led to the notion that they may involve similar mechanisms [48].

Considering the role of inflammation, several studies have attempted to prevent POCD using anti-inflammatory drugs [17,49]. One study on the effects of high-dose intraoperative dexamethasone administration in cardiac surgery showed that it did not reduce the risk of POCD [50]. Furthermore, other studies have found that lidocaine, magnesium, and complement cascade inhibitors also failed to prevent POCD [51–53]. These negative findings and the understanding that not all elderly patients undergoing major surgery develop POCD or not all patients with atherosclerosis develop POCD after cardiac surgery reflect the pathophysiological complexity of POCD.
**Prevention of POCD**

Although there is no firm understanding of the causes of POCD, improving cognitive outcome after surgery remains an important objective for anesthesiologists and surgeons alike. To date, no pharmacological intervention has convincingly been shown to mitigate the incidence or magnitude of POCD [17]. Dexmedetomidine, an anesthetic agent with neural anti-inflammatory effects, has been found to be potentially effective at reducing the incidence of postoperative delirium; however, any evidence that it may be effective at reducing POCD is incomplete [54,55]. Deep sedation has also been identified as a risk factor for delirium, and several studies have found that measuring the depth of anesthesia (with electroencephalogram monitors) was effective at reducing postoperative delirium. However, there is conflicting evidence that POCD can also be prevented with the same measures [56–60]. If possible, deliriogenic [pre]medications, such as benzodiazepines, should also be avoided [61,62]. Pain and increased postoperative opioid consumption are known to increase the risk of delirium and have also been associated with POCD [62]. Although sufficient pain-management is mandatory, opioid-sparing analgesia may be an effective measure at alleviating this risk. Early postoperative mobilization and a fast-track postoperative approach may help in this respect [63].

Generally, for [non-pharmacological] preventive measures to be significantly effective, multiple (interdisciplinary) interventions, covering various domains, should be considered [2,12,17]. Patients with a possible high risk for POCD should be preoperatively identified and cognitively assessed. When possible, predisposing factors should be modified and adjusted so that patients are sufficiently prepared for surgery. Preparing patients and their relatives adequately by informing them about possible postoperative cognitive changes is also beneficial [64]. Extended periods of preoperative fasting and dehydration should be avoided, as should unnecessary postponement of surgery [65]. Peri- and postoperative patient (re)orientation is essential. Encouraging patients to wear their glasses and hearing aids and early removal of catheters and lines are known to be effective at reducing the risk of postoperative delirium and will help orientate patients and mobilize them earlier, which may likely be effective at preventing POCD [62].

Numerous novel approaches that have been shown to improve cognitive function in older adults have also been proposed as possible interventions that may prevent or protect patients against POCD. These proposed interventions involve diet interventions, physical exercise programs, and brain stimulation and cognitive training [17,66]. Although these strategies are known to improve overall cognition, a few of them have been investigated as potential and feasible interventions for POCD [2]. One study by Kawano et al. [67] found that preoperative environmental enrichment, consisting of both cognitive and physical activities, was able to attenuate neuroinflammation and improve cognitive function in old rats after abdominal surgery. In humans, there is some evidence that preoperative physical status may improve postoperative morbidity; however, cognitive advantages, if any, are still unknown [68,69]. Nonetheless, for treatments of cognitive decline, there appears to be some potential in improving lifestyle-based factors, although further investigation is necessary.

**Conclusion**

Many studies have drawn attention to neurocognitive dysfunction after surgery using neuropsychological assessments before and after surgery. The results on the incidence and severity of postoperative cognitive decline vary, mostly due to different definitions for diagnosing POCD.

Although the etiology of POCD is still not fully understood, inflammatory processes are currently considered to be central to its genesis. Presently, no clear anesthetic and surgical components have been found to influence POCD. Nevertheless, several patient-related factors, such as advanced age, have been associated with an increased risk for cognitive decline. As the age of the general population undergoing surgery is growing older, investigations on preventive measures and interventions are warranted, and they should be aptly applied.

**Conflicts of Interest**

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

**Author Contributions**

Setayesh Reza Tasbihgou (Conceptualization; Investigation; Writing – original draft; Writing – review & editing)  
Anthony Ray Absalom (Conceptualization; Project administration; Supervision; Writing – review & editing)

**ORCID**

Setayesh Reza Tasbihgou, https://orcid.org/0000-0002-6147-6163  
Anthony Ray Absalom, https://orcid.org/0000-0001-7563-9157
References


The aim of this paper is to introduce basic concepts and methods for calculating sample size in animal studies. At the planning stage of clinical studies, the determination of the sample size is a very important process to show the validity, accuracy, and reliability of the study. However, not all studies require a sample size to be calculated. Before conducting the study, it is essential to determine whether the study objectives suggest a pilot and exploratory study, as well as the purpose of testing the hypothesis of interest. Since most animal experiments are pilot and exploratory studies, it would be more appropriate to review other considerations for conducting an experiment while maintaining scientific and qualitative levels rather than sample size estimation. Sample size is calculated in various situations in animal studies. Therefore, it can be estimated according to the situations and objectives through the methods of precision analysis, power analysis, and so on. In some cases, nonparametric methods can be employed if the assumptions of normality is not met or a small sample is available for the study.

**Keywords:** Animal study; Exploratory study; Nonparametric sample size; Parametric sample size; Pilot study; Power analysis; Precision analysis.

**Introduction**

It is a crucial process to calculate the sample size before beginning a clinical study is a very important process to demonstrate its validity, accuracy, and reliability. However, not all studies require the calculation of a sample size. It is essential to determine whether or not the study is a pilot and exploratory study along with the purpose of testing the hypothesis of interest. Since most animal experiments are pilot and exploratory studies, it may be more appropriate to consider other things that can be tested while maintaining scientific and qualitative levels rather than sample size estimation. Sample size is calculated in various situations in animal studies. Therefore, it can be estimated according to the situations and objectives through the methods of precision analysis, power analysis, and so on. In some cases, nonparametric methods can be employed if the assumptions of normality is not met or a small sample is available for the study.

Ethical issues should be also considered while determining the sample size in animal studies.
studies. Russell and Burch [3] in the Principles of Humane Experimental Technique (1959) proposed that the 3Rs are similar to ethical considerations applied to any animal experiment by researchers and other institutes conducting these studies. The 3R principles are the harmonization of science and ethics in the field of animal experimentation, and includes replacing, refining, and reduction.

The purpose of this paper is to guide researchers a method for estimating the appropriate sample size in animal studies. Furthermore, this paper helps to understand the calculation of the sample size depending on the stage (pilot, exploratory, and confirmatory study) and the comparison type of the study.

### Pilot and exploratory experiments

Pilot studies are performed to check the feasibility of the measurement precision of the variables that are intended to be measured in the main study or pivotal study and to verify the logistic nature of the proposed experiment. The sample size of the pilot study is based on the researcher's previous experience or guesswork because previous data are not available. Exploratory studies are also conducted to create new hypotheses. In other words, the purpose of these studies are to determine the trend or pattern of responses; therefore, it does not require a significance test. The sample sizes for these studies are sometimes calculated based on previous studies. The data obtained from these studies (standard deviation, the mean difference between the two samples, etc.) is used to calculate the sample size for a pivotal study [4].

### Confirmatory study

A confirmatory study is a controlled study in which the study hypotheses are stated in advance and well-designed. The hypothesis of interest follows directly from the primary objective of the study, is always pre-defined, and is the hypothesis that is subsequently tested after completing the trial [5].

In these studies, it is very important to estimate with due precision the size of the effects attributable to the treatment of interest and to relate these effects to their clinical significance. In confirmatory study, sample size calculation plays an important role in providing evidence to support the claims. Therefore, estimating a valid sample size for the study is particularly important.

### General considerations prior to sample size calculation

Several factors must be considered when calculating the sample size, such as the study's purpose, study phase, type of comparison, primary variable and its characteristic, clinically meaningful difference, experimental design, statistical test, number of controls, randomization ratio, dropouts, covariates, and so on.

### Type of comparison

It is important to clearly state the objective of the intended study because the objective influences the hypothesis of the study. For the study objective, there are four types of comparisons: test for equality, superiority, non-inferiority, and equivalence. The equality test is a two-sided test, while the others are one-sided test (test for equivalence is a two one-sided test). The test for equality is often used to demonstrate the intended objective in pilot and exploratory studies and pre-clinical studies, such as animal studies. In other words, since confirmatory studies are commonly performed after many pilot/exploratory studies, the equality test is often conducted in pilot/exploratory studies, such as animal studies.

To demonstrate the objectives, hypotheses are usually formulated based on the primary study objectives. If it is explained using statistical notations to facilitate understanding, it is expressed as follows (Table 1). $H_0$ and $H_1$ are the alternative and null hypotheses, respectively. Let $\mu_t$ and $\mu_c$ be the true mean of the test and control group and $p_t$ and $p_c$ be the true proportion of the test and control group, respectively. Additionally, let $\delta$ be the clinically significant difference in the equality test, the non-inferiority margin in the non-inferiority test, the superiority margin in the superiority test, and the equivalence margin in the equivalence test.

We assume that the difference $(\mu_t - \mu_c) > 0$ is considered an improvement of the test group as compared to the control group.

<table>
<thead>
<tr>
<th>Type of comparison</th>
<th>Comparing Means</th>
<th>Comparing Proportions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$H_0$</td>
<td>$H_1$</td>
</tr>
<tr>
<td>Test for Equality</td>
<td>$\mu_t - \mu_c \neq \delta$</td>
<td>$\mu_t - \mu_c = \delta$</td>
</tr>
<tr>
<td>Test for Superiority</td>
<td>$\mu_t - \mu_c &gt; \delta$ ($&gt; 0$)</td>
<td>$\mu_t - \mu_c \leq \delta$</td>
</tr>
<tr>
<td>Test for Non-Inferiority</td>
<td>$\mu_t - \mu_c &gt; \delta$ ($&lt; 0$)</td>
<td>$\mu_t - \mu_c \leq \delta$</td>
</tr>
<tr>
<td>Test for Equivalence</td>
<td>$</td>
<td>\mu_t - \mu_c</td>
</tr>
</tbody>
</table>

https://doi.org/10.4097/kja.20662
A typical approach to compare the mean or proportion differences in a study with two independent samples (groups) is to test the following hypotheses shown in Table 1.

**Primary variable**

The outcomes from animal studies are distinguished from quantitative variables, whose values result from counting or measuring something, and qualitative variables as categorical variables. Sample size calculation is often performed based on statistical inference of the primary variable [2]. This paper deals with continuous and categorical variables, including dichotomous variables which define one of the outcomes as a “success” and the other a “failure.”

**Errors**

The significance level ($\alpha$) and statistical power ($1 - \beta$) must be considered when calculating a sample size. The significance level is the maximum allowable value of the type I error. The type I error indicates the probability of rejecting the null hypothesis when it is true. Statistical power is the probability of rejecting $H_0$ when it is false. If the type II error is set to $\beta$, then the statistical power is set to $1 - \beta$. The power analysis is a method of sample size calculation that can be used to estimate the sample size required for a study, given the significance level and statistical power.

Table 2 displays the four situations that can be considered for decision-making on unknown facts when testing the hypotheses.

**Sample size calculation**

Calculation of the sample size before beginning the study is desired to test the intended research objective. Too small sample size can cause lower the sensitivity of the experiment to identify significant differences, whereas too large sample size can waste time, cost, and resources or important investigational endpoint [6]. In the latter case, a trade-off may often occur between the cost-effectiveness and detecting power [2]. As such, it is difficult to determine the sample size for studies, especially in confirmatory studies.

Several studies have introduced methods to easily calculate the sample size. Arifin and Zahiruddin [7] introduced a method to calculate the sample size in animal studies, which are pilot and exploratory in nature, through a simple formula using an ANOVA design. The sample size in animal studies can be calculated for various situations. The statistical approaches also vary including precision analysis, power analysis and so on.

**Precision analysis**

Precision analysis is one of the methods for calculating the sample size. This approach chooses the sample size in such a way that there is a desired precision at a fixed confidence level, that is, a fixed type I error. It is simple and easy to calculate but may have a small probability of detecting a true difference.

The precision of the interval, $100(1 - \alpha)\%$ confidence interval, depends on its width. Because a narrower interval has a more precise interval, this method considers the maximum half-width of the $100(1 - \alpha)\%$ [2].

When $\sigma^2$ is known, the formula of sample size required from a $100(1 - \alpha)\%$ confidence interval for $\mu$ can be chosen as

\[
 n = \frac{Z_{\alpha/2}^2 \sigma^2}{E^2}
\]

where,

- $Z_{\alpha/2}$ is the upper $\frac{\alpha}{2}$th quantile of the standard normal distribution,
- and E is the maximum error in the estimation of $\mu$.

**Power analysis**

The power analysis method is usually used to estimate the sample size in a clinical research. It selects the required sample size to achieve the desired power for detecting a scientifically or clinically
meaningful difference at a fixed type I error [2].

The simple illustration in Table 3 has several assumptions: (1) two sample parallel design, (2) \( \sigma^2 \) is the known population variance, (3) the population variances of test and control group are equal to \( \sigma^2 \), (4) \( \mu_t - \mu_c \) is the true mean difference between a test group (\( \mu_t \)) and a control group (\( \mu_c \)), (5) \( \mu_t - \mu_c > 0 \) is considered an indication of improvement of the test group as compared to the control group, (6) \( \delta \) is the clinically significant difference in the equality test, the non-inferiority margin in the non-inferiority test, the superiority margin in the superiority test, and the equivalence margin in the equivalence test, (7) \( k \) is a constant for the allocation rate, (8) \( n_t \) is the sample size of the test group, and \( n_c \) is the sample size of the control group, and (9) \( z_{\alpha/2}, z_{\alpha}, z_p \) and are \( z_{\alpha/2} \) the upper \( \alpha/2 \)th quantiles of the standard normal distribution, respectively.

Other approaches

There are several methods besides precision and power analysis for calculating the sample size, such as probability assessment and reproducibility probability. These concepts are beyond the scope of this paper.

Other formulae of sample size calculation

Sample size for dichotomous data

Fleiss [8] provided an equation to compare the proportions in the two groups. Let an outcome be an event of interest, such as the occurrence of a disease or death, and proposed the following hypothesis:

\[ H_0: p_t - p_c = 0 \text{ versus } H_1: p_t - p_c \neq 0 \]

Let

\[ n_t = \frac{C (1 - p_t) + C (1 - p_c)}{\delta^2} + \frac{z_{\alpha/2}^2}{d} + 2 \]

where,

\[ d = | p_t - p_c | \]

\( C \) : a constant that depends on the values chosen for \( \alpha \) and \( \beta \), and is for two-sided test

Table 4 can be used to obtain the solution for the above formula and shows sample sizes per arm based on given \( C \) values, significance levels, and power, assuming \( S \) is 4 and \( d \) is 3.

Sample size for comparing two group means

Snedecor and Cochran [9] suggested a method for estimating sample size by comparing the mean differences between two group. To show the mean difference between two groups in parallel design, the following hypotheses are considered:

<table>
<thead>
<tr>
<th>Type of comparison</th>
<th>( H_1 )</th>
<th>( H_0 )</th>
<th>Sample size for control group</th>
<th>Sample size for test group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test for Equality</td>
<td>( \mu_t - \mu_c \neq \delta )</td>
<td>( \mu_t - \mu_c = \delta )</td>
<td>( n_t = C ) \frac{(1 + 1/k) \sigma^2 (z_{(1-\alpha/2)} + z_{\alpha/2})^2}{(\mu_t - \mu_c - \delta)^2} )</td>
<td>( n_t = kn_t )</td>
</tr>
<tr>
<td>Test for Superiority</td>
<td>( \mu_t - \mu_c &gt; \delta )</td>
<td>( \mu_t - \mu_c \leq \delta )</td>
<td>( n_t = C ) \frac{(1 + 1/k) \sigma^2 (z_{(1-\alpha/2)} + z_{\alpha/2})^2}{(\mu_t - \mu_c - \delta)^2} )</td>
<td>( n_t = kn_t )</td>
</tr>
<tr>
<td>Test for Non-inferiority</td>
<td>( \mu_t - \mu_c &gt; \delta )</td>
<td>( \mu_t - \mu_c \leq \delta )</td>
<td>( \delta &gt; 0 ): Superiority</td>
<td>( n_t = kn_t )</td>
</tr>
<tr>
<td>Test for Equivalence</td>
<td>(</td>
<td>\mu_t - \mu_c</td>
<td>&lt; \delta )</td>
<td>(</td>
</tr>
</tbody>
</table>
\[ H_0: \mu_c - \mu_t = 0 \text{ versus } H_1: \mu_c - \mu_t \neq 0 \]

Where,

\[ \mu_c : \text{population mean of the control group} \]
\[ \mu_t : \text{population mean of the test group} \]

Then, the sample size needed to achieve a power of \( 1 - \beta \) can be obtained from the following formula:

\[ n = 1 + 2C \left( \frac{s}{d} \right)^2 \]

where,

\[ s : \text{standard deviation} \]
\[ d : \text{the difference to be detected} \]
\[ C : \text{a constant that depends on the values chosen for } \alpha \text{ and } \beta, \]
\[ \text{and is for a two-sided test} \]

\( \text{Table 5} \) can be used to obtain the sample size per arm for the above formula and shows sample sizes per arm based on given \( C \) values, significance levels, and power, assuming \( s = 4 \) and \( d = 3 \).

**Nonparametric**

In many cases, parametric methods are used to estimate the sample size. However, the estimation of sample size can also be done in a nonparametric way if it is not possible to use large sample sizes, such as animal study. Estimating sample sizes by nonparametric methods is applicable when the sample size is small or when the assumption of normality is not guaranteed. In some animal studies, the assumption of normality may not be fulfilled during the estimation of sample size. Practically, the primary assumptions of the underlying population may not be satisfied. In such cases, nonparametric methods can be considered for testing the differences of location.

\( \text{Fig. 1} \) shows the comparison of the statistical power calculated using the parametric and nonparametric methods through 1,000 simulations as increasing the sample size from 1 to 30 by 1. For (a) and (b), paired t-tests and independent two-sample t-tests are applied, respectively, which are parametric methods. For (c) and (d), Wilcoxon's signed rank test and Wilcoxon's rank sum test (Mann-Whitney's U test) are applied, respectively, which are non-parametric methods. Non-parametric methods of (c) and (d) are corresponding to the parametric methods of (a) and (b), respectively. All alternative hypotheses are two-sided tests for equality with a significance level of 0.05, and the power is calculated by PASS 2020 [10].

\( \text{Fig. 1} \) shows the consistency in the statistical power of the parametric and nonparametric methods as the sample size increases. When estimating the sample size using non-parametric methods, there are some practical issues in which the power under the alternative hypothesis has not been fully studied. However, these non-parametric approaches can be helpful in exploratory...
Software for calculating sample size

The sample size can be easily calculated using various formulae. However, it can be difficult to calculate directly using formulae and may be calculated using computer algorithms. In some cases, computer simulations can be used to determine an appropriate sample size. Some well-known software that researchers can use for clinical researches are:

1. Power Analysis and Sample Size (PASS) software, sample size tools for over 965 statistical tests and confidence interval sce-
narios. (2) nQuery 7.0 Advisor program (Ireland), sample size, and power calculations. (3) G*Power 3 (Faul, Erdfelder, Lang, & Buchner), a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. (4) SAS® version 9.4 (SAS institute Inc., USA) using POWER and GLMPOWER procedures. (5) R version 3.6.5 (R Foundation for Statistical Computing, Austria) using “pwr” package, which is free and open source. (6) Sample Power (SPSS Inc., USA) is a tool for estimating the sample size on the various statistical studies.

More detailed information for comparing software for sample size determination can be found in a paper written by Dattalo [11].

There are many commercial and free software available on the Internet besides those mentioned above. It is also important for the user to check the accuracy and validity of the sample size whether it is appropriately calculated according to the study objectives as well as whether the algorithm of formula provided is accurate.

Conclusion

When estimating the sample size, there are several assumptions and conditions which are defined before beginning the study. Most animal studies are in the pilot and exploratory phase; therefore, it may be difficult to predefine the sample size for the study. Additionally, the ethical issues in animal studies and the sample size calculation in accordance with the 3R principle should be fully reviewed for any animal study. Nevertheless, at the planning stage, calculation of sample size plays a very important role in clarifying the intended objectives of the study. Sometimes, a problem of trade-off might happen when estimating the sample size. The careful appreciation of experimental design and statistics before data collection is the key of successful experiment when conducting an animal study.

Conflicts of Interest

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

Author Contributions

Mun Jung Ko (Conceptualization; Investigation; Methodology; Resources; Writing – review & editing)
Chi-Yeon Lim (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Validation; Visualization; Writing – original draft; Writing – review & editing)

ORCID

Mun Jung Ko, https://orcid.org/0000-0003-2317-9173
Chi-Yeon Lim, https://orcid.org/0000-0003-0178-6976

References


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Demographic and clinical factors associated with same-day discharge and unplanned readmission following shoulder arthroplasty: a retrospective cohort study

Brittany N. Burton¹, John J. Finneran², Aaron Angerstein³, Evelyn Ross⁴, Ana Mitchell⁵, Ruth S. Waterman², Ahmad Elsharydah⁶, Engy T. Said², Rodney A. Gabriel²,⁷

¹Department of Anesthesiology and Perioperative Medicine, University of California Los Angeles, Los Angeles, CA, ²Department of Anesthesiology, University of California San Diego, La Jolla, CA, ³Department of Biological Sciences, University of California San Diego, La Jolla, CA, ⁴School of Medicine, University of California San Diego, La Jolla, CA, ⁵Department of Radiology, University of California Davis, Sacramento, CA, ⁶Department of Anesthesiology and Pain Management, University of Texas Southwestern Medical Center, Dallas, TX, ⁷Department of Medicine, Division of Biomedical Informatics, University of California San Diego, La Jolla, CA, USA

Background: Same-day discharge, defined as discharge from the hospital within 24 h of surgery, has been shown to be safe for joint arthroplasty. We examined demographic and clinical factors associated with same-day discharge and unplanned readmission following shoulder arthroplasty in adult patients.

Methods: Utilizing data from the American College of Surgeons National Surgical Quality Improvement Program database, we extracted information of all patients that underwent shoulder arthroplasty. The primary and secondary outcome of interest was same-day discharge and 30-day unplanned readmission, respectively. We utilized multivariable logistic regression to identify covariates associated with these outcomes.

Results: There were 17,011 patients analyzed when identifying predictors for same-day discharge. There was an increase in same-day discharge from 2007 to 2016. The odds of same-day discharge were significantly better for males (P < 0.001). The odds of same-day discharge was significantly decreased for every 10-year increase in age and for patients with insulin dependent diabetes, poor functional status, chronic obstructive pulmonary disease, congestive heart failure (CHF), bleeding disorder, and comorbidity burden (all P < 0.001). There were 14,276 patients analyzed for hospital readmission. The odds of unplanned readmission were significantly higher for every 10-year increase in age and for patients with poor functional status, CHF, bleeding disorder, and higher comorbidity burden (all P < 0.005).

Conclusions: The results of this study show that preoperative comorbidities and advanced age reduce the odds of same-day discharge. Risk stratification, preoperative optimization, and coordinated care after surgery may be helpful to optimize patients for same-day discharge.

Keywords: Ambulatory; Discharge planning; Health care quality; Optimization; Outpatient; Rehabilitation.
**Introduction**

Total shoulder arthroplasty (TSA) procedures have doubled in the United States over the past ten years [1]. With approximately 70,000 surgeries each year, TSA has become the fastest growing total joint replacement procedure in the United States [1,2]. The number of procedures is expected to further increase given the aging population and the notable success of TSA procedures in restoring function and reducing pain [3,4]. TSA procedures are used to treat various degenerative conditions of the shoulder common in older adult populations [4,5].

Facility utilization constitutes an additional modifiable aspect of overall cost for these procedures. Minimizing hospital length of stay has the potential to greatly reduce health care spending. Same-day discharge, defined as discharge from the hospital within 24 h of surgery, has been shown to be safe for joint arthroplasty. The objective of the present study was to evaluate demographic and clinical factors associated with same-day discharge among adult patients who underwent shoulder arthroplasty (total and hemiarthroplasty) using the American College of Surgeons National Quality Improvement Program (ACS NSQIP) database. A secondary objective was to identify risk factors for 30-day unplanned hospital readmission.

**Materials and Methods**

**Data registry**

Our study was exempt from Institutional Review Board (IRB) approval and the requirement for written informed consent was waived. In the retrospective study, patient data was de-identified and exempt from consent requirements by our IRB. The ACS NSQIP registry was used to extract all patient records [6]. Briefly, ACS NSQIP is a nationally validated surgical outcomes registry used extensively to improve health outcomes. Inter-Rater Reliability Audit of chosen participating sites and other training methods are in place to ensure high quality data abstraction. NSQIP undergoes a systemic sampling process called the 8-day cycle, developed to make certain cases have an equal chance of being selected from each day of the week thereby preventing bias in choosing cases for assessment. The manuscript adheres to Enhancing the Quality and Transparency of Research (EQUATOR) guidelines.

**Data collection**

Cases were defined with Current Procedural Terminology code for shoulder arthroplasty 23472 (total shoulder arthroplasty) and 23470 (hemiarthroplasty). We used the ACS NSQIP database from 2007 to 2016 to evaluate risk factors associated with the primary outcome — same-day hospital discharge. However, ACS NSQIP from 2012 to 2016 was used to evaluate factors associated with the secondary outcome — unplanned readmission — defined as any unplanned readmission (to the same or another hospital) for a postoperative occurrence likely related to the principal surgical procedure within 30 days of surgery. We evaluated the association of the following covariates with the outcomes of interest: sex, body mass index (BMI), age, smoking status, steroid use, dyspnea, functional status, diabetes mellitus, chronic obstructive pulmonary disease (COPD), congestive heart failure (CHF), hypertension (HTN), bleeding disorder, anesthesia type, secondary anesthesia type (regional anesthesia versus none), and American Society of Anesthesiologists (ASA) classification score. BMI categories were < 20 kg/m², 20–24.9 kg/m², 25–29.9 kg/m², 30–39.9 kg/m², 40–49.9 kg/m², ≥ 50 kg/m² (the reference group was those with BMI range 20–24.9 kg/m²).

**Statistical analysis**

R (version 3.3.2) was the statistical computing software used to perform all statistical analysis discussed in our study. Mean differences between patients with same-day discharge versus those without (and with unplanned admission versus without) were compared with the Pearson chi-square and student t-test. A multivariable logistic regression was used to evaluate the association of same-day discharge and unplanned readmission. We first performed univariable logistic regression for each covariate and assessed its association with the outcomes. The primary and secondary outcomes are reported as odds ratios. During the initial model building of the multivariable logistic regression analysis, we only included those covariates with an association with the outcome with a P value < 0.2 from the univariable analysis. Subsequently, backward selection with a P value threshold of < 0.05 was performed to derive the final multivariable model. Covariates included in this final model were then presented as risk factors associated with the outcome. The odds ratio (OR) with associated 95% CI is reported for each covariate.

**Results**

**Same-day discharge**

We identified 17,021 patients who underwent shoulder arthroplasty from 2007 to 2016. After removing 10 observations with missing length of hospital stay, the final analysis included 17,011
### Table 1. Study Characteristics

<table>
<thead>
<tr>
<th>Patient factors</th>
<th>Same-day discharge</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 9,367)</td>
<td>Yes (n = 7,644)</td>
</tr>
<tr>
<td>Male</td>
<td>3367 (36.0)</td>
<td>4120 (53.9)</td>
</tr>
<tr>
<td>Age</td>
<td>70.24 ± 10.36</td>
<td>66.67 ± 10.49</td>
</tr>
<tr>
<td>18–29</td>
<td>13 (0.1)</td>
<td>35 (0.5)</td>
</tr>
<tr>
<td>30–39</td>
<td>65 (0.7)</td>
<td>102 (1.3)</td>
</tr>
<tr>
<td>40–49</td>
<td>238 (2.5)</td>
<td>293 (3.8)</td>
</tr>
<tr>
<td>50–69</td>
<td>1031 (11.0)</td>
<td>1249 (16.3)</td>
</tr>
<tr>
<td>60–69</td>
<td>2815 (30.1)</td>
<td>2781 (36.4)</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>5205 (55.6)</td>
<td>3184 (41.7)</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>&lt; 20</td>
<td>229 (2.4)</td>
<td>106 (1.4)</td>
</tr>
<tr>
<td>20–24.9</td>
<td>1486 (15.9)</td>
<td>1097 (14.4)</td>
</tr>
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<td>2914 (31.1)</td>
<td>2561 (33.5)</td>
</tr>
<tr>
<td>30–39.9</td>
<td>3580 (38.2)</td>
<td>3167 (41.4)</td>
</tr>
<tr>
<td>40–49.9</td>
<td>905 (9.7)</td>
<td>601 (7.9)</td>
</tr>
<tr>
<td>≥ 50</td>
<td>158 (1.7)</td>
<td>89 (1.2)</td>
</tr>
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<td>Unknown</td>
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<td></td>
<td>&lt; 0.001</td>
</tr>
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<td>7545 (80.5)</td>
<td>6504 (85.1)</td>
</tr>
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<td>Non-insulin dependent</td>
<td>1192 (12.7)</td>
<td>866 (11.3)</td>
</tr>
<tr>
<td>Insulin dependent</td>
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<td>274 (3.6)</td>
</tr>
<tr>
<td>Smoker</td>
<td>985 (10.5)</td>
<td>927 (12.1)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No</td>
<td>8570 (91.5)</td>
<td>7259 (95.0)</td>
</tr>
<tr>
<td>Moderate exertion</td>
<td>751 (8.0)</td>
<td>371 (4.9)</td>
</tr>
<tr>
<td>At rest</td>
<td>46 (0.5)</td>
<td>14 (0.2)</td>
</tr>
<tr>
<td>Functional status</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Independent</td>
<td>8878 (94.8)</td>
<td>7473 (97.8)</td>
</tr>
<tr>
<td>Poor</td>
<td>430 (4.6)</td>
<td>121 (1.6)</td>
</tr>
<tr>
<td>Unknown</td>
<td>59 (0.6)</td>
<td>50 (0.7)</td>
</tr>
<tr>
<td>COPD</td>
<td>755 (8.1)</td>
<td>350 (4.6)</td>
</tr>
<tr>
<td>CHF</td>
<td>73 (0.8)</td>
<td>10 (0.1)</td>
</tr>
<tr>
<td>HTN</td>
<td>6497 (69.4)</td>
<td>4759 (62.3)</td>
</tr>
<tr>
<td>Bleeding disorder</td>
<td>326 (3.5)</td>
<td>142 (1.9)</td>
</tr>
<tr>
<td>Primary anesthesia</td>
<td></td>
<td>0.027</td>
</tr>
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<td>General</td>
<td>9008 (96.2)</td>
<td>7347 (96.1)</td>
</tr>
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<td>Regional</td>
<td>343 (3.7)</td>
<td>268 (3.5)</td>
</tr>
<tr>
<td>Unknown</td>
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<td>29 (0.4)</td>
</tr>
<tr>
<td>Additional anesthesia</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>2931 (31.3)</td>
<td>2905 (38.0)</td>
</tr>
<tr>
<td>No</td>
<td>2437 (26.0)</td>
<td>2562 (33.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3994 (42.7)</td>
<td>2175 (28.5)</td>
</tr>
<tr>
<td>ASA class</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1 &amp; 2 Mild disturbance</td>
<td>3616 (38.6)</td>
<td>4216 (55.2)</td>
</tr>
<tr>
<td>3 Severe disturbance</td>
<td>5367 (57.3)</td>
<td>3301 (43.2)</td>
</tr>
<tr>
<td>&gt; 4 Life threatening disturbance</td>
<td>374 (4.0)</td>
<td>117 (1.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>10 (0.1)</td>
<td>10 (0.1)</td>
</tr>
</tbody>
</table>

Values are presented as number of patients (%) or mean ± SD. BMI: body mass index, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease, CHF: congestive heart failure, HTN: hypertension, ASA: American Society of Anesthesiologists.
30-day unplanned hospital readmission

To evaluate factors associated with unplanned readmission, we identified 14,276 patients who underwent shoulder arthroplasty from 2012 to 2016, who had available data regarding hospital readmission. Table 1 lists the study characteristics among the study population dividing the cohorts based on those with same-day discharge versus not. Fig. 1 demonstrates an increase in the prevalence of same-day discharge per year. On an unadjusted analysis, compared to the rate of non-same-day discharge, the rate of same-day discharge was significantly higher for males (36% vs. 53.9%, P < 0.001), overweight (31.1% vs. 33.5%, P < 0.001) and obese (38.2% vs. 41.4%, P < 0.001) patients, and ASA class ≤ 2 (38.6% vs. 55.2%, P < 0.001). Compared to the rate of non-same-day discharge, the rate of same-day discharge was significantly lower for those with non-insulin dependent (12.7% vs. 11.3%, P < 0.001) and insulin dependent (6.7% vs. 3.6%, P < 0.001) diabetes mellitus, dyspnea with moderate exertion (8.0% vs. 4.9%, P < 0.001) and dyspnea at rest (0.5% vs. 0.2%, P < 0.001), poor functional status (4.6% vs. 1.6%, P < 0.001), COPD (8.1% vs. 4.6%, P < 0.001), CHF (0.8% vs. 0.1%, P < 0.001), hypertension (69.4% vs. 62.3%, P < 0.001), bleeding disorder (3.5% vs. 1.9%, P < 0.001), and regional anesthesia (3.7% vs. 3.5%, P = 0.027). Fig. 1 shows the trends in same-day discharge.

Fig. 1. Trends in same-day discharge.

Discussion

We conducted a retrospective cohort analysis of factors associated with same-day hospital discharge and 30-day hospital readmission after shoulder arthroplasty using patient data from a nationally validated surgical outcomes registry. The odds of same-day discharge was lower for every 10-year increase in age and for patients with insulin dependent diabetes, poor functional status, COPD, CHF, bleeding disorder, and ASA class 3 and 4. However, in this study, the odds of same-day discharge was significantly increased for male patients. Patients with comorbidities were also more likely to experience unplanned hospital readmission. Although ambulatory surgery is well established and safe for knee and hip arthroplasty [7], further work is needed to define and understand the risk of adverse outcomes and benefits of ambulatory surgery for shoulder arthroplasty.

Although shoulder arthroplasty is less commonly performed than knee and hip arthroplasty, the demand is projected to increase [8]. The annual procedure volume growth rate of total shoulder arthroplasty and hemiarthroplasty was 9.4% and 5.4%, respectively [8]. From 1993 to 2007, there has been roughly a 2-fold reduction in postoperative hospital length of stay due to improvements in surgical technique and prosthetic design, preoperative patient education, use of intraoperative anesthetics allowing for rapid recovery, and postoperative multimodal analgesia. However, costs associated with shoulder arthroplasty have steadily increased [8–10]. Identifying factors and designing interventions mitigating barriers to cost control is therefore important.

In 2017, United States health care spending grew by 3.9% and comprises roughly 18% of annual spending [11]. Same-day discharge has been identified as a potential opportunity to lower costs while improving patient satisfaction and quality of care for joint arthroplasty [12]. The recent demand for ambulatory surgery may be due to escalating health care costs, and implementing same-day surgery discharged protocols with multidisciplinary care teams may be cost-effective. Same-day discharge is becoming common practice in many medical specialties across academic surgery centers and hospitals. Ambulatory TSA has increased in response to advances in multimodal pain management, patient
Table 2. Study Characteristics

<table>
<thead>
<tr>
<th>Patient factors</th>
<th>Unplanned readmission</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 13,860)</td>
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</tr>
<tr>
<td>Male</td>
<td>6124 (44.2)</td>
<td>181 (43.5)</td>
</tr>
<tr>
<td>Age</td>
<td>68.70 ± 10.24</td>
<td>71.09 ± 11.09</td>
</tr>
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<td>25 (0.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>30–39</td>
<td>117 (0.8)</td>
<td>3 (0.7)</td>
</tr>
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<td>40–49</td>
<td>381 (2.7)</td>
<td>11 (2.6)</td>
</tr>
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<td>50–69</td>
<td>1823 (13.2)</td>
<td>44 (10.6)</td>
</tr>
<tr>
<td>60–69</td>
<td>4720 (34.1)</td>
<td>116 (27.9)</td>
</tr>
<tr>
<td>&gt; 70</td>
<td>6794 (49.0)</td>
<td>241 (57.9)</td>
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<td>BMI</td>
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<td>1699 (12.3)</td>
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<td>830 (6.0)</td>
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<td>13407 (96.7)</td>
<td>373 (89.7)</td>
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<td>Poor</td>
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<td>Unknown</td>
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<td>COPD</td>
<td>896 (6.5)</td>
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<tr>
<td>CHF</td>
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<tr>
<td>HTN</td>
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<tr>
<td>1 &amp; 2 Mild disturbance</td>
<td>6356 (45.9)</td>
<td>118 (28.4)</td>
</tr>
<tr>
<td>3 Severe disturbance</td>
<td>7102 (51.2)</td>
<td>259 (62.3)</td>
</tr>
<tr>
<td>&gt; 4 Life threatening disturbance</td>
<td>386 (2.8)</td>
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<td>Unknown</td>
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<td>0 (0.0)</td>
</tr>
<tr>
<td>Reoperation</td>
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</tbody>
</table>

Values are presented as number of patients (%) or mean ± SD. BMI: body mass index, DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease, CHF: congestive heart failure, HTN: hypertension, ASA: American Society of Anesthesiologists.
screening parameters, and efforts to reduce costs due to inpatient admission. Cost benefit analyses estimate that outpatient procedures can lead to savings of thousands of dollars per patient and millions of dollars over the next ten years [13,14]. Previous studies of ACS NSQIP and single institution data have retrospectively examined predictors of morbidity with same day TSA procedures [13,15,16]. These factors, such as CHF, hematocrit < 38%, BMI, and depression, allow physicians to screen for suitable candidates, further decreasing morbidity post-operatively. Current studies have found no significant differences in the complication rates between same day discharge and inpatient procedures in appropriately screened patients [14].

We identified several comorbidities that were associated with a decrease in same-day discharge. Not surprisingly, patients with insulin-dependent diabetes mellitus, poor functional status, COPD, CHF, bleeding disorders, or higher ASA class were less likely to be discharged on the same day as the surgery. Sher and colleagues show a higher prevalence of impaired functional status, history of pulmonary and cardiac disease, stroke, and ASA class ≥ 3 among patients who were not eligible for same-day discharge following total knee or hip arthroplasty [12]. Similarly, Basques and colleagues report that diabetes mellitus and older age were shown to be associated with higher rates of 30-day readmission following same-day discharger for joint arthroplasty [17]. While many of these conditions are chronic, patients may benefit from preoperative optimization and postoperative multidisciplinary coordinated care pathways.

If patients are candidates for same-day discharge, early physical therapy has been shown to reduce readmission rates among patients undergoing total joint arthroplasty [18], and may be beneficial in this surgical population. Gogineni et al. [19] report no differences in complications rates among patients who underwent outpatient versus inpatient surgery after implementing structured care pathways involving surgeons, anesthesiologists, case management, rehabilitation services, home care companies, hospital administrators, and nursing leaders. Life expectancy has increased in the United States and consequently chronic diseases have become more prevalent. We must counteract the deleterious impact of these chronic conditions by standardizing preoperative care and mobilizing multidisciplinary health teams.

---

### Table 1: Factor Associated with Unplanned Readmission

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per decade)</td>
<td>1.14 (1.03, 1.25)</td>
<td>0.009</td>
</tr>
<tr>
<td>Poor Functional Status</td>
<td>2.80 (1.93, 3.95)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CHF</td>
<td>3.18 (1.54, 6.00)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Bleeding Disorder</td>
<td>2.05 (1.34, 3.01)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ASA Class 3</td>
<td>1.71 (1.37, 2.15)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ASA Class 4</td>
<td>3.94 (2.63, 5.79)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

### Table 2: Factor Associated with Same-day Discharge

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1.91 (1.79, 2.04)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age (per decade)</td>
<td>0.80 (0.78, 0.83)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Insulin Dependent DM</td>
<td>0.65 (0.55, 0.76)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Poor Functional Status</td>
<td>0.53 (0.43, 0.65)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>COPD</td>
<td>0.77 (0.67, 0.88)</td>
<td>0.001</td>
</tr>
<tr>
<td>CHF</td>
<td>0.30 (0.14, 0.56)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Bleeding Disorder</td>
<td>0.66 (0.54, 0.82)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ASA Class</td>
<td>0.61 (0.57, 0.65)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ASA Class 4</td>
<td>0.35 (0.28, 0.44)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

---

**Fig. 2.** Multivariable analysis of factors associated with unplanned readmission. CHF: congestive heart failure, ASA: American Society of Anesthesiologists.

**Fig. 3.** Multivariable analysis of factors associated with same-day discharge. COPD: chronic obstructive pulmonary disease, CHF: congestive heart failure, ASA: American Society of Anesthesiologists.

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Joint arthroplasty is more common among women, who also experience worse health outcomes compared to men [20]. In this study, the odds of same-day discharge was 86% higher for men compared to women. While the causes of this disparity are currently undefined, possible explanations include higher comorbidity burden in women, worse functional status, or other sociodemographic features that worsen outcomes. Further work is needed to substantiate our findings and provide insight into other contributing factors, with the ultimate aim to identify modifiable factors that may improve health outcomes and reduce health care spending.

ACS NSQIP is an excellent database source for evaluating outcomes in ambulatory surgery. However, ACS NSQIP does not include important perioperative variables that would allow for a more detailed and informative study such as cost associated with same-day versus non-same day discharge, severity of preoperative comorbidities, prosthesis used, surgeon’s experience, hospital volume, intraoperative anesthetic agents delivered, intraoperative variables (i.e., case duration and estimated blood loss), and pain management strategies. This retrospective study has limitations that are inherent to retrospective studies that include but are not limited to misclassification bias and confounding. Fortunately, since ACS NSQIP prospectively collects data, the temporal relationship between preoperative and postoperative variables is not ambiguous. Additionally, ACS NSQIP has program demands that may limit the participation of smaller community hospitals.

In conclusion, this is the first study to evaluate factors associated with same-day discharge and unplanned readmission following shoulder arthroplasty. The results of this study show that preoperative comorbidities and advanced age reduce the odds of same-day discharge and increase the odds of unplanned readmission. Risk stratification, preoperative optimization, and coordinated care after surgery may help to safely implement standardized protocols for same-day discharge. Enhanced care pathways may be helpful for patients who are candidates for same-day discharge.

Conflicts of Interest

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

Author Contributions

Brittany Burton (Conceptualization; Data curation; Methodology; Writing – original draft; Writing – review & editing)
John J. Finneran (Writing – review & editing)
Aaron Angerstein (Writing – review & editing)
Evelyn Ross (Writing – review & editing)
Ana Mitchell (Writing – review & editing)
Ruth S. Waterman (Writing – review & editing)
Ahmad Elsharydah (Writing – review & editing)
Engy T. Said (Writing – review & editing)
Rodney A. Gabriel (Conceptualization; Data curation; Formal analysis; Writing – original draft; Writing – review & editing)

ORCID

Brittany N. Burton, https://orcid.org/0000-0001-7078-2480
John J. Finneran, https://orcid.org/0000-0002-0955-155X
Aaron Angerstein, https://orcid.org/0000-0001-9945-4085
Ahmad Elsharydah, https://orcid.org/0000-0002-6243-0618
Engy T. Said, https://orcid.org/0000-0002-7897-1670
Rodney A. Gabriel, https://orcid.org/0000-0003-4443-0021

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Risk factors associated with hypotensive bradycardic events during open shoulder surgery in the beach chair position

Ji Won Choi, Duk Kyung Kim, Hee Joon Jeong, Young Ri Kim, Yoon Joo Chung, Yong Hun Son
Department of Anesthesiology and Pain Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Background: Shoulder surgery in the beach chair position frequently causes hypotensive bradycardic events (HBEs), which are potentially associated with an increased risk of cerebral hypoperfusion. Here, we aimed to investigate the incidence and characteristics of symptomatic HBEs that require pharmacological interventions, and to identify specific risk factors associated with symptomatic HBEs.

Methods: We retrospectively examined the records of all patients aged ≥ 18 years who underwent shoulder arthroty in the beach chair position between January 2011 and December 2018 at Samsung Medical Center. For patients who experienced HBEs while in the beach chair position, the minimum heart rate and systolic blood pressure were noted, as was the total dose of ephedrine or atropine.

Results: Symptomatic HBEs occurred in 61.0% of all cases (256/420). Two patients with symptomatic HBEs experienced postoperative neurological complications. Multivariable logistic regression analysis showed that preoperative interscalene brachial plexus block (ISB) and advanced age were risk factors associated with symptomatic HBEs (odds ratio [OR]: 3.240, 95% CI: 2.003, 5.242, P < 0.001; OR: 1.060 for each 1-year increase, 95% CI: 1.044, 1.076, P < 0.001, respectively). Receiver operating curve analysis revealed that a threshold of 62 years of age had a moderate degree of accuracy for predicting symptomatic HBEs (area under curve: 0.764, 95% CI: 0.720, 0.804, P < 0.001).

Conclusions: Considering the increasing risk of neurocognitive complications with aging, proactive hemodynamic management is needed, especially for elderly patients undergoing shoulder surgery in the beach chair position using ISB.

Keywords: Aged; Brachial plexus block; Bradycardia; Hypotension; Reflex; Shoulder arthroplasty; Sitting position.

Introduction

Shoulder surgery has become an increasingly common orthopedic procedure and is frequently performed in the beach chair position. Major advantages of this position include enhanced shoulder joint access, reduced bleeding, and broader anatomic perspective, facilitating tension-free examination of capsular anatomy [1].

However, this position is associated with considerable hemodynamic instability, which causes an increased risk of cerebral hypoperfusion [2–4]. Cerebral perfusion pressure decreases by approximately 15% in the sitting position in non-anesthetized patients and...
further decreases under anesthesia because of vasodilation and impaired venous return. Hypotensive bradycardic events (HBEs), a form of vasovagal reflex unique to the beach chair position, can potentially increase the risk of neurocognitive complications [5]. In South Korea, neurological injuries related to the beach-chair position for shoulder surgery were identified as typical injury profiles in the recent Korean Society of Anesthesiologists Legislation Committee report [4].

Although disastrous consequences of cerebral hypoperfusion have been limited to only a few reported cases [2,4], HBEs are not infrequent; thus, prediction of HBEs comprises a basic measure for proactive hemodynamic management. Therefore, we performed a retrospective chart review of adult patients who underwent open shoulder surgery in the beach chair position between January 2011 and December 2018 at Samsung Medical Center, Seoul, Republic of Korea, to investigate the incidence and characteristics of HBEs and identify specific risk factors for clinically relevant HBEs.

Materials and Methods

The present study was registered with the Clinical Research Information Service (Ref: KCT0003642). The Institutional Review Board of our hospital (approval number: SMC 2019-01-061, approval date: January 22, 2019) approved the study and waived the requirement for informed consent. This clinical research was done following the ethical principles for medical research involving human subjects in accordance with the Helsinki Declaration 2013.

We retrospectively examined the records of all patients aged ≥ 18 years who underwent shoulder arthrotoomy in the beach chair position during an 8-year period (January 1, 2011–December 31, 2018). Because most shoulder arthroscopic surgeries were performed in the lateral decubitus position at our hospital, we excluded such patients who underwent shoulder arthroscopic surgery from this comparative analysis of HBEs. In addition, patients who underwent concurrent surgeries other than shoulder arthrotoomy, and those who had an artificial pacemaker, were excluded from the study.

All operations were performed by the same senior surgeon, who accrued extensive experience prior to 2011. Patients who underwent shoulder arthrotoomy were routinely positioned with the back portion of the table at an approximately 60-degree angle, and with the hip and knee flexed; they remained in that position throughout the operation. In the beach chair position, the blood pressure cuff or arterial catheter was placed on the arm of the non-operative side, and intravenous access was attained.

Anesthesia was maintained primarily with inhalational anesthetics (sevoflurane or desflurane), which were titrated based on the hemodynamic response of the patient and the judgment of the anesthesia team. In rare cases, anesthesia was maintained with total intravenous anesthesia (TIVA) using propofol and remifentanil.

When interscalene brachial plexus block (ISB) was performed for postoperative pain control and supplemental intraoperative analgesia, 15–20 ml of 0.75% ropivacaine with 1 : 200,000 epinephrine was typically injected via ultrasound-guidance. Immediately before their arrival in the operating room, patients received the block in a separate regional block room.

HBEs were defined as a reduction in heart rate of more than 30 beats per minute (bpm) within a 5-minute interval, any reduction below 50 bpm, and/or a reduction in systolic blood pressure of more than 30 mmHg within a 5-minute interval, or any systolic pressure below 90 mmHg while in the beach chair position [6–8]. These events were treated with intravenous atropine (0.5 mg) or ephedrine (5 mg) (or both), in accordance with our hospital’s protocol. Symptomatic HBEs, the primary outcome of the study, were defined as those HBEs requiring the aforementioned pharmacological interventions.

The minimum heart rate and systolic blood pressure were recorded during each HBE and used in the statistical analysis. The time between reaching the beach chair position and the first occurrence of an HBE was defined as the HBE onset time.

The following were also noted for each case: demographic data, American Society of Anesthesiologists (ASA) physical status, current smoking status (current smokers were those who smoked within 1 week of surgery and had smoked at least 10 cigarettes per day for more than 1 year), alcohol abuse (i.e., an average of 3–4 drinks per day, four or more times per week), history of bradycardia, atrial fibrillation, hypertension, diabetes mellitus (DM), stroke, preoperative medication with β-adrenergic blockers, type of surgery and anesthesia, duration of surgery, estimated blood loss (EBL), preoperative application of ISB, and total dose of atropine or ephedrine as treatment for HBEs. In addition, neurological complications during hospitalization were examined in each case. At our hospital, antihypertensive drugs except diuretics were administered with a sip of water on the day of surgery.

Statistical analysis

Statistical analyses were performed using MedCalc for Windows software (ver. 18.11, MedCalc Software, Belgium). In all analyses, P < 0.05 indicated statistical significance. Univariable analyses were first performed to explore associations between variables of interest and the occurrence of symptomatic HBEs. Continuous variables were tested for normality using the Kolm-
ogorov–Smirnov test. Non-normally and normally distributed continuous variables were analyzed with the Mann–Whitney U test and unpaired t-test, respectively. Categorical variables were analyzed with the χ² test or Fisher’s exact test, as appropriate.

Second, a forward stepwise multivariable logistic regression analysis was conducted to identify independent risk factors for symptomatic HBEs. Any variables that were significant at P ≤ 0.2 in the univariable analysis were candidates for inclusion in the multivariable analysis. Model goodness-of-fit was evaluated using the Hosmer–Lemeshow test. Independent risk factors are expressed as odds ratios (ORs) with 95% CIs.

Receiver operating characteristic (ROC) curves were constructed to explore the sensitivity and specificity of each continuous variable identified as an independent predictor. Then, the optimal cutoff points for each predictor were determined at the maximum area under the curve (AUC) for the corresponding ROC curve.

Results

Of the eligible subjects, 11 were excluded from the final analyses because of concurrent surgeries other than shoulder arthroscopy (n = 9) or artificial pacemaker insertion state (n = 2). In total, 420 patients were analyzed (Fig. 1).

HBEs occurred in 311 patients (74.0%), of whom 256 (61.0% of all subjects) experienced symptomatic HBEs that required pharmacological interventions. The most common form of symptomatic HBE was hypotension alone (195/256, 76.2%). Notably, 53 of the patients who had symptomatic HBEs experienced both hypotension and bradycardia, whereas eight patients experienced bradycardia alone.

Two patients with symptomatic HBEs exhibited postoperative neurological complications (contralateral isolated hypoglossal nerve palsy in a 74-year-old man and acute brain infarct in the basal ganglia in a 77-year-old woman). In both of these patients, symptoms were resolved by conservative treatment during hospitalization.

Univariable and multivariable analyses of patients with and without symptomatic HBEs

In univariable analyses, significant differences were observed between patients with and without symptomatic HBEs in terms of gender, age, current smoking status, ASA physical status, EBL, duration of surgery, history of hypertension, DM, bradycardia, preoperative use of β-blocker, preoperative ISB, and type of anesthesia (P < 0.05, Table 1).

In addition to these 12 variables, one variable associated with symptomatic HBEs (at P ≤ 0.2) in the univariable analysis (operation site) was included in the multivariable logistic regression analysis. Finally, preoperative ISB and advanced age were identified as independent risk factors associated with symptomatic HBEs. Preoperative ISB increased the risk of HBEs by nearly three-fold (OR: 3.240, 95% CI: 2.003, 5.242, P < 0.001). When age was included as a continuous variable, advanced age was a strong risk factor for HBEs (OR: 1.060 for each 1-year increase, 95% CI: 1.044, 1.076, P < 0.001). ROC analysis indicated that the optimal age threshold to predict symptomatic HBEs was > 62 years (sensitivity: 84.8%, specificity: 62.2%); a threshold of 62 years had moderate accuracy (AUC: 0.764, 95% CI: 0.720, 0.804, P < 0.001) (Fig. 2).

When restricted to patients who received ISB, the site of blockade did not influence the risk of symptomatic HBEs (76.1% [137/180] on the right side vs. 69.6% [64/92] on the left side, P = 0.245).

Characteristics of symptomatic HBEs

The majority of symptomatic HBEs (207/256, 80.9%) occurred within 30 min after the beach chair position was achieved; the median (interquartile range) symptomatic HBE onset time was 15.0 min (range: 5.0, 30.0 min). While atropine was administered once in each case where it was needed, ephedrine was administered more than twice in 64.6% of patients who needed such treatment. In 20 patients, ≥ 30 mg of ephedrine was administered during surgery (Table 2).

Discussion

The present study showed that clinically relevant HBEs requiring pharmacological intervention were a common phenomenon, occurring in 61.0% of adult patients who underwent open shoulder surgery in the beach chair position. To the best of our knowledge, the present study is the first to evaluate HBEs that occurred solely during open shoulder surgery. Although the definitions of
is primarily because HBEs are brief, and most respond rapidly to the administration of anticholinergics or ephedrine. However, such events can lead to devastating complications associated with cerebral hypoperfusion, due to overestimation of cerebral perfusion pressure (frequently lower than blood pressure measured at the arm) and vascular compromise related to malpositioning of the head and neck [2].

In the present study, the majority of symptomatic HBEs (80.9%) occurred within 30 min after achieving the beach chair position, which is consistent with the time described in prior reports [3,8]. HBEs and orthostatic hypotension may have a similar triggering mechanism and involve the same efferent reflex limb [11]. The classical definition of orthostatic hypotension is a reduction in blood pressure within 3 min of standing. However, Roy et al. [12] reported that a considerable number of patients experienced a reduction in blood pressure within 10–45 min of beginning tilt-table testing.

HBEs are generally accepted as a form of vasovagal syncope mediated by the Bezold-Jarisch reflex, which occurs when venous pooling and increased sympathetic tone induce a low-volume hypopercontractile ventricle [2,3,9,13]. By this mechanism, surgical positioning with the patient in the beach chair position induces an abrupt withdrawal of sympathetic outflow and an increase in

---

**Table 1. Comparison of Clinical Characteristics between Patients with and without Symptomatic Hypotensive Bradycardic Events**

<table>
<thead>
<tr>
<th>Variable</th>
<th>With symptomatic HBEs (n = 256)</th>
<th>Without symptomatic HBEs (n = 164)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (F/M)</td>
<td>179 (69.9)/77 (30.1)</td>
<td>73 (44.5)/91 (55.5)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>70.3 ± 12.1</td>
<td>52.3 ± 20.0</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.2 ± 3.6</td>
<td>25.3 ± 3.6</td>
<td>0.723</td>
</tr>
<tr>
<td>EBL (ml)</td>
<td>258.5 ± 217.9</td>
<td>189.1 ± 197.5</td>
<td>0.001*</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>119.1 ± 30.4</td>
<td>107.7 ± 38.7</td>
<td>0.002*</td>
</tr>
<tr>
<td>Current smoking</td>
<td>12 (4.7)</td>
<td>23 (14.0)</td>
<td>0.001*</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>34 (13.3)</td>
<td>17 (10.4)</td>
<td>0.372</td>
</tr>
<tr>
<td>ASA PS (I/II/III)</td>
<td>29 (11.3)/176 (68.8)/51 (19.9)</td>
<td>70 (42.7)/76 (46.3)/18 (11.0)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Operation site (right/left)</td>
<td>166 (64.8)/90 (35.2)</td>
<td>96 (58.5)/68 (41.5)</td>
<td>0.193</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>162 (63.3)</td>
<td>51 (31.1)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>History of DM</td>
<td>53 (20.7)</td>
<td>20 (12.2)</td>
<td>0.025*</td>
</tr>
<tr>
<td>History of atrial fibrillation</td>
<td>13 (5.1)</td>
<td>6 (3.7)</td>
<td>0.495</td>
</tr>
<tr>
<td>History of bradycardia</td>
<td>26 (10.2)</td>
<td>5 (3.0)</td>
<td>0.007*</td>
</tr>
<tr>
<td>Preoperative use of β-blocker</td>
<td>31 (12.1)</td>
<td>10 (6.1)</td>
<td>0.043*</td>
</tr>
<tr>
<td>Preoperative ISB</td>
<td>201 (78.5)</td>
<td>71 (43.3)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Type of anesthesia</td>
<td></td>
<td></td>
<td>0.002*</td>
</tr>
<tr>
<td>ISB only</td>
<td>5 (2.0)</td>
<td>2 (1.2)</td>
<td></td>
</tr>
<tr>
<td>Inhalational</td>
<td>183 (71.5)</td>
<td>89 (54.3)</td>
<td></td>
</tr>
<tr>
<td>Inhalational + remifentanil</td>
<td>67 (26.2)</td>
<td>71 (43.3)</td>
<td></td>
</tr>
<tr>
<td>TIVA</td>
<td>1 (0.3)</td>
<td>2 (1.2)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as numbers (%) or mean ± SD. HBEs: hypotensive bradycardic events, BMI: body mass index, EBL: estimated blood loss, ASA PS: American Society of Anesthesiologists physical status, DM: diabetes mellitus, ISB: interscalene brachial plexus block, TIVA: total intravenous anesthesia. *Statistically significant difference (P < 0.05).
vagal tone, which results in bradycardia and/or hypotension.

In this regard, a preoperative state of increased sympathetic tone might predispose patients to subsequent HBEs. Consistent with this hypothesis, epinephrine administered with a local anesthetic mixture for ISB [7] or added to irrigation fluid during shoulder arthroscopy [8] increased the incidence of HBEs. However, studies regarding the preventive effect of preoperative administration of β-adrenergic blockers have shown conflicting results [6,13]. In the present study, preoperative use of β-adrenergic blockers did not constitute an independent risk factor associated with the onset of HBEs. These mixed results may be attributed to the difference between acute intraoperative medication and chronic antihypertensive medication. Moreover, such results may be influenced by the different effects on β1- and β2-adrenergic receptors of β-adrenergic blockers according to the type and dose, both in prior studies and in our study.

In the present study, preoperative ISB was an independent risk factor associated with the onset of HBEs. Its association with HBEs has been proposed by many investigators [3,6,7,9]; they suggested that the ISB procedure, or the use of epinephrine as an additive to the local anesthetic solution, might contribute to the development of HBEs in the beach chair position. Notably, ipsilateral stellate ganglion block is frequently accompanied by ISB (in up to 75% of cases); subsequent stellate ganglion block induces a reduced sympathetic and/or increased parasympathetic influence, thereby increasing the risk of HBEs [14,15]. However, one prospective randomized study revealed a similar incidence of HBEs between patients who underwent general anesthesia alone and those who underwent general anesthesia combined with ISB [10].

The most likely source of the difference between that study and ours is the age of the study cohorts (52.0 ± 9.5 vs. 63.3 ± 17.9 years) and different HBE evaluation periods (i.e., throughout surgery beginning immediately after the start of TIVA vs. restricted to the time in which the patient was in the beach chair position).

Depending on the ISB side, differences in hypotension and/or bradycardia develop due to hemispheric lateralization of autonomic cardiovascular control (i.e., sympathetic predominance in the right hemisphere and parasympathetic predominance in the left hemisphere) [15]. Based on this theory, one retrospective study proposed right-side ISB as a possible contributing factor to the occurrence of HBEs [9]. In that study, the incidence of HBEs in patients with right-sided blocks was 27.3% (12/44), whereas it was 5.3% (1/19) in patients with left-sided blocks. However, there was no predominance of right-sided blocks among patients with symptomatic HBEs in the present study (76.1% in right-sided blocks vs. 69.6% in left-sided blocks, P = 0.245). Another study also failed to find a predominance of right-sided blocks associated with symptomatic HBEs [6].

In the present study, advanced age was identified as a strong risk factor associated with the onset of symptomatic HBEs. An age of > 62 years, which was the optimal threshold in ROC analysis, predicted symptomatic HBEs with a moderate degree of accuracy. Aging is associated with a reduction of sympathetic-parasympathetic control of cardiac rhythm, which manifests as an increased prevalence of orthostatic hypotension. Although different afferent pathways are involved, advanced age has also been identified as an independent risk factor of vagally mediated bradycardia after peritoneal stretching or manipulation of abdominal visceral organs [16]. It is uncertain whether age-related autonomic changes directly promote the Bezold-Jarisch reflex. Presumably, age-related autonomic and baroreflex dysfunction might increase the risk of HBEs in the elderly [17].

In particular, an increased risk of HBEs in the elderly is clinically important in that appropriate regulation of cerebral blood flow declines in an age-related manner [18]. In addition, minimum cerebral perfusion pressure increases to the hypertensive range in an age-related manner [18]. Thus, a brief HBE can increase the risk of cerebral ischemia and contribute to neurocognitive complica-
tions in the elderly. Indeed, in the present study, postoperative neurological complications occurred solely in elderly patients with symptomatic HBEs (hypoglossal nerve palsy in a 74-year-old man and acute brain infarct in a 77-year-old woman). Because no intracranial vascular lesion or mass was identified postoperatively in either of these two cases, intraoperative cerebral hypoperfusion could not be ruled out as a causative mechanism [19].

This study had several potential limitations. First, the involvement of multiple practitioners for the management of HBEs might have resulted in inconsistency regarding the assessment of symptomatic HBEs. When HBEs occurred, 0.5 mg atropine or 5 mg ephedrine was administered intravenously, in accordance with our institutional treatment protocol (typically based on severity and duration). Thus, we do not believe that the characteristics of symptomatic HBEs were influenced by the presence of multiple practitioners. Second, a variety of beach chair position angles were used (i.e., generally between 45 and 80 degrees, according to surgeon preference); thus, our results using a 60 degree angle did not match those obtained in studies where the beach chair position angle differed from ours [20]. Lastly, we did not precisely assess the severity of symptomatic HBEs, due to the inherent limitations of the retrospective study design. However, the minimum heart rate and systolic blood pressure, as well as the total dose of atropine or ephedrine administered as treatment for HBEs, may serve as indicators of HBE severity.

In conclusion, the present study revealed a high incidence (61.0%) of clinical relevant HBEs requiring pharmacological interventions in adult patients who underwent open shoulder surgery in the beach chair position. In addition, ISB prior to general anesthesia and advanced age were identified as risk factors associated with clinically relevant HBEs. Thus, in the context of the age-related increase in the risk of neurocognitive complications, careful hemodynamic monitoring and vigilant maintenance of adequate cerebral perfusion pressure are needed, especially for elderly patients undergoing shoulder surgery in the beach chair position using ISB.

Conflicts of Interest

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

Author Contributions

Ji Won Choi (Conceptualization; Methodology; Validation)
Duk Kyung Kim (Conceptualization; Formal analysis; Methodology; Writing – original draft)
Hee Joon Jeong (Formal analysis; Investigation)
Young Ri Kim (Data curation; Investigation)
Yoon Joo Chung (Data curation; Formal analysis)
Yong Hun Son (Investigation; Methodology)

ORCID

Ji Won Choi, https://orcid.org/0000-0001-7403-2863
Duk Kyung Kim, https://orcid.org/0000-0002-6555-2100
Hee Joon Jeong, https://orcid.org/0000-0003-2051-7659
Young Ri Kim, https://orcid.org/0000-0002-5110-5481
Yoon Joo Chung, https://orcid.org/0000-0002-4294-0207
Yong Hun Son, https://orcid.org/0000-0001-8586-7313

References

Evaluation of the relationship between lactacidemia and postoperative complications after surgery for peritoneal carcinomatosis

Marta Soriano Hervás, Rosa Játiva-Porcar, Daniel Robles-Hernández, Anna Serra Rubert, Blanca Segarra, Cristina Oliva, Javier Escrig, José Antonio Llueca

Departments of Anesthesiology, Obstetrics and Gynecology, General Surgery, University General Hospital of Castellón, Castellón de La Plana, Spain

Background: Cytoreductive surgery was developed as a treatment for peritoneal carcinomatosis. However, this surgery is associated with important complications. The present study aimed to assess the relationship between lactacidemia and the rate of associated complications during the immediate postoperative period in the intensive care unit (ICU) in patients undergoing cytoreductive surgery.

Methods: This was a retrospective observational study. A total of 57 patients underwent cytoreductive surgery. All patients were admitted to the ICU immediately after the surgery. Data on lactic acid levels at the time of admission and discharge from the ICU were collected. Postsurgical complications that occurred during the ICU stay were recorded according to failure-to-rescue analysis and their severity stratified according to the Clavien-Dindo classification.

Results: The lactic acid levels at admission to the ICU were significantly higher in patients who developed complications, with an almost tripled unadjusted relative risk (2.9, 95% CI: 1.6, 5.3), than in those who did not develop complications for the lactacidemia threshold established in the cumulative sum curve graphs. After adjustment for confounding effects, the relative risk became even higher (3.1, 95% CI: 1.8, 3.6). Lactic acid levels were still significantly higher in this group at the time of discharge from the ICU.

Conclusions: Serum lactate level is a risk factor for postoperative complications in patients undergoing cytoreductive surgery for peritoneal carcinomatosis. This study suggests that the risk of developing severe complications almost triples with a lactic acid level of 2.5 mmol/L or higher at the time of admission in the ICU.

Keywords: Cytoreduction surgical procedures; Intensive care units; Lactic acid; Mortality; Peritoneal neoplasms; Postoperative complications.
ly improve the survival of patients with this condition [4]. However, in performing complex procedures, the associated morbidity and mortality must be taken into account [5]. CRS associated or not with HIPEC requires close monitoring throughout the entire perioperative period for optimal management.

Elevated levels of lactic acid (lactacidemia) has been shown to be correlated with tissue hypoxia and to predict increased perioperative morbidity and mortality [6,7]. According to Spiliotis et al. the average of 3 and 4 postoperative day lactate level is an independent predictor of morbidity and mortality in patients undergoing CRS and HIPEC. Our study shows a definite threshold in lactacidemia levels for an increased risk of complications.

Hence, the objective of this study was to evaluate the relationship between lactacidemia and the rate of associated complications during the immediate postoperative period in the intensive care unit (ICU) at the University General Hospital of Castellón between 2014 and 2016 in patients undergoing CRS.

**Materials and Methods**

All cases during a 2-year period (2014–2016) were included, which corresponded to the initial series of patients diagnosed with peritoneal carcinomatosis who underwent CRS in the Multidisciplinary Unit of Abdominal pelvic oncology Surgery of the University General Hospital of Castellón. All procedures were performed by the same surgical team. Information on the patients’ clinical and pathological characteristics, surgical procedures, and residual disease at surgery were prospectively collected and retrospectively analyzed for the purpose of this study.

All patients were admitted during the immediate postoperative period in the ICU of our hospital. The study was approved by the Institutional Review Board of the University General Hospital of Castellón on June 25, 2019 (approval number: HGCLAC01). The study is registered in the Clinical Trials Registry (Registration number: NCT04307654). The clinical research was done following the ethical principles for medical research involving human subjects in accordance with the Helsinki Declaration 2013.

**Data collection**

Data on lactic acid levels, measured using arterial blood samples, were collected at the time of admission and discharge from the ICU. Postsurgical complications that developed during the stay in the ICU were recorded according to failure-to-rescue analysis [8] (Table 1) and their severity stratified according to the Clavien-Dindo classification [9]. When several complications occurred in the same patient, the complication with the highest degree was considered.

**Statistical analysis**

Quantitative variables are summarized as median and interquartile range or mean ± SD. Categorical variables are presented using relative frequencies and percentages. For inferential analysis, the Mann-Whitney U test and Fisher’s exact test were used, as appropriate. Cumulative sum curves (CUSUMs) were used to obtain the most discriminating cutoff point of lactic acid level in relation to complications. These are the cumulative differences between an expected result, the general prevalence of complications, and the result observed in each case. Thus, these curves reveal the changes in the trend of the result of interest through different values of the prediction variable [10].

An adjustment for confounding effects was performed with logistic regression using the multivariate propensity score method. Possible confounding factors were considered, including Charlson age score, presence of ascites, current tumor (primary or relapsed), carcinomatosis index [11], number of visceral resections, blood loss, and norepinephrine dosage.

Statistical analyses were performed with the statistical program STATA version 15.1 (Stata Corp., USA).

**Table 1. Complications Used in Traditional Failure-to-rescue Analysis**

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Arrhythmias, Arrest, Infarction, Congestive heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>Pneumonia, Pneumothorax, Bronchospasm, Respiratory compromise, Aspiration pneumonia</td>
</tr>
<tr>
<td>Circulatory</td>
<td>Hypotension, Shock, Hypovolemia</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Stroke, Transient ischemic attack, Seizure, Psychosis, Coma</td>
</tr>
<tr>
<td>Vascular</td>
<td>Deep vein thrombosis, Pulmonary embolus, Arterial clot, Phlebitis</td>
</tr>
<tr>
<td>General</td>
<td>Internal organ damage, Return to surgery</td>
</tr>
<tr>
<td>Infection</td>
<td>Deep wound infection, Sepsis, Gangrene, Amputation</td>
</tr>
<tr>
<td>Others</td>
<td>Gastrointestinal bleeding, Blood loss, Peritonitis; Intestinal obstruction, Renal dysfunction, Hepatitis, Pancreatitis, Decubitus ulcers, Orthopedic complication, Compartment syndromes</td>
</tr>
</tbody>
</table>

From Silber et al. [8].
Results

During 2014 and 2016, a total of 57 patients underwent CRS. The demographics of the patients and the disease are shown in Table 2. Ovarian tumors (stages IIIC and IV International Federation of Gynecology and Obstetrics) were the most prevalent. Most of the patients scheduled for this surgery did not have significant comorbidity, and a carcinomatosis index of > 20 was observed in only 1 of every 5 cases. No major demographical differences were detected between patients who developed complications in the ICU and those who did not (Table 2).

Table 3 summarizes the surgical treatment factors that could influence the incidence of postoperative complications, as well as the oncological results of surgery and postoperative morbidity and mortality. No significant differences were detected between the groups without and with complications with respect to the type of surgery. However, in patients without complications in the ICU, the degree of complications that appeared in the surgical ward was significantly lower than in those who developed complications in the ICU. All 4 (7%) deaths in the series occurred during the stay in the ICU, which represents 14% of patients who developed complications in the ICU.

The lactic acid levels at admission to the ICU were significantly higher in those who presented complications, with an unadjusted odds ratio of 10.1 (95% CI: 2.5, 44) and an almost tripled unadjusted relative risk (2.9, 95% CI: 1.6, 5.3), than in those without complications for the threshold of lactacidemia established in the CUSUM graphs. After adjustment for confounding effects using multivariate propensity scores, the adjusted odds ratio became 16 (95% CI: 2.4, 103) and the adjusted relative risk was 3.1 (95% CI: 1.8, 3.6). Fig. 1 shows that, at the time of discharge from the ICU, the lactic acid levels were still significantly higher in the group of patients who presented complications. Fig. 2 shows the levels of lactic acid in the group of patients who did not develop complications.

It was observed in the CUSUM graphs that a lactic acid level of 2.5 mmol/L marks the threshold for an increased risk of complications. Fig. 3 shows the relationship between lactacidemia at admission in ICU and the development of complications. Fig. 4 shows the relationship between lactacidemia at admission in the ICU and death. The inflexion in the curves from that point means that the observed complications and deaths exceeded the expected values; the expected-observed difference negatively accumulated with statistical significance (P < 0.001 for complications; P = 0.02 for mortality) as lactic acid levels increased. The predominant grade of complications for levels up to 2.5 mmol/L was grade II (complications that do not require intervention), whereas it was grade III for higher levels, with grade IV complications and the 4 deaths of the series also appearing in this cohort. These data are shown in Table 4.

The patients’ features and operative variables according to lactic acid levels at admission in the ICU are shown in Table 5. The rela-

Table 2. Patient Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total series (n = 57)</th>
<th>Complications in ICU</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No (n = 29)</td>
<td>Yes (n = 28)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>61 (52, 67)</td>
<td>64 (58, 66)</td>
<td>60 (50, 67.5)</td>
</tr>
<tr>
<td>Current tumor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>41 (72)</td>
<td>20 (69)</td>
<td>21 (75)</td>
</tr>
<tr>
<td>Relapsed</td>
<td>16 (28)</td>
<td>9 (31)</td>
<td>7 (25)</td>
</tr>
<tr>
<td>Carcinomatosis type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>2 (4)</td>
<td>1 (3)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Ovarian</td>
<td>47 (82)</td>
<td>24 (83)</td>
<td>23 (82)</td>
</tr>
<tr>
<td>Endometrial</td>
<td>2 (4)</td>
<td>1 (3)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Pseudomyxoma</td>
<td>1 (2)</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Primary</td>
<td>4 (7)</td>
<td>2 (7)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Gastric</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Neoadjuvant treatment</td>
<td>21 (37)</td>
<td>8 (28)</td>
<td>13 (46)</td>
</tr>
<tr>
<td>Carcinomatosis index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–10</td>
<td>26 (46)</td>
<td>11 (38)</td>
<td>15 (54)</td>
</tr>
<tr>
<td>11–20</td>
<td>20 (35)</td>
<td>12 (41)</td>
<td>8 (29)</td>
</tr>
<tr>
<td>+20</td>
<td>11 (19)</td>
<td>6 (21)</td>
<td>5 (18)</td>
</tr>
<tr>
<td>CA125</td>
<td>174 (51, 800)</td>
<td>174 (58, 1280)</td>
<td>177.5 (50, 500)</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or frequency (%). ICU: intensive care unit. *Mann-Whitney U test, †P value: Fisher’s exact test.


Table 3. Procedure Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total series (n = 57)</th>
<th>Complications in ICU</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (n = 29)</td>
<td>Yes (n = 28)</td>
<td></td>
</tr>
<tr>
<td>Digestive anastomosis</td>
<td>39 (68)</td>
<td>20 (69)</td>
<td>19 (68)</td>
</tr>
<tr>
<td>Lymphadenectomy</td>
<td>47 (82)</td>
<td>25 (86)</td>
<td>22 (79)</td>
</tr>
<tr>
<td>HIPEC</td>
<td>19 (33)</td>
<td>10 (34)</td>
<td>9 (32)</td>
</tr>
<tr>
<td>Duration (min)</td>
<td>480 (400, 600)</td>
<td>540 (410, 600)</td>
<td>458 (375, 585)</td>
</tr>
<tr>
<td>Visceral resections</td>
<td>48 (84)</td>
<td>25 (86)</td>
<td>23 (82)</td>
</tr>
<tr>
<td>Number of resections</td>
<td>4 (3, 6)</td>
<td>4 (3, 6)</td>
<td>4 (2.5, 5)</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1000</td>
<td>7 (12)</td>
<td>5 (17)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>1000–2000</td>
<td>20 (35)</td>
<td>8 (28)</td>
<td>12 (43)</td>
</tr>
<tr>
<td>2000–3000</td>
<td>25 (44)</td>
<td>14 (48)</td>
<td>11 (39)</td>
</tr>
<tr>
<td>+3000</td>
<td>5 (9)</td>
<td>2 (7)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>Cytoreduction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC-0</td>
<td>49 (86)</td>
<td>25 (86)</td>
<td>24 (86)</td>
</tr>
<tr>
<td>CC-1</td>
<td>4 (7)</td>
<td>3 (10)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>CC-2</td>
<td>3 (5)</td>
<td>0 (0)</td>
<td>3 (11)</td>
</tr>
<tr>
<td>CC-3</td>
<td>1 (2)</td>
<td>1 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Lactic acid level at ICU admission (mmol/L)</td>
<td>2.3 (1.2, 3.2)</td>
<td>1.4 (1.1, 2.3)</td>
<td>2.7 (2.25, 5.1)</td>
</tr>
<tr>
<td>Lactic acid level at ICU discharge (mmol/L)</td>
<td>0.8 (0.6, 0.8)</td>
<td>0.6 (0.5, 0.8)</td>
<td>0.8 (0.7, 0.9)</td>
</tr>
<tr>
<td>Noradrenaline (μg/kg/min)</td>
<td>0.3 (0.15, 0.6)</td>
<td>0.2 (0.1, 0.4)</td>
<td>0.3 (0.28, 0.8)</td>
</tr>
<tr>
<td>Clavien-Dindo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No complication</td>
<td>11 (19)</td>
<td>10 (35)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Grade I</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Grade II</td>
<td>19 (33)</td>
<td>11 (38)</td>
<td>8 (29)</td>
</tr>
<tr>
<td>Grade III</td>
<td>19 (33)</td>
<td>8 (27)</td>
<td>11 (39)</td>
</tr>
<tr>
<td>Grade IV</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>2 (7)</td>
</tr>
<tr>
<td>Grade V (death)</td>
<td>4 (7)</td>
<td>0 (0)</td>
<td>4 (14)</td>
</tr>
<tr>
<td>Complications in ward</td>
<td>31 (54)</td>
<td>18 (62)</td>
<td>13 (46)</td>
</tr>
<tr>
<td>Accumulated complications by patient (ICU + ward)</td>
<td>1 (0, 2)</td>
<td>1 (0, 2)</td>
<td>1 (0, 2)</td>
</tr>
<tr>
<td>Death in ICU</td>
<td>4 (7)</td>
<td>4 (14)</td>
<td>0.035</td>
</tr>
<tr>
<td>Death in ward</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Values are presented as median (interquartile range) or frequency (%). HIPEC: hyperthermic intraperitoneal chemotherapy, ICU: intensive care unit. *Mann-Whitney U test, †P value: Fisher’s exact test.

The analysis of our study data indicated that the level of lactate is an important predictor of postsurgical complications. Lactate is produced by most of the tissues in the human body, with muscle tissue being the main production site [12]. Under normal conditions, lactate is quickly cleared by the liver and kidneys. During glycolysis, under aerobic conditions, pyruvate is oxidized via pyruvate dehydrogenase to acetyl-CoA that enters the Krebs cycle, obviating lactate production. In anaerobic conditions, pyruvate dehydrogenase is inhibited and pyruvate becomes lactate. Under these circumstances, lactate is the final product of glycolysis and becomes a substrate for gluconeogenesis in the Cori cycle. Its production is increased under hypoperfusion or stress conditions, causing an increase in glycolysis [12–14]. Although lactate levels may be elevated in several conditions, it has been effectively used as a measure of tissue hypoxia [1,6,15]. However, this is not uniformly accepted, as the level may increase under other conditions [13,14,16,17].

The findings of this study suggested that the risk of developing severe complications almost triples with a lactic acid level of 2.5 mmol/L or higher at the time of admission in the ICU, when the anesthetic phase has just ended.

Several studies have evaluated the clinical use of lactate level in postoperative patients [7,18,19]. The effectiveness of lactate level...
Fig. 1. Level of lactic acid in the group of patients who developed complications in the intensive care unit (ICU).

Fig. 2. Level of lactic acid in the group of patients who did not develop complications in the intensive care unit (ICU).

Fig. 3. Cumulative sum curve (CUSUM) for complications. The arrow points to the most discriminating cutoff point of lactic acid level with respect to the presence of complications from each value of lactic acid level. ICU: intensive care unit.

Fig. 4. Cumulative sum curve (CUSUM) for death. The arrow points to the most discriminating cutoff point of lactic acid level with respect to death from each value of lactic acid level. ICU: intensive care unit.

Table 4. Morbidity and Mortality in the ICU according to Lactic Acid Level

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total series (n = 57)</th>
<th>Lactic acid</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&lt; 2.5 mmol/L (n = 33)</td>
<td>≥ 2.5 mmol/L (n = 24)</td>
</tr>
<tr>
<td>Death in ICU</td>
<td>4 (7)</td>
<td>0 (0)</td>
<td>4 (17)</td>
</tr>
<tr>
<td>Complications in ICU</td>
<td>28 (49)</td>
<td>9 (27)</td>
<td>19 (79)</td>
</tr>
<tr>
<td>Clavien-Dindo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No complication</td>
<td>11 (19)</td>
<td>8 (24)</td>
<td>3 (13)</td>
</tr>
<tr>
<td>Grade I</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Grade II</td>
<td>19 (33)</td>
<td>17 (52)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Grade III</td>
<td>19 (33)</td>
<td>8 (24)</td>
<td>11 (46)</td>
</tr>
<tr>
<td>Grade IV</td>
<td>2 (4)</td>
<td>0 (0)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Grade V (death)</td>
<td>4 (7)</td>
<td>0 (0)</td>
<td>4 (17)</td>
</tr>
</tbody>
</table>

Values are presented as frequency (%). ICU: intensive care unit. P value: Fisher’s exact test.

https://doi.org/10.4097/kja.20089
Table 5. Patients' Features and Operative Variables according to Lactic Acid Level at Admission to the Intensive Care Unit

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 57)</th>
<th>Lactic acid &lt; 2.5 mmol/L (n = 33)</th>
<th>≥ 2.5 mmol/L (n = 24)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>60.0 ± 9.9</td>
<td>61.1 ± 9.8</td>
<td>60.1 ± 10.2</td>
<td>0.680</td>
</tr>
<tr>
<td>Current tumor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>41 (72)</td>
<td>27 (82)</td>
<td>14 (58)</td>
<td>0.051</td>
</tr>
<tr>
<td>Relapse</td>
<td>16 (28)</td>
<td>6 (18)</td>
<td>10 (42)</td>
<td></td>
</tr>
<tr>
<td>Charlson comorbidity index</td>
<td>2.0 ± 2.2</td>
<td>2.0 ± 2.3</td>
<td>2.0 ± 2.1</td>
<td>0.931</td>
</tr>
<tr>
<td>Neoadjuvant treatment</td>
<td>21 (37)</td>
<td>11 (33)</td>
<td>10 (42)</td>
<td>0.521</td>
</tr>
<tr>
<td>Total CPI</td>
<td>12.3 ± 8.7</td>
<td>13.1 ± 9.4</td>
<td>12.1 ± 7.8</td>
<td>0.610</td>
</tr>
<tr>
<td>CPI stratified</td>
<td></td>
<td></td>
<td></td>
<td>0.542</td>
</tr>
<tr>
<td>1–10</td>
<td>26 (46)</td>
<td>14 (42)</td>
<td>12 (50)</td>
<td></td>
</tr>
<tr>
<td>11–20</td>
<td>20 (35)</td>
<td>11 (33)</td>
<td>9 (38)</td>
<td></td>
</tr>
<tr>
<td>+20</td>
<td>11 (19)</td>
<td>8 (24)</td>
<td>3 (12)</td>
<td></td>
</tr>
<tr>
<td>Optimal cytoreduction</td>
<td>53 (93)</td>
<td>30 (91)</td>
<td>23 (96)</td>
<td>0.470</td>
</tr>
<tr>
<td>Intervention duration (min)</td>
<td>496.0 ± 150.0</td>
<td>528.0 ± 137.0</td>
<td>452.0 ± 160.0</td>
<td>0.060</td>
</tr>
<tr>
<td>Visceral resection number</td>
<td>5.0 ± 3.1</td>
<td>5.3 ± 3.7</td>
<td>4.1 ± 2.2</td>
<td>0.531</td>
</tr>
<tr>
<td>Intraoperative blood loss (ml)</td>
<td>2157.4 ± 941.1</td>
<td>2172.2 ± 987.4</td>
<td>2138.3 ± 893.8</td>
<td>0.891</td>
</tr>
<tr>
<td>Norepinephrine dose (μg/kg/min)</td>
<td>0.5 ± 0.5</td>
<td>0.2 ± 0.2</td>
<td>0.8 ± 0.6</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or frequency (%). CPI: carcinomatosis peritoneal index [11].

as a marker of morbidity and mortality in the postoperative period of patients undergoing CRS has also been demonstrated [6]. Our study confirms this relationship between lactic acid level and the development of complications.

Our findings are compatible with those of other studies [19–21]. In a prospective study that included 88 patients undergoing major abdominal surgery, it was observed that patients with elevated lactate levels had a significantly higher complication rate than patients without incidents in the postoperative course and whose lactate levels were in the normal range [19]. Another study found an association between blood lactate levels and organ failure and death [20]. Likewise, other studies indicated that surgical patients who develop complications have a greater deficit of tissue oxygenation during the intervention [21].

Previous studies have employed lactate level as a measure of tissue hypoperfusion, using its clearance as a resuscitation guide [13,14]. Those studies indicated that not only the increase in lactate levels but also the time until normalization of the levels were associated with postoperative morbidity and mortality. The relationship between lactic acid elevation and postsurgical morbidity in CRS has also been shown by Spiliotis et al. [6] in a study on patients undergoing CRS and HIPEC. The authors did not find an association between intraoperative lactic aid levels and postoperative morbidity and mortality. However, they highlighted the clinical relevance of lactate measurement on postoperative days 3 and 4, in that an increase of 1 mmol/L in the average lactate value on days 3 and 4 increases the risk of a minor complication by 1.9, the risk of a major complication by 10.9, and the risk of mortality by 32.1%. In our study, the risk of developing complications almost tripled when lactate levels were > 2.5 mmol/L.

One of the strengths of the present study lies on the homogeneity of the cohort of patients with abdominal carcinomatosis who were treated by the same specialized multidisciplinary team. Furthermore, it was possible to find a clear threshold of lactic acid level that discriminates the outcomes in terms of morbidity and mortality.

With respect to the limitations of this study, one was its observational design. The data were from a small series and from a single center during the immediate postoperative period in the ICU, thus making generalization impossible, although they supported the findings of similar studies. Our data did not show statistical differences in lactate levels with respect to surgery duration, disease stage, or patients’ comorbidities, probably because of the small sample size. Further, it has been hypothesized that several incidents during anesthesia [22–24] result in lactate elevation. This analysis would be strengthened by incorporating earlier time points (including intraoperative time points) of lactic acid measurement. In the future, analyzing these details of the anesthetic procedure constitutes an interesting research field. Similarly, data that relate the delay in the clearance of lactate to a greater number of complications were not available; measuring the rate at which lactic acid levels do (or do not) improve is another information that needs investigation.

Serum lactate level is a predictive factor for postoperative com-
Complications in patients undergoing CRS for peritoneal carcinomatosis. More studies with a larger number of patients and with more preoperative (liver function, renal function, drugs that interact with liver function), intraoperative (complexity of surgery, peritoneal carcinomatosis index, tissue oxygen supply, central oxygen saturation, anesthetic incidents), and postoperative (lactate clearance index) data should be performed to fully elucidate this phenomenon.

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Conflicts of Interest

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

Author Contributions

Marta Soriano Hervás (Writing – original draft)
Rosa Játiva-Porcar (Investigation)
Daniel Robles-Hernández (Investigation)
Anna Serra Rubert (Investigation)
Blanca Segarra (Investigation)
Cristina Oliva (Investigation)
Javier Escrig (Data curation; Formal analysis; Investigation; Methodology; Writing – review & editing)
José Antonio Llueca (Data curation; Formal analysis; Investigation; Writing – review & editing)

ORCID

Marta Soriano Hervás, https://orcid.org/0000-0001-5635-667X
Rosa Játiva-Porcar, https://orcid.org/0000-0002-0706-9639
Daniel Robles-Hernández, https://orcid.org/0000-0002-8861-2452
Anna Serra Rubert, https://orcid.org/0000-0002-7535-057X
Blanca Segarra, https://orcid.org/0000-0003-3203-0725
Cristina Oliva, https://orcid.org/0000-0003-0298-4018
Javier Escrig, https://orcid.org/0000-0002-4599-5828
José Antonio Llueca, https://orcid.org/0000-0003-3723-8795

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14. Weil MH, Alfii AA. Experimental and clinical studies on lactate


The effect of interscalene brachial plexus block with propofol sedation on preventing perioperative hypothermia during arthroscopic shoulder surgery

Ji Hye Lee, Hyun Joo Heo, Yu Yil Kim, Seung Min Baek, Ki Man Kim, Da Wa Jung

Department of Anesthesiology and Pain Medicine, Presbyterian Medical Center, Jeonju, Korea

Background: Interscalene brachial plexus block (ISBPB) is commonly used with general anesthesia for postoperative pain management in shoulder surgery. This study investigated the incidence of hypothermia and changes in the body temperature in patients undergoing arthroscopic shoulder surgery under ISBPB with propofol sedation.

Methods: This retrospective study enrolled 220 patients who underwent arthroscopic shoulder surgery. Patients were divided into general anesthesia (n = 34) and ISBPB with propofol sedation (n = 186) groups, and medical records were retrospectively compared. In addition, patients from the ISBPB group were further divided according to age (elderly [≥ 65 years], n = 98 vs. young [< 65 years], n = 88), and the incidence of hypothermia and changes in the body temperature were compared.

Results: Twenty-seven patients (12.3%) experienced perioperative hypothermia (range: 35.3–35.9°C). The incidence of perioperative hypothermia was 29.4% and 9.1% in the general anesthesia and ISBPB groups, respectively, and there was a significant difference between the two groups (P = 0.002). The incidence of perioperative hypothermia according to age in the ISBPB group was 9.2% and 9.1% in the elderly and young groups, respectively, and there was no significant difference between the two groups (P = 0.983).

Conclusions: The incidence of perioperative hypothermia during arthroscopic shoulder surgery under ISBPB with propofol sedation is lower than that under general anesthesia. Furthermore, when using ISBPB with propofol sedation, the incidence of perioperative hypothermia in elderly patients is similar to that in younger patients.

Keywords: Arthroscopy; Body temperature; Brachial plexus block; Interscalene; Sedation; Shoulder.

Introduction

Inadvertent perioperative hypothermia (core body temperature < 36°C), caused by impairment of thermoregulation due to anesthesia and a low operating room temperature, occurs frequently during surgery. It also occurs in patients undergoing arthroscopic shoulder surgery because this is commonly performed under general anesthesia, and a large amount of cold irrigation fluid is used at relatively high pressures to ensure visibility of the operative field [1,2]. Despite mild body temperature decreases of approximately 1–2°C, perioperative hypothermia can lead to various complications, including serious...
cardiovascular problems and increased risk of bleeding [3–7].

Various methods have been reported to prevent hypothermia during an arthroscopic shoulder surgery [1,2,8–13], and only few studies assessing interscalene brachial plexus block (ISBPB), which is widely used for postoperative pain control in shoulder surgery, have been reported [8–10]. A previous study reported that preoperative ISBPB can be useful in preventing hypothermia by reducing the amount of volatile anesthetics in patients undergoing arthroscopic shoulder surgery under general anesthesia [8]. However, other studies have reported that hypothermia occurs more frequently in elderly patients or when active warming is not performed despite using preoperative ISBPB with general anesthesia [9,10]. As such, the effect of ISBPB on preventing perioperative hypothermia is not clear. In addition, ISBPB was used as a supplement to general anesthesia in these studies, and the role of ISBPB is to reduce the thermoregulatory impairment caused by general anesthesia. There is no previous study comparing the effects of ISBPB and general anesthesia on hypothermia. ISBPB is used as the main anesthetic method for arthroscopic shoulder surgery with propofol sedation in our hospital. Therefore, the present retrospective study aimed to evaluate the incidence of perioperative hypothermia and changes in body temperature when ISBPB with propofol sedation was used as the primary anesthetic modality during arthroscopic shoulder surgery.

Materials and Methods

Study sample

The present study was approved by the Institutional Review Board of Presbyterian Medical Center, Jeonju, Korea (PMCIRB 2020-03-007) and registered at the Clinical Research Information Service (Ref: KCT0004918). The clinical research was done following the ethical principles for medical research involving human subjects in accordance with the Helsinki Declaration 2013. The present study was included 245 patients who underwent arthroscopic shoulder surgery between September 1, 2018, and February 29, 2020. Patients who were converted to general anesthesia due to incomplete ISBPB (n = 4), converted from arthroscopic to open surgery (n = 7), and those who underwent sedation using other sedatives without propofol (n = 14) were excluded (Fig. 1). The 220 patients were enrolled and divided into the general anesthesia group (Group GA, n = 34) and the ISBPB with propofol sedation group (Group ISBPB, n = 186). In addition, differences according to age (elderly patients ≥ 65 years, younger patients < 65 years) were compared in patients from the ISBPB group.

Methods

Data were retrospectively collected and analyzed using anesthetic and post-anesthetic care unit (PACU) records. All patients were monitored by noninvasive blood pressure measurements, electrocardiogram (ECG), and pulse oximetry. However, no premedication and pre-warming were performed before anesthesia.

As for the anesthetic method, ISBPB was performed except 1) when the patient wanted general anesthesia, 2) in patients who had a tendency of bleeding or who were taking anticoagulants, 3) when ISBPB was difficult to perform due to abnormal findings such as infection of the area where the nerve block was performed.

General anesthesia was induced with propofol, remifentanil, and rocuronium, and maintained with inhalation anesthetics using desflurane (or sevoflurane) and 50% oxygen-air mixture. Body temperature was measured with an esophageal stethoscope with temperature sensor (DeRoyal®, DeRoyal Industries Inc., USA).

ISBPB was performed by the anesthesiologist under ultrasound and nerve stimulator guidance with an in-plane technique using a mixture of 0.75% ropivacaine and 2% lidocaine. The pin-prick test was used to assess the adequacy of the nerve block, and propofol was administered with a target-controlled infusion pump to achieve appropriate sedation (Modified observer’s alertness/sedation [MOAA/S] score 1–3). The body temperature was measured on the side contralateral to the surgical area using a tympanic thermometer (ThermoScan IRT 4520, Braun, Germany). While supplying oxygen via a facial mask, respiration was continuously monitored during surgery by end tidal CO₂ and ECG. The oral airway was used when the upper airway was obstructed.

All patients underwent surgery in the beach-chair position by the same orthopedic surgeon. During the surgery, passive warming using a cotton blanket was performed, and active warming was performed using a forced-air warming device (WarmTouch™ 6000, Covidien, USA) placed on the knee area of the patient in

![Flowchart of patient allocation. ISBPB: interscalene brachial plexus block, GA: general anesthesia.](https://doi.org/10.4097/kja.20152)
both groups. In addition, humidified and heated respiratory circuit was used in the general anesthesia group. A three-liter normal saline bag, which was stored at room temperature, was used as the irrigation fluid.

Body temperature investigated was measured over time as follows: in the ward before leaving to the operating room (baseline); on arrival to the operating room; in 15 min intervals until the end of anesthesia; and on admission to the PACU. Changes in body temperature and the incidence of perioperative hypothermia (the lowest temperature) were examined and compared between the two groups. The severity of hypothermia was classified into Mild (35.5–35.9°C), Moderate (35.0–35.4°C), and Profound (< 35.0°C).

Statistical analysis

Statistical analysis was performed using SPSS ver. 23 (IBM Corp., USA), and patient characteristics are expressed as mean ± standard deviation (SD). Categorical data were analyzed using the chi-squared test or Fisher’s exact test. In addition, a logistic regression analysis adjusted with propensity score was performed to assess the correlation between the type of anesthesia and incidence of hypothermia. A P value < 0.05 was considered to be statistically significant.

Results

The present study included 220 patients (108 female, 112 male) with a mean ± SD age of 63.5 ± 11.1 years. There were no significant differences in demographic and perioperative data except sex (P = 0.013) between Group GA and Group ISBPB (Table 1).

Body temperature on arrival to the operating room were 36.4 ± 0.3°C in both groups and gradually decreased over time in Group GA and Group ISBPB, but there was no significant difference between the two groups (Fig. 2). Overall, perioperative hypothermia occurred in 27 (12.3%) patients, with the body temperature range...
ing between 35.3°C and 35.9°C and all cases occurred during the intraoperative period. The incidence of hypothermia was 29.4% and 9.1% in Group GA and Group ISBPB, respectively, and a significant relevance was found between perioperative hypothermia and the anesthetic method used (P = 0.002, odds ratio: 0.172, 95% CI: 0.057, 0.517). Two patients with perioperative hypothermia in Group GA experienced moderate hypothermia (Table 2).

In group ISBPB, there was no significant difference in demographic and perioperative data between elderly (≥ 65 years) and younger (< 65 years) patients, except age, height, weight, and propofol dosage. The dosage of propofol used for sedation was significantly higher in younger patients than elderly patients (5.9 ± 1.4 vs. 5.0 ± 1.4 mg/kg/h, respectively; P < 0.001). The incidence of hypothermia was similar in elderly and younger patients (9.2% vs. 9.1%, P = 0.983).

### Discussion

In the present study, the incidence of perioperative hypothermia was significantly lower in patients using ISBPB with propofol sedation than general anesthesia (9.1% vs. 29.4%, P = 0.002) during arthroscopic shoulder surgery. In addition, the incidence of perioperative hypothermia between elderly and younger patients in the ISBPB group was similar (9.2% vs. 9.1%, P = 0.983). In demographic data, there was no significant difference between the two groups, except for sex. The female sex is a risk factor for hypothermia, but the difference in sex (female/male = 10/24 in Group GA) was considered not to significantly affect the results [13,14].

Perioperative hypothermia should be prevented through active and appropriate methods as it can cause various, and sometimes serious complications. According to the National Institute for Health and Care Excellence Clinical Guideline, perioperative body temperature should be monitored at < 30 min intervals before the induction of anesthesia until the end of surgery. Moreover, the operating room temperature should be maintained at ≥ 21°C for management of the body temperature, while fluids or blood should be warmed before use. When the body temperature falls below 36.5°C during surgery, it is recommended that a forced air warming device be used [15]. Other reported methods for maintaining perioperative body temperature include pre-warming and warmed inspired gas [11,16]. Arthroscopic shoulder surgery is a common surgical procedure in orthopedic surgery. It requires the use of a large amount of irrigation fluid during surgery to ensure a clear operating field of view, and this, in addition to anesthesia, is one of several important factors that can decrease body temperature during surgery [1]. Room-temperature or cold irrigation fluid is absorbed by the systemic circulation through injured blood vessels and soft tissues in the shoulder region, which is relatively close to the center of the body, resulting in a decrease in body temperature. Kim et al. [2] reported that the incidence of hypothermia was 91.3% when room-temperature fluid was used and 17.4% when warmed fluid (37–39°C) was used. However, whether the use of warmed irrigation fluid can reduce perioperative hypothermia remains unclear [1,12]. Among the various methods for maintaining body temperature during the perioperative period, it is also important to choose an anesthetic method that is more advantageous for maintaining the body temperature according to the type of surgery. However, research investigating anesthetic modalities for perioperative temperature management is lacking, and our study therefore investigated this.

Lim et al. [8] reported that performing ISBPB in the preoperative period with general anesthesia reduced the amount of inhalation anesthetic required and consequently decreased the degree of perioperative hypothermia. A combination of general anesthesia and ISBPB may be beneficial for perioperative temperature management by reducing the impairment of thermoregulation by anesthetic agents. Regional (ISBPB) or general anesthesia can be used in shoulder surgery. However, regional anesthesia has a few limitations, such as requiring additional local anesthesia after ISBPB in the posterior area of the shoulder, and patients experiencing severe discomfort due to positioning during surgery because the operation is commonly performed in the sitting or ‘deck’ position. Regional anesthesia is mainly used in combination with general anesthesia for postoperative pain management in shoulder surgery. To overcome these limitations of regional anesthesia, we

### Table 2. Incidence and Severity of Hypothermia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (n = 220)</th>
<th>Group GA (n = 34)</th>
<th>Group ISBPB (n = 186)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothermia</td>
<td>27 (12.3)</td>
<td>10 (29.4)</td>
<td>17 (9.1)</td>
<td>0.002†</td>
</tr>
<tr>
<td>Mild (35.5–35.9°C)</td>
<td>25</td>
<td>8</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Moderate (35.0–35.4°C)</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Profound (&lt; 35.0°C)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number of patients (%). GA: general anesthesia, ISBPB: interscalene brachial plexus block. *Logistic regression analysis adjusted with propensity score, †Statistical significance was found between perioperative hypothermia and anesthetic methods (GA vs. ISBPB; odd ratio: 0.172, 95% CI: 0.057, 0.517).
performed sedation using propofol with ISBPB. By inhibiting thermoregulatory vasoconstriction, propofol can reduce the core body temperature similar to sevoflurane in general anesthesia [17]. Despite using propofol, which can cause hypothermia, the incidence of perioperative hypothermia was lower under ISBPB with propofol sedation than under general anesthesia with inhalation agents in the present study.

In elderly patients, the ability to control the body temperature is diminished; thus, the risk of hypothermia is increased under general anesthesia. Chun et al. [9] reported that although ISBPB was performed before general anesthesia and active warming was performed during an arthroscopic shoulder surgery, a significant temperature reduction occurred in elderly patients compared to young adult patients. The incidence of hypothermia in elderly patients was 93.1%, of whom 39.9% experienced a severe decrease in body temperature (≤ 34.9°C). However, in the present study, the incidence of hypothermia in the elderly patients of Group ISBPB was 9.2%, and there was no difference compared to younger patients. In addition, it was significantly lower than that reported by Chun et al. [9]. We speculate that ISBPB with sedation using propofol better preserved the ability to control the body temperature than general anesthesia in elderly patients.

The present investigation had limitations inherent to studies with retrospective designs. Firstly, the difference in the number of cases between the two groups was large. Thus, we performed the statistics adjusted with propensity score. Secondly, the ambient room temperature is an important cause of decreases in body temperature during surgery; however, we were not able to assess the operating room temperature in the present study. Thirdly, tympanic and esophageal thermometers were used in the two groups, and there was no protocol when using the thermometer. Finally, because active warming using a forced-air warming device was performed, it is difficult to clearly determine the effect of ISBPB alone. As such, future prospective studies investigating the effects of anesthesia combining ISBPB and sedation on perioperative body temperature management are required.

In conclusion, the incidence of perioperative hypothermia during arthroscopic shoulder surgery under ISBPB with propofol sedation is lower than that during general anesthesia. Furthermore, when using ISBPB with propofol sedation, the incidence of perioperative hypothermia in elderly patients is similar to that of younger patients.

**Conflicts of Interest**

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

**Author Contributions**

Ji Hye Lee (Writing – original draft)

Hyun Joo Heo (Data curation; Formal analysis)

Yu Yil Kim (Conceptualization; Supervision; Writing – review & editing)

Seung Min Baek (Data curation; Investigation)

Ki Man Kim (Data curation; Investigation)

Da Wa Jung (Data curation; Investigation)

**ORCID**

Ji Hye Lee, https://orcid.org/0000-0003-3269-3844

Hyun Joo Heo, https://orcid.org/0000-0003-2507-6629

Yu Yil Kim, https://orcid.org/0000-0003-3455-9251

Seung Min Baek, https://orcid.org/0000-0003-0290-0208

Ki Man Kim, https://orcid.org/0000-0002-4257-9167

Da Wa Jung, https://orcid.org/0000-0002-1566-7903

**References**


tive interscalene brachial plexus block aids in perioperative tempera-
Prevention of epidural catheter migration: a comparative evaluation of two tunneling techniques

Sujeet Gautam¹, Anil Agarwal¹, Pravin Kumar Das², Sandeep Khuba¹, Sanjay Kumar¹

Department of Anesthesiology, ¹Sanjay Gandhi Post Graduate Institute of Medical Sciences, ²Dr Ram Manohar Lohia Institute of Medical Sciences, Uttar Pradesh, Lucknow, India

Background: Epidural analgesia failure episodes can be reduced by catheter fixation techniques with a lower incidence of catheter migration. In this clinical study, we compared the roles of two epidural catheter tunneling techniques for the prevention of epidural catheter migration.

Methods: Patients undergoing major abdominal surgery were randomized into three groups of 50 patients each based on the method used to secure the epidural catheter. In the control group (CG), the epidural catheter was secured without tunneling. Tunneling groups 1 and 2 (TG1 and TG2) were defined as tunneling with and without a catheter loop, respectively. The primary outcome measure was the migration of the epidural catheter, while the secondary outcome measures were the adequacy of analgesia and signs of inflammation. All patients were followed up by the acute pain service team twice daily in the postoperative period until the epidural catheter was removed. The results were analyzed by the one-way analysis of variance (ANOVA), chi-square test, and Fisher’s exact test. P values < 0.05 were considered significant.

Results: The three groups were similar with respect to patient characteristics. Catheter migration was significantly reduced in TG2 (two patients) compared to those in the other two groups, i.e., TG1 (eight patients) (P = 0.045) and CG (17 patients) (P = 0.001). No differences were found amongst the three groups in analgesia adequacy and catheter site inflammation (P > 0.05).

Conclusions: Catheter migration was significantly reduced by tunneling without a catheter loop in TG2 as compared to the other two groups. Therefore, we suggest routine use of tunneling without a catheter loop technique in anesthesia practice and look forward to future studies with larger sample sizes.

Keywords: Catheter associated infection; Catheter migration; Epidural analgesia; Epidural catheter tunneling; Epidural injection; Postoperative pain.

Introduction

Epidural analgesia is considered an ideal choice for the management of postoperative pain. It provides peri-operative analgesia superior to that provided by parenteral analgesics along with additional benefits including the reduced incidence of cardio-respiratory and gastrointestinal complications after major abdominal surgery [1,2]. Therefore, it is important to maximize the efficacy of postoperative epidural analgesia by minimizing the factors responsible for its failure in the postoperative period.

The displacement and migration of epidural catheters is a commonly reported equip-
ment failure that results in inadequate epidural analgesia [3]. Technical issues in the form of premature epidural catheter withdrawal and catheter-bacterial filter assembly disconnection are responsible for epidural analgesia failure in up to 15% postoperative cases [3]. The standard methods of fixation cannot prevent migration in more than 50% of epidural catheters [4], which might lead to epidural analgesia failure if the catheter migrates outward or inward, giving rise to subdural, subarachnoid, or intravascular injection of drugs. Simple and cost-effective methods of catheter fixation with a low incidence of catheter migration are an appropriate answer to this problem.

The proposed epidural catheter fixation techniques include standard dressing, adhesive transparent dressing, tunneling, and epidural catheter clamp (Lockit clamp®, Smiths Medical, Czech Republic) [5–8]. Catheter migration is caused by patient movement [9], spine flexion and extension [10], spontaneous peeling of the adhesive dressing after getting wet due to perspiration, blood, discharges from the surgical incision, or skin movement during changes in patient positioning. Catheter migration secondary to skin movement cannot be avoided completely by fixing the catheter to the skin with the help of adhesive dressing; fixation techniques that minimize the traction on the catheter by skin rolling due to patient movement should be more effective in minimizing catheter migration.

This randomized control study compared the role of two epidural catheter tunneling techniques for the prevention of epidural catheter migration. The primary objective of this study was the assessment of epidural catheter migration.

**Materials and Methods**

The protocol for this randomized control study was approved by the institutional ethical committee (IEC code: IEC-07-IP-82) and registered in the Clinical Trials Registry-India (Registration number: CTRI/2016/11/007453). Written informed consent was obtained from all study participants. The clinical research was done following the ethical principles for medical research involving human subjects in accordance with the Helsinki Declaration 2013.

This study included adult patients aged 20–65 years with American Society of Anesthesiologists physical status I and II scheduled for major upper abdominal surgery under general anesthesia along with thoracic epidural analgesia. The surgical procedures included gastrectomy, colectomy, pancreaticoduodenectomy, exploratory laparotomy, and hepaticojejunostomy.

The exclusion criteria included patient refusal, uncontrolled systemic diseases, signs of local or systemic infection, coagulation disorders, and anatomical abnormalities.

Patients were recruited during the pre-anesthetic evaluation; each patient satisfying the inclusion criteria was randomly assigned to one of the three groups, with 50 patients in each group. Patient randomization was done by a project nurse not involved in the study with the help of a computer-generated table of random numbers. The random allocation sequence was sealed in an envelope; the anesthesia resident assigned to place the thoracic epidural catheter on the day of surgery opened these envelopes on the morning of surgery. The thoracic epidural catheter was placed in the T7 to T10 intervertebral spaces during the preoperative period under aseptic precautions. The epidural catheter (BD Perisafe®, Becton, Dickinson and Company, USA) was placed using a paramedian approach with loss of resistance technique; the epidural catheter with three lateral orifices was inserted with 5 cm of the catheter lying within the epidural space.

The epidural catheter was fixed along the patient’s back in the midline using sterile transparent adhesive film measuring 25 × 10 cm (Tegaderm®, 3M Healthcare, Germany); the catheter was fixed with the patient sitting upright or in a lateral position [9]. The transparent film permitted regular inspection of the epidural catheter; the dressing was changed if blood collection was found underneath the dressing during acute pain service rounds. The epidural catheters were secured as per the group allocation.

Control Group (CG): A loop of epidural catheter was formed at the catheter insertion site and fixed with transparent adhesive dressing tape.

Tunneling Group 1 (TG1: tunneling with a catheter loop): The epidural catheter was secured by tunneling. A subcutaneous tunnel of approximately 4 cm length was prepared by injecting 5 mL of 2% lignocaine with adrenaline along the paramedian plane, 1 cm lateral to the catheter insertion site; the catheter tunneling was facilitated by metal stylet of a 16-G intravenous cannula (Venflon®, Becton Dickinson Medical Pte Ltd., Singapore). The metal stylet was passed through the subcutaneous tunnel to exit 1 cm lateral to the catheter insertion site (Fig. 1). The distal end of the epidural catheter was passed through the stylet and pulled through the subcutaneous tunnel.

Tunneling Group 2 (TG2: tunneling without a catheter loop): The epidural catheter was completely buried in the subcutaneous tunnel without any loop.

Catheter tunneling was performed in the following steps:

**Step I:** After epidural catheter placement in the epidural space, a Tuohy needle was withdrawn 2–3 cm with the catheter remaining within the needle to prevent catheter shearing during the preparation of the subcutaneous tunnel (Fig. 2A).

**Step II:** A subcutaneous stab incision was made alongside the
Secondary outcome measures were analgesia adequacy and signs of inflammation.

All patients were followed up by the acute pain service resident twice daily in the postoperative period until the epidural catheter was removed. The anesthesiologist placing the epidural catheter initiated an acute pain service enrollment form containing patient demographic data, details of epidural catheter placement including the vertebral level of the catheter placement, depth of the epidural space, and catheter mark at the catheter insertion site in the CG and TG1 or at the tunnel exit site in the TG2. These catheter marks were also noted before catheter removal and the difference between two values was calculated as the catheter migration in individual patients. Inward migrations of 1 cm or more and outward migrations of 2 cm or more were considered significant 10. Epidural analgesia was discontinued in cases of inadequate analgesia, with outward migrations exceeding 2 cm; inadequate analgesia was suggested by the requirement for alternative analgesia methods or replacement of the epidural catheter 11. Each patient was also assessed daily for catheter migration, catheter dressing, analgesia adequacy, and catheter insertion site inflammation (defined as an area of erythema and induration > 5 mm around the skin exit site and/or visible pus) 10.

Outcome measures and assessment

The primary outcome measure was epidural catheter migration; the secondary outcome measures were analgesia adequacy and signs of inflammation.

All patients were followed up by the acute pain service resident twice daily in the postoperative period until the epidural catheter was removed. The anesthesiologist placing the epidural catheter initiated an acute pain service enrollment form containing patient demographic data, details of epidural catheter placement including the vertebral level of the catheter placement, depth of the epidural space, and catheter mark at the catheter insertion site in the CG and TG1 or at the tunnel exit site in the TG2. These catheter marks were also noted before catheter removal and the difference between two values was calculated as the catheter migration in individual patients. Inward migrations of 1 cm or more and outward migrations of 2 cm or more were considered significant 10. Epidural analgesia was discontinued in cases of inadequate analgesia, with outward migrations exceeding 2 cm; inadequate analgesia was suggested by the requirement for alternative analgesia methods or replacement of the epidural catheter 11. Each patient was also assessed daily for catheter migration, catheter dressing, analgesia adequacy, and catheter insertion site inflammation (defined as an area of erythema and induration > 5 mm around the skin exit site and/or visible pus) 10.

Statistical analysis

The sample size calculation was based on the primary outcome measure, i.e., the incidence of catheter migration. Assuming that the epidural catheter tunneling would reduce the incidence of catheter migration from 30% in the control group to 5% in the tunneling group, a sample size of 43 patients was required in each group.
group for the results to be significant (with $\alpha = 0.05$ and power $= 80$). To address dropouts, we enrolled 50 patients in each group. Demographic data were analyzed with one-way analysis of variance (ANOVA) and chi-square tests. The catheter migration incidence was analyzed with chi-square tests, while the incidence of analgesia adequacy and signs of inflammation were analyzed with Fisher’s exact tests. The method of analysis was decided prospectively and incorporated the intention-to-treat principle. IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., USA) was used to perform the statistical analyses. $P < 0.05$ was considered significant.

**Results**

A total of 184 patients were assessed for participation in the study between March and August 2015; of these, 150 patients were included (Fig. 3). The study analysis could not be completed in seven patients as they were unable to continue epidural infusion (epidural catheter dislodged in two patients, one each during patient shifting and changing clothes, pericatheter leak in four patients, and dural tap in one patient during epidural catheter placement). These patients were included for analysis of patient characteristics but not for the analysis of catheter migration because the epidural catheter was withdrawn prematurely.

The three groups were similar with respect to patient characteristics, level of epidural catheter placement, length of epidural catheter placed inside the epidural space, and duration of epidural analgesia (Table 1).

Catheter migration was seen in all the groups, but was significantly lower in TG1 (eight patients, $P = 0.038$) and TG2 (two patients, $P = 0.001$) as compared to that in the CG (17 patients) (Table 2); there was also a significant reduction in catheter migration in TG2 as compared to that in TG1 ($P = 0.045$) (Table 2). The CG patients had a higher incidence of both inward and outward catheter migration as compared to those in TG2; none of the patients in TG2 had inward catheter migration. (Table 2).

A total of 16 patients reported analgesia failure (eight patients in the control group; five patients in the TG1 and three patients in the TG2); out of these sixteen patients, catheter migration was observed in eight patients (Table 2). Catheter site inflammation was observed in one patient in the CG and three patients in the TG2 ($P = 0.617$).

**Discussion**

The present study concluded that both tunneling techniques re-

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**Table 1. Patient Characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n = 50)</th>
<th>Tunneling group 1 (n = 50)</th>
<th>Tunneling group 2 (n = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>42.9 ± 10.7</td>
<td>42.7 ± 14.3</td>
<td>42.9 ± 10.2</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>55.8 ± 9.3</td>
<td>56.6 ± 10.2</td>
<td>54.9 ± 10.1</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>32/18</td>
<td>35/15</td>
<td>33/17</td>
</tr>
<tr>
<td>Intervertebral space</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T7-8</td>
<td>15</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>T8-9</td>
<td>19</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>T9-10</td>
<td>16</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Depth of epidural space</td>
<td>5.0 ± 1.6</td>
<td>5.1 ± 1.4</td>
<td>5.5 ± 1.4</td>
</tr>
<tr>
<td>Days of epidural catheterization</td>
<td>5.7 ± 1.3</td>
<td>5.4 ± 1.4</td>
<td>5.9 ± 1.2</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or numbers.

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Fig. 3. CONSORT flow diagram.
duced epidural catheter migration. The tunneling without a catheter loop in TG2 appeared superior to other tunneling techniques used in TG1, as the incidence of epidural catheter migration in TG2 was one-fourth that in TG1.

The epidural catheter for postoperative epidural analgesia usually remains for three to five postoperative days; during this period, there was the possibility for catheter migration due to patient transfer, changes in patient position, patient ambulation, peeling of catheter dressing because of sweat or fluid discharge and friction between the patients’ back and the bed surface. These factors may result in traction on the epidural catheter by the skin and subcutaneous tissue due to skin rolling and movement.

The epidural catheter tunneling without a catheter loop in TG2 buries the epidural catheter subcutaneously so that there is only one site where the catheter traverses through the skin. In the traditional technique of epidural catheter tunneling in TG1, the epidural catheter traverses through the skin three times; hence, there is a possibility of greater skin traction being applied on the epidural catheter in TG1 as compared to that in TG2. This may have contributed to the lower incidence of epidural catheter migration in TG2 in the present study.

The incidence of epidural catheter migration in the present study was 4% in TG2 as compared to 17% in TG1 and 36% in the CG. We thought that a comparison of the results of the present study to those of previously published clinical trials would provide useful information. Thus, we applied the catheter migration criteria used in the present study to those of previously published studies and found an incidence of epidural catheter migration of 12–48% with transparent adhesive dressing [5,6] and 5–32% for various techniques used for epidural catheter fixation [6–10]. With epidural catheter tunneling, the incidence of inward catheter migration incidence was lower (4–12%) than that of outward migration (5–32%) [6,9,10]. Abukhudair et al. [12] reported no significant difference in the incidence of epidural catheter dislodgement between groups with or without tunneling; Sharma et al. [13] reported a significant increase in the incidence of side effects including erythema and bleeding with epidural catheter tunneling.

Analyses of catheter tunneling alone as a modality for epidural catheter fixation reported an incidence of epidural catheter migration associated with catheter tunneling of 12–32% [4,10,11] compared to 4% in the TG2 in the present study. Tripathi and Pandey [7] reported a 3% incidence of catheter dislodgement in the tunneling group but did not describe any details of outward catheter migration. Hence, the modified tunneling technique used in TG2 helped to reduce the incidence of epidural catheter migration.

In a multicenter registry analysis of 22,411 patients with continuous thoracic epidural analgesia, epidural catheter tunneling was associated with a lower risk of thoracic epidural catheter-related infections; however, the mechanism by which tunneling decreases infection is not clear [14]. The most common route of bacterial pathogen migration is along the cutaneous track of the epidural catheter [15]; epidural catheter tunneling allows better fixation, which reduces catheter movement underneath the skin, thus minimizing bacterial movement and colonization along the catheter [14]. The tunneling without a catheter loop in TG2 in the present study not only provided better catheter fixation but also shifted the catheter skin entry point at a distance from the site of entry into the epidural space. This may offer an additional barrier to bacterial infection.

The limitations of the present study are, first, the lack of blinding due to differences in the techniques used to secure the epidural catheter in the three groups. Second, the requirement for a small stab incision during epidural catheter tunneling in TG2, which resulted in catheter site inflammation in three patients in this group. Third, the study sample was inadequate to comment on analgesia failure or catheter insertion site inflammation. Final-

### Table 2. Incidence of Outcome Measures

<table>
<thead>
<tr>
<th>Outcome measure incidence</th>
<th>Control group (n = 47)</th>
<th>Tunneling group 1 (n = 48)</th>
<th>Tunneling group 2 (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catheter migration</td>
<td>17 (36)</td>
<td>8 (17)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>P value*</td>
<td>0.038</td>
<td>0.001</td>
<td>0.045</td>
</tr>
<tr>
<td>Inward migration</td>
<td>5 (11)</td>
<td>2 (4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>P value*</td>
<td>0.268</td>
<td>0.026</td>
<td>0.004</td>
</tr>
<tr>
<td>Outward migration</td>
<td>12 (25)</td>
<td>6 (13)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>P value*</td>
<td>0.123</td>
<td>0.004</td>
<td>0.004</td>
</tr>
<tr>
<td>Failure of analgesia</td>
<td>8 (17)</td>
<td>5 (10)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Signs of inflammation</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

Values are presented as numbers (%). *Intergroup comparisons of the control group with Tunneling groups 1 and 2, †Intergroup comparison of Tunneling group 1 with Tunneling group 2.
ly, the directions differed between subcutaneous tunneling in TG1 and TG2; in addition to the presence or absence of a catheter loop, this might have also contributed to the reduced incidence of epidural catheter migration in TG2 as compared to that in TG1.

Catheter migration was significantly reduced by tunneling without a catheter loop in TG2 as compared to the other two groups. Therefore, we suggest routine use of tunneling without a catheter loop technique in anesthesia practice and look forward to future studies with larger sample sizes.

**Conflicts of Interest**

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

**Author Contributions**

Sujeet Gautam (Conceptualization; Formal analysis; Methodology; Writing – original draft; Writing – review & editing)
Anil Agarwal (Data curation; Methodology; Project administration; Writing – review & editing)
Pravin Kumar Das (Data curation; Formal analysis; Investigation; Methodology; Supervision)
Sandeep Khuba (Investigation; Methodology; Resources; Software)
Sanjay Kumar (Investigation; Methodology; Project administration; Supervision)

**ORCID**

Sujeet Gautam, https://orcid.org/0000-0001-9462-521X
Anil Agarwal, https://orcid.org/0000-0002-5231-9609
Pravin Kumar Das, https://orcid.org/0000-0001-8441-8401
Sandeep Khuba, https://orcid.org/0000-0002-1840-1131
Sanjay Kumar, https://orcid.org/0000-0003-2875-5838

**References**

Clinical usefulness of ultrasound as an early diagnostic tool for neuroleukemiosisis-a case report-

Soon Ju Baek, Jung Woong Lee, Sukyung Chung, Shu Chung Choi, Jin Young Chon

Department of Anesthesiology and Pain Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea

Background: Neuroleukemiosis is a rare complication of leukemia. The diagnosis may be delayed owing to non-specific symptoms and the need for special diagnostic modalities.

Case: A 70-year-old man in his sixth year of remission from acute myeloid leukemia was referred to the pain clinic for shooting and radiating pain in the left posterior leg. A lumbar spine magnetic resonance imaging showed mild disc bulging of the L2-3, which was insufficient to explain the patient's symptoms. With insufficient pain response to lumbar epidural block and piriformis injection, we examined both sciatic nerves using an ultrasound and identified an enlarged hypoechoic mass on the left sciatic nerve at mid-thigh level. After that, we biopsied the mass under general anesthesia, and histology confirmed it to be neuroleukemiosisis.

Conclusions: Ultrasound is an inexpensive, non-invasive, simple, and quick diagnostic modality that can be used as a screening tool in the diagnosis of neuroleukemiosisis.

Keywords: Complications; Diagnosis; Extramedullary myeloid cell tumor; Leukemia; Neoplastic; Ultrasonography.

Although the peripheral nervous system is commonly involved in cancer patients, it is rarely affected in leukemia [1–4]. Leukemic infiltration of the peripheral nerves (neuroleukemiosisis) presents with non-specific symptoms depending on the nerve affected. Special diagnostic tools should be considered in patients presenting with this non-specific constellation of symptoms. Current diagnostic modalities include magnetic resonance imaging (MRI), positron emission tomography/ computerized tomography, electromyography/nerve conduction studies, and studies of cerebrospinal fluid and bone marrow. However, these modalities are expensive, invasive, and time-consuming.

This case report was approved by the Institutional Review Board of The Catholic University of Korea, Yeouido St. Mary’s Hospital (SC20ZESE0024).

Case Report

A 70-year-old man in his sixth year of remission from acute myeloid leukemia was referred to the pain clinic in July 2017 from the department of neurology for shooting and radiating pain in the left posterior compartment of the leg and sole of the foot that was progressively worsening. The pain intensity was 7/10 according to a numerical rating scale, and the nature of the pain was spontaneous, lancinating, and was accompanied by a sensation of extreme cold. Examination revealed mild calf muscle atrophy of the left leg.
and decreased power (grade 3/5) on plantar flexion and inversion of the left ankle. The left deep tendon ankle reflex was absent.

The electromyography/nerve conduction studies showed reduced response of the left posterior tibial nerve. A lumbar spine magnetic resonance imaging (MRI) showed diffuse lumbar disc degeneration and mild bulging of the L2-3 disc with left foraminal extension, which were insufficient to explain the patient’s symptoms. On infrared thermography, hypothermia in the left leg was observed (Fig. 1). Laboratory findings, including complete blood cell count, C-reactive protein, erythrocyte sedimentation rate, etc. were all normal. Symptomatic pain management with non-steroidal anti-inflammatory drugs, high doses of gabapentin, tricyclic antidepressants, and serotonin-norepinephrine reuptake inhibitors were ineffective. Opioid (oxycodone hydrochloride) was effective only at high doses (80 mg/day). Additional lumbar epidural block and piriformis injection based on the patient’s symptoms before the electromyography/nerve conduction studies were done, but the patient’s pain was not alleviated.

Based on the electromyography/nerve conduction results, we planned for sciatic nerve block. Before the block, we examined both sciatic nerves using ultrasound and found an enlarged hypoechoic and edematous mass on the left sciatic nerve at mid-thigh level (Fig. 2). The sciatic nerve block was conducted using guided ultrasound in the sub-gluteal region. Mepivacaine (10 ml, 0.5%) was injected on the thin triangular shaped nerve inside the fascial plane between the gluteus maximus and quadratus femoris muscles. After the sciatic nerve block, the pain was temporarily relieved.

MRI of the left thigh showed diffuse swelling and internal enhancement of the left sciatic nerve, with peri-lesional fluid collection at mid- to distal-thigh level (Fig. 3). Cerebral spinal fluid and bone marrow studies were conducted to exclude the possibility of relapse of leukemia in peripheral nerves, and no abnormal findings were observed in the test. However, neuroleukemiosis was confirmed by histology of biopsy obtained under general anesthesia in October 2017. Based on the biopsy findings, the patient was started on chemotherapy (cytarabine). The neuropathic pain and motor weakness persisted. After two months from time of referral, he died of pneumonia.

Discussion

Neuroleukemiosis is a very rare complication of leukemia. Until now, only 15 cases have been reported (Table 1) [1–12]. Including the case described in this report, the mean age of patients was 40.2 years, and four patients were aged < 20 years. Among the 15 cases, 10 (66.7%) were men. All cases involved ≥ one extremity, and four (including the current one) involved only one extremity. In
<table>
<thead>
<tr>
<th>Author (yr)</th>
<th>Age/Sex</th>
<th>Diagnosis</th>
<th>Involved regions</th>
<th>Symptom appearance during remission</th>
<th>Source of confirmation</th>
<th>EMG/NCS</th>
<th>CSF study</th>
<th>BM study</th>
<th>Other studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harris (1921)</td>
<td>17/M</td>
<td>ALL</td>
<td>Multi-extremities</td>
<td>X</td>
<td>Autopsy</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Rowland and Schnick</td>
<td>51/F</td>
<td>CLL</td>
<td>Multi-extremities</td>
<td>X</td>
<td>Biopsy</td>
<td>Abnormal</td>
<td>Elevated protein</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Krendel et al. (1987)</td>
<td>65/M</td>
<td>AMoL</td>
<td>Multi-extremities</td>
<td>O</td>
<td>Autopsy</td>
<td>Abnormal</td>
<td>Elevated protein and glucose</td>
<td>Normal</td>
<td>Cervical CT/myelogram: normal, lumbar-thoracic myelogram: normal</td>
</tr>
<tr>
<td>Nishi et al. (1991)</td>
<td>52/F</td>
<td>AMKL</td>
<td>Multi-extremities and face</td>
<td>X</td>
<td>Autopsy</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Billstrom and Lundquist (1992)</td>
<td>71/F</td>
<td>AMmL</td>
<td>Multi-extremities and face</td>
<td>O</td>
<td>Autopsy</td>
<td>Abnormal</td>
<td>Atypical and blast forms</td>
<td>Normal</td>
<td>N/A</td>
</tr>
<tr>
<td>Vital et al. (1993)</td>
<td>48/F</td>
<td>AMoL</td>
<td>Multi-extremities and face</td>
<td>O</td>
<td>Biopsy</td>
<td>Abnormal</td>
<td>Blast forms</td>
<td>Normal → relapse</td>
<td>N/A</td>
</tr>
<tr>
<td>Vital et al. (1993)</td>
<td>24/M</td>
<td>AMoL</td>
<td>Multi-extremities and face</td>
<td>O</td>
<td>Biopsy</td>
<td>Abnormal</td>
<td>Blast forms</td>
<td>Normal → relapse</td>
<td>N/A</td>
</tr>
<tr>
<td>Lekos et al. (1994)</td>
<td>63/F</td>
<td>AML</td>
<td>Multi-extremities</td>
<td>O</td>
<td>Autopsy</td>
<td>Abnormal</td>
<td>Increased leukocyte</td>
<td>Relapse</td>
<td>MRI: focal swelling on the nerves</td>
</tr>
<tr>
<td>Platten et al. (2007)</td>
<td>33/M</td>
<td>AML</td>
<td>Multi-extremities</td>
<td>X</td>
<td>Biopsy</td>
<td>Abnormal</td>
<td>N/A</td>
<td>N/A</td>
<td>MRI: marked swelling on the involved nerves with surrounding lobulated soft tissue mass. Gallium scan: Ga-67 uptake in the involved regions.</td>
</tr>
<tr>
<td>Liu et al. (2007)</td>
<td>10/M</td>
<td>ALL</td>
<td>Mono-extremities</td>
<td>O</td>
<td>Biopsy</td>
<td>N/A</td>
<td>Normal</td>
<td>Relapse</td>
<td>MRI: Intense T1 post-gadolinium enhancement. PET: abnormal 18fluoro-deoxyglucose (FDG) uptake tacking along the neurovascular bundle in the left thigh</td>
</tr>
<tr>
<td>Aregawi et al. (2008)</td>
<td>21/M</td>
<td>ALL</td>
<td>Multi-extremities</td>
<td>O</td>
<td>Biopsy</td>
<td>Abnormal</td>
<td>Normal → elevated protein, cell count</td>
<td>Normal</td>
<td>MRI: mass on the involved regions</td>
</tr>
<tr>
<td>Wang et al. (2015)</td>
<td>44/M</td>
<td>AML</td>
<td>Mono-extremities</td>
<td>O</td>
<td>Biopsy</td>
<td>Abnormal</td>
<td>Normal</td>
<td>Normal</td>
<td>MRI: mass on the involved nerves</td>
</tr>
<tr>
<td>Voin et al. (2017)</td>
<td>18/M</td>
<td>AML</td>
<td>Multi-extremities</td>
<td>O</td>
<td>Biopsy</td>
<td>N/A</td>
<td>Increased leukocyte</td>
<td>N/A</td>
<td>MRI: mass on the involved nerves</td>
</tr>
<tr>
<td>Voin et al. (2017)</td>
<td>16/M</td>
<td>AML</td>
<td>Mono-extremities</td>
<td>O</td>
<td>Biopsy</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>MRI: mass on the involved nerves</td>
</tr>
<tr>
<td>Current (2019)</td>
<td>70/M</td>
<td>AML</td>
<td>Mono-extremities</td>
<td>O</td>
<td>Biopsy</td>
<td>Abnormal</td>
<td>Normal</td>
<td>Normal</td>
<td>US: marked swelling on the involved nerves. MRI: diffuse swelling and internal enhancement. PET/CT: normal. IRT: hypothermia on the affected leg</td>
</tr>
</tbody>
</table>

most of the cases (73.3%), neuropathy appeared during the remission period. A sensory deficit was observed in all patients and most (93.3%) had motor weakness. Autonomic deficit was reported in only two cases. The most underlying leukemia was acute myeloid leukemia. In most cases (73.3%), the symptoms developed during the remission period, had led to misdiagnosis or delayed diagnosis. Because nerve conduction, cerebrospinal fluid, and bone marrow studies showed inconsistent findings, confirmation of neuroleukemiosis was through biopsy or autopsy. In this current case, we could not decide on a nerve biopsy as it could have worsened the motor weakness because the sciatic nerve is a mixed nerve.

The blood-nerve barrier consists of tight junctions, which separates the peripheral nerve from the circulating blood. Neuroleukemiosis is thought to be caused by infiltration of leukemic cells into the nerves after disability of the blood-nerve barrier by unknown factors [13]. Intractable neuropathic pain, numbness, and weakness can be the first signs of neuroleukemiosis. With only neuropathic symptoms present, it is easy to misdiagnose a leukemic mass infiltrating the peripheral nervous system, especially if the blood smear and bone marrow biopsy are negative for leukemia [12].

Differential diagnosis for neuroleukemiosis include Guillain-Barre syndrome, neurotoxicity from chemotherapy and abscess [5]. Nerve biopsy is the gold standard method, but nerve conduction study and radiological investigations, especially MRI and positron emission tomography are helpful in localizing the lesion [13]. Most treatments combine systemic chemotherapy and radiation therapy. When selecting the chemotherapy regimen, agents that can penetrate the blood-nerve barrier should be used [13]. In addition, peripheral nerve blockers may be performed to relieve the patient’s pain. The presence of neuroleukemiosis portends poor outcome [13].

Ultrasound is a simple device that is often used to guide nerve block. An ultrasound examination has an advantage over other diagnostic tools for peripheral nerve diseases in that it is both accurate and quick [14]. An abnormal finding can be found by fully examining the nerves from proximal to distal using ultrasound, and comparing them with the opposite nerve structure. The main pathologic findings upon ultrasound of the peripheral nerve are enlarged nerve, increased hypo- or hyper echogenicity, enlarged fascicles, increased thickness of the epineurium, and increased endoneural/perineural blood flow [15]. Although ultrasound findings alone are not sufficient to confirm, the above-mentioned abnormal findings can be found by comparing left/right, digital/proximal regions. Compared with electromyography/nerve conduction studies, ultrasound was found to be a simpler diagnostic and screening tool for peripheral nerve sheath tumors such as neurofibromatosis, also enables targeted MRI analysis.

Because neuroleukemiosis is a rare complication of leukemia, its diagnosis can be overlooked and therefore delayed, affecting prognosis. Ultrasound examination is a simple, inexpensive, non-invasive, and quick diagnostic modality for diseases causing peripheral neuropathy, including neuroleukemiosis.

For our patient, a diagnosis of neuroleukemiosis was delayed for six months because of the non-specific symptoms manifested during remission period of acute myeloid leukemia. Moreover, results from the complete blood cell count, cerebrospinal fluid, and bone marrow studies were normal. Initially, we suspected that the patient’s pain resulted from radiculopathy originating in the spine. However, upon ultrasound we observed an enlarged hypoechoic and edematous segmental mass on the sciatic nerve with normal adjacent muscle. No fluid collection was detected around the nerves since the pathological process occurred inside the nerve membrane owing to the invasion of the nerve membrane. Radiculopathy that originates from the lumbar spine usually shows no signs of peripheral nerve edema. If trauma was the cause, damage to muscles around the nerve should be observed, but in this case, only nerve lesions were observed. These findings were different from radiculopathy caused by disc herniation and trauma; hence, we quickly ruled out these etiologies.

In this case, we described a patient with unexplained new-onset neuropathy due to leukemic infiltration of the peripheral nerve during remission period. Ultrasound is helpful when patients with neuroleukemiosis have difficulty using MRI or positron emission tomography as a cost issue, or when it is difficult to perform a biopsy immediately.

Conflict of Interest

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

Author Contributions

Soon Ju Baek (Conceptualization; Writing – original draft; Writing – review & editing) Jin Young Chon (Conceptualization; Writing – review & editing) Jung Woong Lee (Writing – review & editing) Sukyung Chung (Writing – review & editing) Shu Chung Choi (Writing – review & editing)
References

Propofol is the most popular drug used for the induction and maintenance of anesthesia, but causes excitatory activities, such as myoclonus, opisthotonus, and rarely, generalized seizures [1]. Prolonged non-resolving seizure activity is termed status epilepticus (SE) and is a medical emergency with significant associated morbidity and mortality. Pharmacological management is done with benzodiazepines and antiepileptic drugs, along with prompt resuscitation and source control. SE, when continued despite the administration of two antiepileptic drugs, is called refractory status epilepticus (RSE). The seizure-like phenomenon due to propofol is widely reported in the literature. However, RSE caused by propofol is rare and is a diagnostic dilemma.

Case: A 44-year-old male patient presented with RSE during the intraoperative period and was under general anesthesia on propofol infusion. The seizure was resistant to benzodiazepines and phenytoin. Thereafter, the seizure subsided after the discontinuation of propofol infusion, and the patient was shifted to fentanyl and dexmedetomidine infusion for the maintenance of anesthesia. The postoperative follow-up was uneventful.

Conclusions: This article focuses on the management of intractable intraoperative seizure and highlights the need for the exploration of seizure characteristics caused by propofol.

Keywords: Anesthesia; Intraoperative complications; Myoclonus; Propofol; Status epilepticus; Tonic-clonic seizure.

Propofol is the most popular drug used for the induction and maintenance of anesthesia, but causes excitatory activities, such as myoclonus, opisthotonus, and rarely, generalized seizures [1]. Prolonged non-resolving seizure activity is termed status epilepticus (SE) and is a medical emergency with significant associated morbidity and mortality. Pharmacological management is done with benzodiazepines and antiepileptic drugs, along with prompt resuscitation and source control. SE, when continued despite the administration of two antiepileptic drugs, is called refractory status epilepticus (RSE). The management of RSE includes the induction of general anesthesia with propofol, thiopental, midazolam, or ketamine. However, management becomes intricate when RSE is caused by propofol. We report here a case of intraoperative RSE caused by propofol.

The patient has provided written informed consent for publication of this case report. This manuscript adheres to the applicable Enhancing the QUAlity and Transparency Of health Research (EQUATOR) guideline.

Case Report

A 44-year-old male patient (weight 60 kg) was posted for C2–C5 astrocytoma excision under general anesthesia. The surgery was performed at All India Institute of Medical Sciences Patna, India in 2019. The patient did not have any coexisting disease or history of seizure. Anesthesia was induced with injection of propofol, fentanyl, and vecuronium followed by tracheal intubation. The propofol infusion at a rate of 75–100 μg/kg/min was
started for the maintenance of anesthesia as motor and somatosensory evoked potential monitoring was planned for the patient. The bispectral index (BIS), invasive blood pressure, and central venous pressure were also monitored in addition to standard monitoring. Furthermore, the patient was made prone for surgery. Thirty minutes after the start of propofol infusion, as the surgeon was dissecting the superficial muscular layers after skin incision, the patient developed generalized tonic–clonic seizure (GTCS) involving all four limbs and truncal muscles. A sudden increase in blood pressure, heart rate, end tidal CO\textsubscript{2}, and BIS were also noted. The injection of 2 mg midazolam was then immediately given intravenously (IV). Although the intensity of seizure decreased, GTCS continued, for which a repeat dose of midazolam was given, but in vain. As the seizure was not controlled, a loading dose of 15 mg/kg phenytoin was given IV over 20 minutes. Nonetheless, the seizure continued with a seizure-free interval of 5 minutes. The injection of 250 mg thiopentone was then administered IV as a last resort for treating SE, which successfully aborted the episode for approximately 20 minutes, only to reappear again. Meanwhile, investigations such as electrolytes and arterial blood gases (ABG) were done to rule out aggravating factors. ABG indicated metabolic acidosis with hyperlactatemia, and electrolytes were within the normal range. A provisional diagnosis of propofol-induced seizure was made, and propofol infusion was discontinued. Anesthesia was then maintained on fentanyl, dexmedetomidine infusion and isoflurane to maintain a minimum alveolar concentration of 0.5–0.8, and surgery was allowed to proceed. The rest of the intraoperative and postoperative periods were uneventful, and the postoperative computerized tomography of the brain and electroencephalogram were within normal limits. The patient was symptom-free after three months of follow-up.

Discussion

Propofol is widely used as an induction agent for general anesthesia, and its common side effects are hypotension, respiratory depression, and local intravascular pain at the injection site. Neurological complications caused by propofol are widely reported and include GTCS, focal motor seizures, increased tone with twitching and rhythmic movements, opisthotonus and involuntary movements, collectively termed as seizure-like phenomenon (SLP). The mechanism of SLP due to propofol is mostly unknown, but potentially due to the imbalance between the activity of excitatory and inhibitory neurons in the GABA pathway [2]. Propofol-induced SLP does not have any fixed pattern of occurrence with respect to timing, duration, clinical presentation, age group, and the health of the patient involved [1]. In addition, no clear consensus exists regarding the prevention and management of such adverse events.

Walder et al. [1], in a systemic review, analyzed 81 cases of SLP of which one of the principal findings was the predominance of SLP during induction, emergence, or delay after anesthesia and sedation. Only two cases of its occurrence arose during maintenance [3,4]. The lower incidence of SLP during maintenance of anesthesia resulted from masking by neuromuscular blockage (NMB), a steady state level of propofol concentration, and less cerebral excitation [1]. Our case was unique as it occurred during the maintenance phase and was presented as SE, which was refractory to treatment by two antiepileptic drugs. Only a few reported cases of propofol-induced SE have been available, most of which emerged in the postoperative period. Additionally, a report from Japan stated that prolonged GTCS was initiated 10 minutes after propofol infusion after the brachial plexus block [5]. One case of propofol-induced SE during general anesthesia has also been reported in a patient with benign epilepsy with centrotemporal spikes, which lasted for 14 hours [6].

RSE is a condition where SE continues despite the administration of two antiepileptic drugs (e.g., benzodiazepines and phenytoin) and is associated with a high risk of complications. Complications of RSE include excitotoxic CNS injury, hyperthermia, pulmonary edema, arrhythmias, cardiovascular collapse, metabolic derangement, acute kidney and liver injury, rhabdomyolysis, and fractures [7]. Moreover, RSE has a high-mortality rate, and less than one-third of patients return to their premorbid level of functioning [8].

Seizures in the intraoperative period are difficult to diagnose when NMB is used, but suggestive signs include tachycardia, hypertension, increased end tidal CO\textsubscript{2}, pupillary dilatation, increased oxygen consumption, and increased muscle tone [7]. Management includes the administration of antiepileptic drugs and the correction of precipitant factors. In our case, the seizure was apparent because we did not use NMB in the maintenance of anesthesia. The treatment of RSE includes administering general anesthesia with propofol, thiopentone, midazolam, or ketamine. However, our patient was already on high-dose propofol infusion when he developed RSE. As no precipitating factors were found, we opted to discontinue propofol and started dexmedetomidine and fentanyl for the maintenance of anesthesia, which stopped the seizure episodes.

Apart from being used as an induction agent for general anesthesia, propofol is also widely utilized in the treatment of seizure due to its anticonvulsant properties. Nevertheless, rare case reports of the pro-convulsant effects of propofol [1–6] emphasize the need for the exploration of seizure characteristics caused by
propofol.

**Conflict of Interest**

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

**Author Contributions**

Abhyuday Kumar (Conceptualization; Validation; Visualization; Writing – original draft)
Amarjeet Kumar (Validation; Visualization; Writing – review & editing)
Neeraj Kumar (Validation; Visualization; Writing – review & editing)
Ajeet Kumar (Supervision; Visualization; Writing – review & editing)

**ORCID**

Abhyuday Kumar, https://orcid.org/0000-0002-9247-6713
Amarjeet Kumar, https://orcid.org/0000-0002-4272-5750
Neeraj Kumar, https://orcid.org/0000-0002-9161-7000
Ajeet Kumar, https://orcid.org/0000-0002-1464-6684

**References**

COVID-19 pandemic: ethical and legal aspects of inadequate quantity and quality of personal protective equipment for resuscitation

Patrick Wong¹, Wan Yen Lim², Huei Leng Chee², Rehana Iqbal³

¹Department of Anesthesia and Pain Medicine, Waikato District Health Board, Hamilton, New Zealand, ²Department of Anesthesiology, Singapore General Hospital, Singapore, ³Department of Anesthesiology, City Mediclinic Hospital, Dubai, United Arab Emirates

The coronavirus disease 2019 (COVID-19) pandemic has implications for cardiopulmonary resuscitation (CPR). Chest compression is an aerosol generating procedure that is associated with a high risk of disease transmission to healthcare workers (HCWs) [1]. Before commencing CPR, guidelines recommend usage of a minimum respiratory personal protective equipment (PPE), “an FFP3 mask (FFP2 or N95 if FFP3 is not available)” [1].

Adherence to guidelines may have been challenged in two scenarios. First, there was an “inadequate quantity” (supply) of N95 masks during this pandemic. This rendered the HCWs unable to physically adhere to the guidelines. Second, masks may have been or may have been perceived to be of “inadequate quality” for several reasons [1]. The N95 mask has a lower filtration performance than the first-choice FFP3 mask, i.e., 95% vs. 99% [1], although the clinical significance of this is unknown. Additionally, counterfeit and poor quality N95 masks are being sold. Since chest compression involves vigorous movements, it may lead to poor mask seal, decreased protection rates, and mask failure including strap slipping [2]. Finally, N95 masks undergoing extended use and reuse are associated with disease transmission and decreased functionality [3].

Ethical dilemmas and confusions arise in both scenarios. In the “inadequate quality” scenario, the HCW is expected to perform a duty (CPR) adhering to the guidelines (wearing a N95 mask). Hence, it is uncertain whether the HCW should proceed with an actual or perceived “inadequate quality” PPE. Moreover, existing PPE guidelines are not specific to CPR, and some guidelines recommend powered air-purifying respirators (PAPRs) during CPR in patients with COVID-19 [4]. As the risk of disease transmission during CPR is uncertain, it is unclear whether we should aim for the “maximum” level protection, or be satisfied with “adequate.” However, refusal to treat may result in disciplinary or legal action against the HCW.

Various statements and considerations pertaining to a doctor’s duty to treat (or not) are shown in Table 1. The duty to treat is guided by the ethical principles of beneficence, non-maleficence, autonomy, and justice [5,6]. As these principles apply to the patient, HCWs and society, there may be conflicting priorities. HCWs have an obligation to prevent self-infection and onward transmission of infections to other patients, their colleagues and relatives, and the wider community [1]. Further, the ethical principle of justice takes into account the right of not being killed by another human being [6] (with a serious infectious disease). Justice also requires hospitals to provide adequate PPE.

Moreover, there are the doctrines of expressed consent, implied consent, special training, reciprocity, and professional oaths and codes [5]. Expressed consent includes signing of a contract on the basis that adequate PPE would be provided [5]. Arguments against
Table 1. Legal Aspects and Guidance of PPE Provision and Healthcare Worker's Rights

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<td>Allow health workers the right to remove themselves from a work situation if they have a reasonable justification to believe that it presents an imminent and serious danger to their lives or health.</td>
<td>Resuscitation should not be started or continued in cases where the safety of the provider cannot be sufficiently assured.</td>
<td>If a patient poses a risk to the health workers’ health or safety, they should take all available steps to minimize the risk before providing treatment or making other suitable alternative arrangements for providing treatment.</td>
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Employer's duty

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<td>Ensure that all necessary preventive and protective measures are taken to minimize occupational safety and health risks.</td>
<td>Provide adequate infection control and prevention and PPE supplies (masks, gloves, goggles, gowns, hand sanitizer, soap and water, cleaning supplies) in sufficient quantity to those caring for suspected or confirmed patients with COVID-19.</td>
<td>Every employer shall ensure that suitable PPE is provided to his employees who may be exposed to a risk to their health or safety while at work except where and to the extent that such risk has been adequately controlled by other means which are equally or more effective.</td>
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Legal requirements and guidance regarding PPE provision are shown in Table 1. The legal duty to ensure that “safety is reasonably practicable” [8] is open to interpretation. If employers breach their duty of providing adequate PPE (in appropriate quantity and quality), they may be liable to prosecution depending on local regulations [7]. Furthermore, negative publicity and legal risk may ensue [9]. On the other hand, disadvantages of non-disclosure include the inability to conduct investigations and provide treatment (e.g., counselling and isolation), risk of further transmission, and potential harm (e.g., COVID-19) [9]. To balance this, “disclosure should be the norm, even when the probability of harm is extremely low” [9].

“Inadequate” PPE causes many ethical dilemmas for the HCWs. Global supplies of quality-controlled PPE must be robust to cope with the surging demands of the pandemic. Further studies are needed to confirm the risk of disease transmission and the clinical significance of the various levels of PPE protection. If protection is inadequate, corresponding guidelines must evolve to better protect HCWs.
Conflicts of Interest

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

Author Contributions

Patrick Wong (Conceptualization; Data curation; Supervision; Validation; Writing – original draft; Writing – review & editing)
Wan Yen Lim (Data curation; Writing – original draft; Writing – review & editing)
Huei Leng Chee (Writing – review & editing)
Rehana Iqbal (Validation; Writing – review & editing)

ORCID

Patrick Wong, https://orcid.org/0000-0002-3212-9496
Wan Yen Lim, https://orcid.org/0000-0002-0335-0255
Huei Leng Chee, https://orcid.org/0000-0001-6692-3789
Rehana Iqbal, https://orcid.org/0000-0001-9418-8902

References


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Brugada syndrome (BS) is an inherited autosomal dominant ion channelopathy that increases the risk of ventricular tachycardia, ventricular fibrillation, and sudden cardiac death. It has an incidence of one to five per 10,000 people in Europe to as high as 20 per 10,000 people in Southeast Asia [1]. Channelopathies were highlighted as one of the most common causes of maternal mortality from heart disease in pregnancy in the 2016 Mother and Babies: Reducing Risks through Audits and Confidential Enquiries in United Kingdom report. Physiological stress observed in labor, fever, exaggerated vagal tone, electrolyte disturbances, and sodium channel blockers can precipitate malignant ventricular arrhythmias in BS. Remifentanil patient-controlled analgesia (Remi PCA) is a well-established, feasible alternative to labor epidural analgesia [2]. We present the safe and successful use of intravenous (IV) Remi PCA for labor in a parturient with BS.

A 30-year-old primipara with a body mass index of 25.3 kg/m² (booking weight 69 kg, height 165 cm) with BS was referred to the obstetric cardiac clinic in her early pregnancy. She had a family history of cardiac arrest (her brother experienced cardiac arrest at the age of 19 years), leading to familial genetic screening and detection of SCN5A mutation. The patient’s baseline electrocardiogram (ECG) result was normal, but she had a Brugada ECG pattern (coved-type ST segment elevation > 2 mm, followed by a negative T wave in “high” V1–V3 leads) on Ajmaline testing (Fig. 1, pattern highlighted by the arrow). She was offered an implantable cardioverter defibrillator, considering her family history, but she declined to have one. Throughout pregnancy, there were no issues with her rhythm disturbance, she had a fairly good exercise tolerance, and no structural abnormalities were reported on transthoracic echocardiography.

She was discussed at the cardiac obstetric anesthesia multidisciplinary team (MDT) meeting. A vaginal delivery was planned, and the patient was informed regarding labor analgesia options including 50% medical nitrous oxide and 50% oxygen mix (Entonox®, BOC, United Kingdom), intramuscular diamorphine, Remi PCA, and a labor epidural analgesia. Key recommendations of the MDT included planned induction in the delivery suite, appropriate noninvasive hemodynamic monitoring, hourly temperature monitoring, keeping serum potassium > 4 mmol/L and magnesium > 0.8 mmol/L during the peripartum period, appropriate analgesia use and attachment of external defibrillator pads, and availability of the defibrillator in the delivery room. A list of medications to be avoided was included in her cardiac care plan from the website (www.brugadadrugs.org) that included ergometrine, metoclopramide, misoprostol, suxamethonium, tramadol, amiodarone, and ketamine.

Once the woman was in established labor at 38 weeks in our delivery suite, continuous ECG, pulse oximetry (SpO₂), and noninvasive blood pressure (NIBP) monitoring was initiated, and external defibrillator pads were applied to her chest. The patient requested a Remi PCA, which was programmed to administer a bolus of 20 μg of IV remifentanil with a 3-minute lockout as per unit protocol. Continuous nasal oxygen was administered...
at 2 L/min, and her heart rate (HR), ECG, respiratory rate, NIBP, SpO\textsubscript{2}, and sedation score were monitored every 15 minutes for the first hour then every half hourly with one-to-one midwifery care as per our hospital policy. She proceeded to have an uneventful vacuum-assisted vaginal delivery in the room. Her mean maternal HR, arterial pressure during labor analgesia, SpO\textsubscript{2}, and temperature were 96 beats/min, 92 mmHg, 97%, and 36.9°C during the peripartum period, respectively. Oxytocin 5 I.U. was administered in the form of slow IV infusion over 20 minutes to maintain uterine tone. Pain was reasonably well controlled with Remi PCA throughout, and she was significantly satisfied with the analgesia. A total of 1.58 mg of remifentanil was administered during labor (which lasted just over 4 hours) until the delivery of the neonate. APGAR scores for the neonate were 7, 9, and 10 at 1, 5, and 10 minutes, respectively.

We believe this is one of the first case reports of successful use of Remi PCA for labor analgesia in a parturient with BS. We failed to determine any case report published in the English literature regarding successful use of Remi PCA for labor analgesia in this cohort. We found one case of BS where Remi PCA was commenced at 40 μg bolus with a 2-minute lockout, but the patient reported dizziness. Hence, the medication was discontinued [3]. We used a lower dose of 20 μg and a 3-minute lock-out interval, which is well established in the literature. One-to-one care with a senior midwife was provided, with midwife being present throughout the duration of PCA. No hemodynamic instability or respiratory events such as apnea or hypoxia or hypotension or any other side effects were noted in our parturient. Although local anesthetics (LAs) are used for epidural labor analgesia in BS, arrhythmias have been reported due to their sodium-channel blocking properties, specifically following the use of bupivacaine. Thus, LAs should be induced with caution in BS [4].

Remi PCA was selected by our patient and was included in our multidisciplinary care plan as we believed that it had more advantages compared to a labor epidural analgesia. It is a short-acting, reversible, and an effective analgesic. There are previous case reports describing its successful use in non-obstetric patients with BS and in suppressing the pressor response of laryngoscopy and intubation in BS patients having a general anesthetic as it is fairly cardio stable. Considering the possible association between fever and epidural analgesia, a trigger for arrhythmia in BS is also minimized. A recent trial also suggested that Remi PCA could potentially decrease the risk of instrumental deliveries, reducing the risk of exposure of the parturient to LA in the theatre from spinal or epidural anesthesia [5].

We found Remi PCA to be both safe and effective with appropriate monitoring and one-to-one midwifery care and recommend its use as a useful alternative to labor epidural analgesia in BS. We encourage clinicians using Remi PCA to report their outcomes in women with BS to further confirm its safety and efficacy.
Conflicts of Interest

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

Author Contributions

Carla Gould (Data curation; Writing – original draft)
Kailash Bhatia (Conceptualization; Supervision; Writing – review & editing)

ORCID

Carla Gould, https://orcid.org/0000-0001-8000-6776
Kailash Bhatia, https://orcid.org/0000-0001-8108-1196

References

Infusion pumps are extensively used in clinical settings to administer fluids and drugs. Syringe pumps are especially useful because they are easy to prepare and convenient when small volumes of liquid medications need to be infused over a relatively long duration [1]. Despite the use of syringe pumps in everyday practice, the safe use of infusion devices is often overlooked by medical staff. Numerous hazards of infusion pumps have been reported [1–3].

The requirement for patient consent was waived by the Institutional Review Board of our institution (H-2003-019-089). A 32-year-old healthy pregnant woman was scheduled for emergency cesarean section. She was at 37+5 weeks of gestation and had undergone cesarean section four years ago. The preoperative examinations revealed normal results. After providing informed consent for anesthesia, the patient entered the operation room, and routine monitoring was performed. Her vital signs were stable. An anesthesia nurse installed a 20-ml syringe containing remifentanil (0.1 mg/ml) on a syringe pump (Injectomat TIVA Agilia®, Fresenius Kabi, Germany) and connected it to an intravenous line via a three-way stopcock. The syringe pump was powered off because the patient needed to be sterilized and draped before the induction of anesthesia.

After a few minutes, the patient closed her eyes, and an anesthesiologist asked her to open her eyes to confirm consciousness. She opened her eyes immediately but closed them soon again. Then, upward ocular deviation occurred. She did not respond to any command and became apneic. Flat capnography was observed and the Bispectral index fell to 75 at the same time. SpO₂ dropped to 89%, and mask bagging with 100% O₂ was started. At that time, her blood pressure and heart rate were 99/56 mmHg and 75 beats/min, respectively, and SpO₂ was quickly recovered to 100% after applying mask ventilation. We attempted to determine the reason for her unconsciousness and checked the syringe pump. A crack in the syringe was noted, through which air bubbles had entered and pushed the remifentanil solution into the patient (Fig. 1, Video 1). We immediately disconnected the remifentanil solution from the patient’s intravenous line. Consequently, only 10 ml of remifentanil solution remained in the syringe. After a brief notice to the obstetrician, 250 mg of thiopental sodium and 40 mg of rocuronium were injected. Tracheal intubation was performed without difficulty, and 5 min later, a male baby was delivered. No other notable events occurred during the remaining intraoperative period. The patient and her baby were discharged a week later.

After the events, the distribution and storage of the syringe were investigated, but there were no problems. We tested 10 more syringes installed in the same syringe pump, and all of them were similarly damaged. Also, the syringes were not damaged in other syringe pumps of the same model. The syringe pump was sent to the department of bioengineer-
In our hospital. They found that the syringe pump was aged and the clamp did not lock gently but became instantaneously pressurized and broke the syringe during installation. We did not report this case to the Korean patient safety reporting and learning system (KOPS, https://www.kops.or.kr) because we thought the problem was isolated to this particular syringe pump. However, two months later, the same adverse event occurred with another syringe pump of the same model in the surgical intensive care unit. Free flow of 1.5 mg of remifentanil was noticed after hypotension and bradycardia became apparent in a 93-year-old female patient. Her vital signs immediately returned to normal after dopamine infusion. We have reported this case to KOPS because we supposed that other similar cases may occur in the future.

This case raises several important points. Firstly, there is no consensus regarding how long syringe pumps should be used in terms of safety and cost-effectiveness. The two pumps have been used for seven years without any problems before this event. Old medical devices have the potential to malfunction at any time without any warning signs. Often, aging medical devices are discarded only after an adverse event occurs in the patient that ranges from minor to fatal. Another important point is patient monitoring during the use of infusion pump [3]. Although the syringe pump was placed only approximately 5 cm higher than the patient, air entered through a crack by siphon effect. The three-way stopcock connecting to the syringe pump was opened, and it did not have an anti-siphoning valve in this case. Both allowed free flow of remifentanil to the patient. The alarm did not sound because the syringe pump was not powered on. Moreover, the damaged syringe was difficult to be noticed because the crack was small and partially covered by the clamp. Therefore, if the patient was left without monitoring, unconsciousness and apnea could have gone unnoticed that would have led to a fatal consequence in both the mother and the baby.

It is necessary to actively report medical device adverse events. In the first case, we did not report it because we thought it was only a problem with the syringe pump used in this case. Two months later, the same problem occurred, and the second case had almost gone unreported as well; however, the anesthesiologist who was involved in the second case had heard about the first case. The clinical trials for medical devices are conducted under strictly controlled conditions, so it is difficult to say that the safety of medical devices is completely evaluated in these trials. Therefore, to supplement the limitations of pre-market evaluations of medical device safety, the post-market surveillance system continues to manage medical device adverse events even after the device is licensed [3,4]. However, there are various obstacles for medical staff or manufacturers to voluntarily report medical device adverse events to the reporting system, including fear of blame, lack of time, perceived ineffectiveness of reporting, complexity of reporting, and lack of knowledge of the reporting system [5]. Therefore, it is necessary to encourage the idea that voluntary reporting is important for patient safety and the improvement and development of medical device performance and to provide education on how to report adverse events to the reporting system.

**Conflicts of Interest**

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**Author Contributions**

Hyea-Jin Kim (Funding acquisition; Writing – original draft; Writing – review & editing)
Ah-Heum Cho (Conceptualization; Writing – review & editing)
Daehoan Moon (Data curation; Writing – review & editing)
Ji-Youn Lee (Data curation; Writing – review & editing)
Hyewon Hwang (Writing – review & editing)

**Supplementary Material**

Video 1. After the event, remifentanil was discarded and 20 ml of normal saline solution was filled into the damaged syringe and connected to an intravenous line of the patient. Air bubbles entering the syringe and pushing the solution into the patient, even when the power is off.

Kim et al. · Free flow caused by syringe pump
References

Erector spinae plane block: a new modality of pain relief in a difficult situation

Nisha Rajmohan, Jithendra Thiruvathtra, Rolita Prathima Lobo, Suresh Gangadharan Nair

Department of Anesthesia and Critical Care, Aster Medcity, Kochi, Kerala, India

Ankylosing spondylitis (AS) can present significant challenges to the anesthesiologist because of potential difficult airway, technical issues with neuraxial anesthesia and associated cardiovascular and respiratory complications [1]. It is a chronic inflammatory disease of the axial skeleton with fusion of joints of the spine and multisystem involvement. It is also an independent risk factor for epidural hematoma, therefore, placement of an epidural catheter requires an X-ray or ultrasound guidance [1]. Hence inadequate postoperative pain relief can be a major issue in these patients.

We report a case of open total gastrectomy with Roux-en-Y anastomosis and feeding jejunostomy (FJ) performed under general anesthesia and bilateral continuous erector spinae plane (ESP) block in a patient with AS. Appropriate patient consent was obtained prior to the procedure carried out in October 2019.

A 58-year-old male weighing 60 kg who was a known case of AS, was diagnosed with adenocarcinoma of the stomach and posted for open total gastrectomy with Roux-en-Y anastomosis and FJ. Airway examination revealed severe restriction of neck movements. However, Mallampati classification (class II), thyromental distance (6 cm), and inter incisor gap (4 cm) were normal. He had difficulty in lying supine without a high pillow under his head. He had no other comorbidities and all investigations including echocardiogram were normal. General anesthesia was induced and monitoring done as per institutional protocol. McGrath video laryngoscope (McGRATH MAC®, Aircraft Medical Ltd., UK) and 14F and 70 cm-long Frova Intubating Introducer (Cook Incorporated, USA) aided in the intubation.

The patient was positioned in right lateral position for ESP block. A 13–6 MHz linear ultrasound probe (Sonosite X-Porte, SonoSite Inc., USA) was placed in the sagittal plane, 3 cm from the midline at the level of T7 transverse process, and the trapezius and erector spinae (ES) muscles were identified. An 18 gauge Touhy needle was inserted in cephalad direction until the tip touched the transverse process and lay deep to the ES muscle. One ml of bupivacaine 0.25% was used to confirm the space. Twenty-five ml 0.25% bupivacaine with 8 mg dexamethasone was injected on each side followed by bilateral epidural catheter insertion deep to the ES muscle. An infusion of Ropivacaine 0.2% with fentanyl (2 μg/ml) was initiated on both sides at 7 ml/h. Anesthesia was maintained with a combination of air, oxygen, and isoflurane (1%). Any increase in pulse rate or blood pressure above 30% of the baseline was planned to be managed by bolus doses of fentanyl (1 μg/kg). However, we did not have to give opioid supplementation throughout the surgery. Patient also received regular doses of intravenous paracetamol (1 gm thrice daily) in the postoperative period. After extubation, the patient did not require any additional opioid analgesia, and ropivacaine infusion was continued for 5 days. He was able to participate in deep breathing and coughing exercises and was mobilized on postoperative day (POD)
During intensive care unit stay, his numeric rating scale (NRS) for pain was maintained below 2/10. At the time of discharge (POD 10), he was comfortable and pain-free. Postoperative pain in upper abdominal surgeries causes significant pulmonary complications, worsens outcomes, and prolongs hospital stay [2]. Inadequate pain relief has been shown to be responsible for 23.3% of readmissions after surgery [2]. The modes of postoperative analgesia are limited in a patient with AS. ESP block under ultrasound guidance is the solution to these issues. We decided to give the block at T7 with catheters inserted bilaterally. Drug injected at this level spreads in cephalic and caudal direction resulting in adequate somatic and visceral analgesia. This is an advantage over other abdominal wall blocks. We introduced the catheters preoperatively to reduce the stress response during surgery. We found that the patient remained hemodynamically stable in contrast to a continuous epidural infusion in which frequent episodes of hypotension are often encountered [3,4]. He did not require additional doses of fentanyl intraoperatively after the initial dose at induction. During the postoperative period, the patient maintained an NRS of less than 2. Avoidance of opioids helped prevent nausea, vomiting, and excessive sedation. The use of bilateral continuous block ensured ongoing pain relief [2].

There is a lack of consensus on the type, dose, and concentration of local anesthetic for this block [3]. We used ropivacaine 0.2% with fentanyl 2 μg/ml at the rate of 7 ml/h, which provided adequate analgesia. The chance of dislodgement of these catheters are remote because the catheters’ site was far removed from the surgical site. Good analgesia and absence of motor blockade helped early mobilization, which played an important role in the prophylaxis against deep vein thrombosis. It also ensured active participation in incentive spirometry and chest physiotherapy. ESP block is also believed to have an antiemetic effect, which is advantageous in gastrointestinal surgery [2]. Although ESP block has been used extensively in thoracic, cardiac, and laparoscopic surgery, there are very few reports on its use in upper abdominal surgery [3–5].

ESP block is technically easy to perform with excellent safety profile, which can be considered for postoperative analgesia in upper abdominal surgeries, in patients in whom neuraxial techniques are difficult or contraindicated.

### Conflicts of Interest

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

### Author Contributions

Nisha Rajmohan (Conceptualization; Data curation; Formal analysis; Investigation; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft)

Jithendra Thiruvathtra (Conceptualization; Data curation; Investigation; Validation; Writing – review & editing)

Rolita Prathima Lobo (Data curation; Formal analysis; Investigation; Software; Writing – review & editing)

Suresh Gangadharan Nair (Formal analysis; Project administration; Supervision; Writing – review & editing)

### ORCID

Nisha Rajmohan, https://orcid.org/0000-0003-1389-179X

Jithendra Thiruvathtra, https://orcid.org/0000-0002-8595-502X

Rolita Prathima Lobo, https://orcid.org/0000-0003-1682-0743

Suresh Gangadharan Nair, https://orcid.org/0000-0003-3633-4179

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Transmission of severe acute respiratory syndrome coronavirus 2, leading to coronavirus disease (COVID-19) is thought to occur primarily through respiratory droplets, while airborne transmission may occur with the generation of aerosols. Upper gastrointestinal endoscopy is deemed a potentially infectious aerosol-generating procedure; consequently, healthcare workers present at the premises are at a high risk, particularly because of the physical proximity to the patients.

Various professional guidelines recommend multi-pronged strategies for the use of endoscopes in the management of patients with COVID-19. This include deferring non-essential endoscopy, appropriate use of personal protective equipment (PPE), standard infection control practices, strict isolation precautions in negative-pressure rooms, and adequate disinfection protocols.

After obtaining written informed consent, we describe the management of a 30-year-old man who had a history of thalassemia intermedia and presented with a 1-day history of fever, sore throat, and myalgia. A positive nasopharyngeal swab test confirmed COVID-19.

On day 3, the patient developed productive cough. On day 7, he developed acute cholangitis. Imaging showed cholecdocholithiasis, likely a pigment stone secondary to chronic hemolysis. On day 18, in view of recurrent abdominal pain and worsening derangement of liver enzymes despite antibiotics, endoscopic retrograde cholangiopancreatography (ERCP) was performed instead of waiting for COVID-19 clearance, as was initially planned. As the patient was clinically stable with adequate oxygen saturation on room air, the procedure was performed under sedation.

To reduce the risk of contamination, we used a barrier enclosure during the procedure. The barrier enclosure was a transparent acrylic trapezoidal box placed over the patient’s head and upper torso during ERCP (Fig. 1A). It measured 60 × 55 × 61 cm (Fig. 1B).

The patient was initially placed in a supine position in the box, and lignocaine was sprayed to anesthetize the pharynx. The patient was then turned to a prone position in the box, and a nasal cannula was applied. Sedation was induced with titrated boluses of midazolam, fentanyl, and propofol.

Similar boxes, conceptualized for use with intubation, have garnered much interest in recent months. Kearsley highlighted concerns regarding the use, while others speculated on the physics and virulence of droplets and aerosols in infection transmission, thus questioning the utility of such an enclosure.

The patient coughed when lignocaine was sprayed into the pharynx and gagged slight-
ly at the start of the procedure. Droplet infectivity is multifactorial, depending on the droplet size, number, velocity, and viral load [3]. It is thought that ranges of droplet size and number are produced in a single coughing event. The smaller the size, the longer they remain suspended in the air. As large droplets dry, it is unknown if smaller aerosols are produced. Some aerosols are produced with normal breathing, while coughing produces aerosols profusely. The box may trap secretions and large respiratory droplets during the passage of the endoscope, suctioning, or patient coughing. Further, this may decrease the virus burden reaching the healthcare worker. In a simulation by Canelli et al. [4], the use of a barrier enclosure for intubation contained fluorescent dye within the inner surfaces of the enclosure, suggesting reduced macroscopic contamination of the immediate surroundings.

The effect of barrier devices on airborne particles, however, may be less benign. Simpson demonstrated that airborne transmission to the healthcare worker increased substantially when using an aerosol containment device [5]. Additionally, since the virus may remain viable in aerosols for 3 h [6], infectious aerosols can be released on box removal. Hence, the barrier should only be removed when the risk for aerosolization is deemed to be low and performed in a controlled manner to minimize the dispersal of viral particles.

The opening in the box held the endoscope in place after optimal positioning; however, with fixed openings, access to the patient for suctioning and repositioning was restricted. When the patient started moving excessively, an assistant reached the patient via the openings opposite the endoscopist while sedation was titrated. The openings allowed the anesthetist and assistant to intervene, but for patients with a high risk for deterioration, requirement of emergent intubation, or morbid obesity, the box may impede a quick access.

The procedure was completed in 1 h with the pigment stone removed and biliary stent inserted. The patient remained stable throughout. He was asked to turn to the supine position in the box, and a surgical mask was applied. The processes of box removal and decontamination were performed with much care to avoid contaminating the surroundings with droplets remaining on the inner surface of the box or the patient’s blanket or bed.

The half-life of the virus on plastic is 6.5 h [6]; therefore, careful removal of the box and meticulous decontamination are imperative. It required considerable effort with numerous wipes used to ensure that every crevice was clean. A liquid or vapor disinfectant could serve as a more convenient decontamination method. The postoperative course was uneventful, and the patient was transferred back to the general ward.

The barrier enclosure is an alternative physical barrier to large droplets or splatters during endoscopy, particularly if PPE is not available. However, the user must be mindful of the limitations that come with its use, including a potential for increased airborne particle exposure, if not properly utilized.

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Conflicts of Interest

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

Author Contributions

Jing Zhong Wee (Writing – original draft)
Vera Lim (Conceptualization; Writing – review & editing)
Jee Jian See (Writing – review & editing)

ORCID

Jing Zhong Wee, https://orcid.org/0000-0001-6558-480X
Vera Lim, https://orcid.org/0000-0002-3445-5842
Jee Jian See, https://orcid.org/0000-0003-3564-1222

References

Pregabalin-induced hypoglycemia in a dialysis patient

Takahiro Tamura¹, Yushi Ueda Adachi², Maiko Satomoto³

¹Department of Anesthesiology, Nagoya University Graduate School of Medicine, Nagoya,
²Department of Anesthesia and Intensive Care Medicine, International University of Health and Welfare, Nasushiobara, ³Department of Anesthesiology, Ohmori Medical Center, Toho University, Tokyo, Japan

This correction is being published to correct authorship list. The first author listed in the above article, who the corresponding author requested deletion, should be removed.

Before correction:
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The correct information is found below:
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6Lee S and Lee DK. What is the proper way to apply the multiple comparison test? Korean J Anesthesiol 2018; 71: 353-60.
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- “±” 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 *, †, ‡, §, II, ¶, **, ††, ‡‡... 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.

Figures and illustrations
- 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.
Figures should be explained briefly in the footnotes. The format is the same as the table format.

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.

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.

- The video clip(s) should have simple file names (e.g., Video 1***, Video 2***) and include the appropriate extension (e.g., mov, mpg).

- The maximum number of video clips is 20.

- 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.

- 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.

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) 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

- Title and Running title.

- 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 and white.

- Discussion: Briefly discuss the case, and state conclusions directly related to diagnosis and anesthetic management.

- References: Do not exceed 15 references. For exceeding the number of references, it should be negotiated with the Editorial Board.

- Tables and figures: Proportional to clinical and experimental studies.
3) 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.

4) Letters to the Editor
Letters to the Editor also should include brief constructive comments on the articles published in KJA and interesting cases. 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. 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 authors is allowable. Letter may be edited by the Editorial Board and if necessary, responses of the author of the subject paper may be provided.

5) Book Reviews and Announcements
Book reviews as well as News of Scientific Societies and scientific meeting dates in Korea or abroad can be included. Their formats will be same as Letter to the Editor.

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 November 2019 submissions.