Korean Journal of Anesthesiology

2021 April · Volume 74 · Number 2

Pages 89-188

pISSN: 2005-6419 eISSN: 2005-7563

KOREAN JOURNAL of ANESTHESIOLOGY

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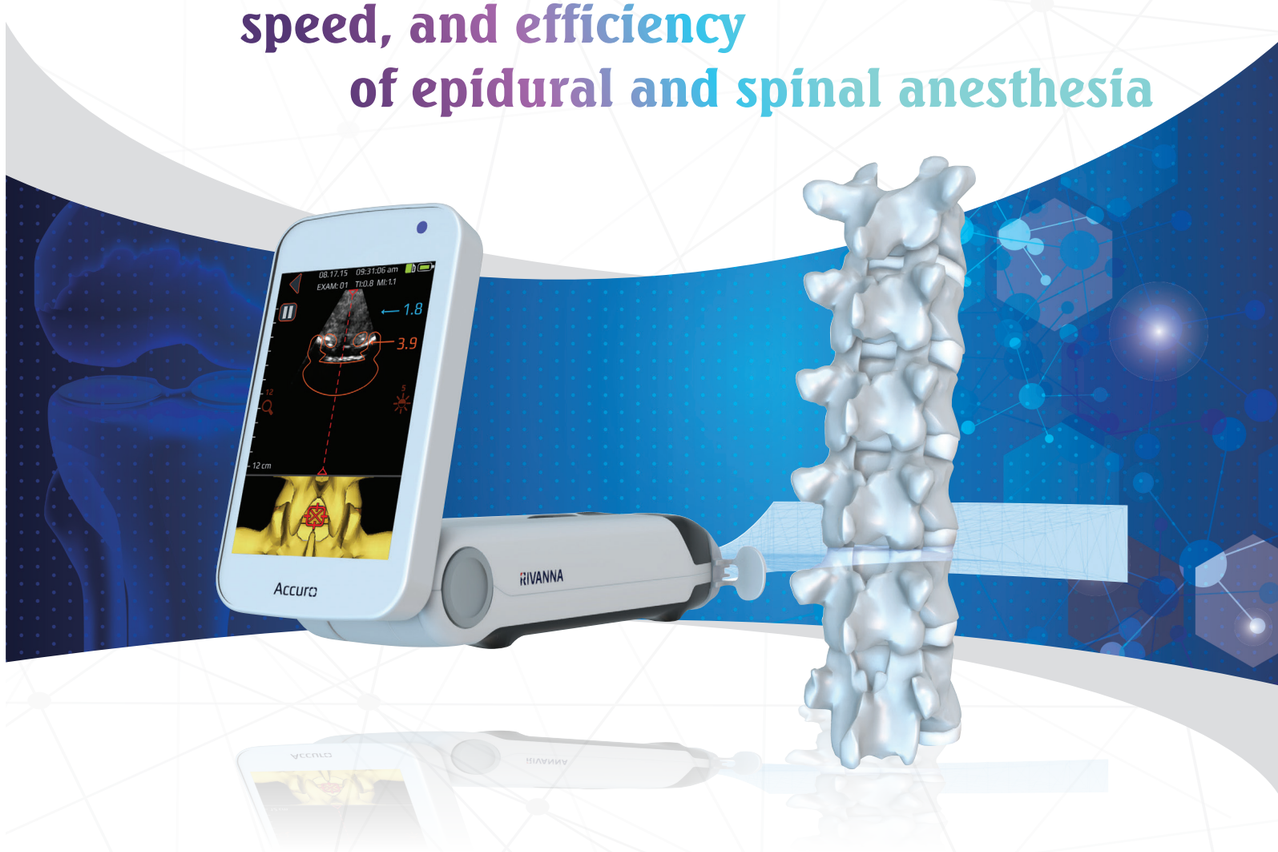

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KOREAN JOURNAL of ANESTHESIOLOGY

pISSN: 2005-6419
eISSN: 2005-7563

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.

The journal has been partly supported by the Korean Federation of Science and Technology Societies. KJA is indexed/tracked/covered by ESCI (Emerging Sources Citation Index), KCI (indexed by the National Research Foundation of Korea), PubMed, PubMed Central, EBSCOhost Databases, KoreaMed, KoMCI Web, KoreaMed Synapse, Science Central, SCOPUS, Embase, CAS (Chemical Abstracts Service), WPRIM (Western Pacific Regional Index Medicus), DOI, DOAJ (Directory of Open Access Journal) and Google Scholar. It has been indexed in MEDLINE by U.S. National Library of Medicine. The KCI journals have been seamlessly integrated into the Web of Science since 2014.

Korean Journal of Anesthesiology Volume 74, Number 2, 1 April 2021

The circulation number per issue is 400.

Contacting the KJA

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

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Tae Kyun Kim, Young Lan Kwak

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Tel: +82-2-795-5129 Fax: +82-2-792-4089 Email: anesthesia@kams.or.kr journal@anesthesia.or.kr

Printed by M2PI

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April 2021
Volume 74, Number 2

pISSN: 2005-6419
eISSN: 2005-7563

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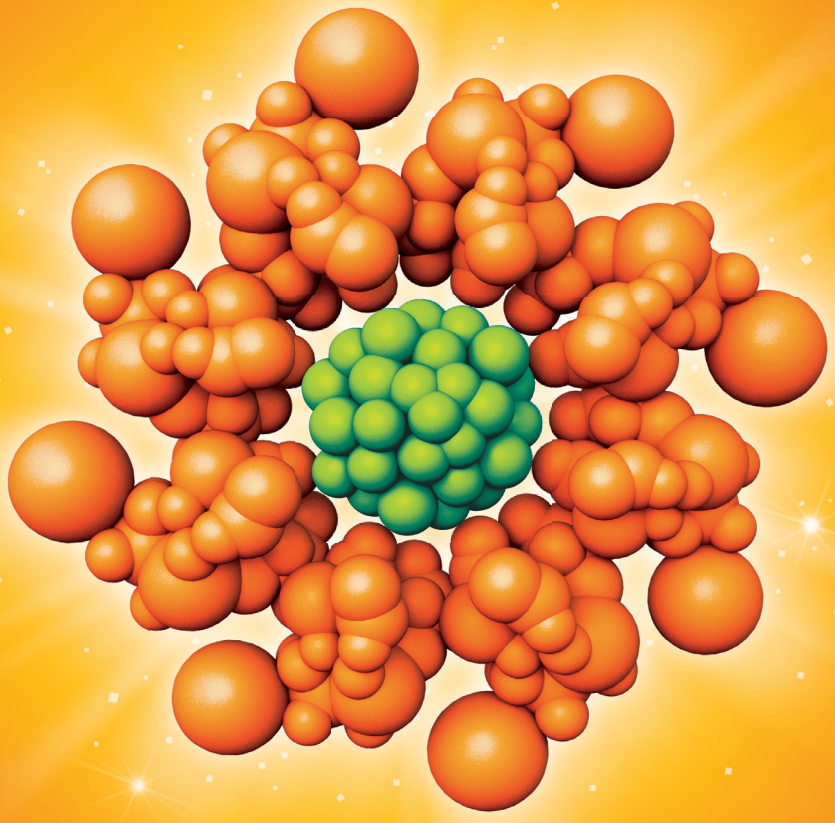
EXPERIENCE THE BRIDION EFFECT[1,2]



Bridion (sugammadex) offered significantly fast and predictable recovery in most patients with moderate to profound rocuronium-induced neuromuscular blockade (NMB).[1,2]

Reappearance of T_2 for reversal of a NMB : 98% of Bridion (sugammadex) patients had recovered to a TOF ratio of 0.9 compared with only 11% of neostigmine patients within 5 minutes. In comparison, it took 101 min for 98% of patients receiving neostigmine to recover to a TOF ratio of 0.9.[1]

Reappearance of 1-2 PTCs. : The median (range [interquartile range]) time to recovery of the TOF ratio to 0.9 was 2.7 (1.2-16.1 [2.1-4.1]) min in the Bridion (sugammadex) group versus 49.0 (13.3-145.7 [35.7-65.6]) min in the neostigmine group.[2]

Indication of Bridion is reversal of neuromuscular blockade induced by rocuronium or vecuronium.[3]

The safety and efficacy of Bridion for pediatric and adolescents under the age of 18 has not been established.[3]

*** For more information, please refer to the full prescribing information.**

T_2 : The second twitch, **TOF :** Train-of-four, **PTC :** Posttetanic count

Bridion®(Sugammadex) 100 mg Selected Safety Information

[Indications and Usage] Reversal of neuromuscular blockade induced by rocuronium or vecuronium. **[Dosage and Administration] Adults:** Routine reversal: A dose of 4 mg/kg Bridion is recommended as IV injection if recovery has reached at least 1-2 post-tetanic counts(PTC) following rocuronium or vecuronium induced blockade. A dose of 2 mg/kg Bridion is recommended as IV injection, if spontaneous recovery has occurred up to at least the reappearance of T_2 following rocuronium or vecuronium induced blockade. **Immediate Reversal of Rocuronium-Induced Blockade:** A dose of 16 mg/kg Bridion is recommended if there is a clinical need to reversal neuromuscular blockade soon(approximately 3 minutes) after administration of rocuronium as IV injection. The safety and efficacy with the use of Bridion for immediate reversal following vecuronium induced blockade has not been established. **Renal Impairment:** No dosage adjustment is necessary for patients with mild or moderate renal impairment(creatinine clearance ≥30 mL/min and <80 mL/min). Bridion is not recommended for use in patients with severe renal impairment(creatinine clearance <30 mL/min) or dialysis. **Elderly Patients:** Elderly patients tend to delay recovery from neuromuscular blockade, but dose adjustment is not necessary. **Obese Patients:** The dose of this drug in obese patients should be based on actual weight(ABW). **Hepatic Impairment:** No dosage adjustment is necessary for patients with mild and moderate hepatic impairment. Since no clinical studies have been conducted with patients with hepatic impairment, caution should be taken in patients with severe hepatic impairment or hepatic impairment with coagulation disorders. **[Warnings and Precautions] Contraindications:** Patients with known hypersensitivity to Bridion or any of its components. **Careful Administration:** 1) Patients with renal impairment 2) Patients with hepatic impairment 3) Patients with decrease of cardiac output 4) Patients with edema state 5) Patients with a history of allergic reaction 6) Patients with a history of pulmonary complications(Possible occurrence of bronchospasm) 7) Patients with coagulation disorders 8) Patients with arrhythmia 9) The elderly 10) Pregnant or women who may be pregnant. **Adverse Reactions:** 1) The safety of Bridion has been evaluated based on an integrated safety database of approximately 1,700 surgical patients and 120 healthy adult volunteers. The most commonly reported adverse reactions in patients who experienced surgery were anaesthetic complications. **Immune System:** 1) Hypersensitivity(≥1/1,000, <1/100), the others: Anaesthetic complications(body movement in the middle of anesthesia or operation, coughing, grimacing and sucking of the tracheal tube)(≥1/100, <1/10), involuntary awakening during anesthesia(≥1/1,000, <1/100). 2) In clinical trials with surgical patients, hypersensitivity including anaphylaxis has been reported infrequently. The frequency of occurrence of hypersensitivity reactions in post-marketing surveys is unknown. Hypersensitivity reactions that occurred varied from isolated skin reactions to serious systemic reactions(i.e., anaphylaxis, anaphylactic shock) and have occurred in patients with no prior exposure to Bridion. Symptoms associated with these reactions can include: flushing, urticaria, erythematous rash, severe hypotension, tachycardia, swelling of tongue, swelling of pharynx, bronchospasm and pulmonary obstructive events. Severe hypersensitivity reactions can be fatal. 3) Post-marketing clinical trials of obese patients(BMI ≥40 kg/m^2) showed that the adverse reaction profile was generally similar between patients who were administered actual body weight(ABW) and patients who were administered ideal body weight(IBW). **General Cautions:** 1) Ventilatory support is mandatory for patients until adequate spontaneous respiration is restored following reversal of neuromuscular blockade. 2) In order to prevent recurrence of neuromuscular blockade, the recommended doses for routine should be used. 3) When drugs which potentiate neuromuscular blockade are used in the post-operative phase, special attention should be paid to the possibility of recurrence of neuromuscular blockade. 4) Recurrence of neuromuscular blockade may occur due to displacement of rocuronium or vecuronium from BRIDION by other drugs(i.e., Toremifene, fusidic acid). 5) When neuromuscular blockade was reversed intentionally in the middle of anaesthesia in clinical trials, signs of light anaesthesia were noted occasionally(movement, coughing, grimacing and sucking of the tracheal tube). 6) In patients for whom intubation is expected to be difficult, the method of airway maintenance should be considered beforehand. If rocuronium-induced neuromuscular blockade cannot or does not allow airway intubation, it should be promptly restored from neuromuscular blockade. 7) Coagulation parameters should be carefully monitored in patients with known coagulopathies when sugammadex is administered. 8) In patients with severe renal failure(creatinine clearance <30 mL/min), the excretion of Bridion or the Bridion-rocuronium complex was delayed; however, in these patients there were no signs of re-occurrence of neuromuscular blockade. This drug is not recommended for use in patients with severe renal impairment. 9) Dedicated studies in patients with hepatic impairment have not been conducted. Patients with severe hepatic impairment or hepatic impairment with coagulation disorders should be cautious when administering this drug. 10) Bridion has not been studied for reversal following rocuronium or vecuronium administration in the ICU. 11) Do not use Bridion to reverse neuromuscular blockade induced by nonsteroidal neuromuscular blocking agents such as succinylcholine or benzylisoquinolinium compounds, steroidal neuromuscular blocking agents, pancuronium other than rocuronium or vecuronium. 12) Conditions associated with prolonged circulation time such as cardiovascular disease, old age or edema state(i.e., severe hepatic impairment) may be associated with longer recovery times. 13) The patients should be carefully observed for the possibility of drug hypersensitivity reactions(including anaphylactic reactions). If any abnormality is observed, appropriate measures should be taken immediately. 14) Each 1 mL solution contains 9.7 mg sodium. If more than 2.4 mL(contain approximately 23 mg sodium) solution needs to be administered, this should be taken into consideration by patients on a controlled sodium diet. 15) In rare instances, cases of marked bradycardia, some of which have resulted in cardiac arrest, have been observed within minutes after the administration of Bridion for reversal of neuromuscular blockade. **Drug Interactions :** 1) Toremifene: For toremifene, which has a relatively high binding affinity for Bridion and for which relatively high plasma concentrations might be present, some displacement of vecuronium or rocuronium from the complex with this drug could occur. 2) Fusidic acid: IV administration of fusidic acid in the pre-operative phase may give some delay in the recovery of the T_2/T_1 ratio to 0.9. No recurrence of neuromuscular blockade is expected in the post-operative phase, since the infusion rate of fusidic acid is over a period of several hours and the blood levels are cumulative over 2-3 days. 3) Hormonal contraceptives: The interaction between 4 mg/kg Bridion and a progestogen was predicted to lead to a decrease in progestogen exposure(34% of AUC). **Pregnancy & Lactation Administration:** There are no clinical trial data for exposure to this drug during pregnancy. It is administered only if the benefits of administration exceed the risk. No data are available regarding the presence of Bridion in human milk, the effects of Bridion on the breast fed infant, or the effects of Bridion on milk production. Breastfeeding is not recommended during the administration of this drug. **Pediatric Administration:** The safety and efficacy of this drug in children aged younger than 18 years have not been established. **Elderly Administration:** Exercise caution when administering BRIDION to elderly patients who tend to delay recovery from neuromuscular blockade.(Revised: 2021.01.26)

※Before administering BRIDION, please read the full prescribing information.

Study design[1] : This randomised, multicentre, parallel-group trial included 98 adult patients. Patients received intravenous propofol for induction followed by sevoflurane maintenance anaesthesia. Neuromuscular blockade was monitored using acceleromyography and a train-of-four(TOF) mode of stimulation. Patients were randomly allocated to receive sugammadex 2.0 mg/kg or neostigmine 50 μg/kg(with glycopyrrolate 10 μg/kg) at reappearance of the second response of the TOF(mean 16% twitch height of first response) after the last dose of rocuronium. The primary endpoint was the time from sugammadex or neostigmine administration to recovery of the TOF ratio to 0.9.

Study design[2] : This phase Ⅲ, randomized study enrolled surgical patients, aged 18 year or older with American Society of Anesthesiologists physical status Ⅰ-Ⅳ. 74 patients were randomized to receive sugammadex(4.0 mg/kg) or neostigmine(70 μg/kg) plus glycopyrrolate(14 μg/kg). Anesthetized patients received an intubating dose of rocuronium(0.6 mg/kg), with maintenance doses(0.15 mg/kg) as required. Neuromuscular monitoring was performed by acceleromyography. Sugammadex or neostigmine was administered at reappearance of 1-2 posttetanic counts(profound neuromuscular blockade). The primary efficacy parameter was the time from sugammadex or neostigmine-glycopyrrolate administration to return of the train-of-four ratio to 0.9.

References : 1. Blobner M, *et al*. Reversal of rocuronium-induced neuromuscular blockade with sugammadex compared with neostigmine during sevoflurane anaesthesia: results of a randomised, controlled trial. *Eur J Anaesthesiol*. 2010;27(10):874-881. **2.** Jones RK, *et al*. Reversal of profound rocuronium-induced blockade with sugammadex: a randomized comparison with neostigmine. *Anesthesiology*. 2008;109(5):816-824. **3.** Bridion Product Label. Ministry of Food and Drug Safety.

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KJA
Korean Journal of Anesthesiology

Review Article

Korean J Anesthesiol 2021;74(2):91-102
https://doi.org/10.4097/kja.21006
pISSN 2005-6419 • eISSN 2005-7563

Received: January 6, 2021
Accepted: January 11, 2021

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Previous presentation in conferences:
This work has been presented in part at The 97th Scientific Meeting of The Korean Society of Anesthesiology, Nov 2020, Grand Hyatt Incheon, Incheon, Korea. Title of the invited lecture: COVID-19 associated Coagulopathy: The Role of Viscoelastic Testing.

The role of rotational thromboelastometry during the COVID-19 pandemic: a narrative review

COVID-19 유행 중 회전성 혈전탄성묘사법의 역할: 비체계적 문헌 고찰

Klaus Görlinger[1,2], Hawra Almutawah[3], Fatimah Almutawaa[3], Maryam Alwabari[3], Zahra Alsultan[3], Jumanah Almajed[3], Mahmoud Alwabari[3], Maryam Alsultan[3], Duri Shahwar[4], Khaled Ahmed Yassen[4]

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코로나바이러스감염증-19 (COVID-19)의 유행은 현재 전 세계적 보건 위기로 인식되고 있다. 이 바이러스 감염은 흔히 치명적인 혈전색전증 합병증의 발생률이 높은 응고 항진(hypercoagulability) 상태와 연관되어 있으며, 대다수의 경우 COVID-19 환자에서 응고 시간(clotting time)은 영향을 거의 받지 않거나 매우 약하게 받기 때문에 응고 항진 상태를 표준 응고검사(standard coagulation tests, SCT)만으로 감지하기는 어렵다. 본 리뷰에서는 지금의 COVID-19 유행 상황에서 회전성 혈전탄성묘사법(rotational thromboelastometry, ROTEM®)과 같은 점탄성 응고검사법(viscoelastic tests)의 역할에 대해 알아보고자 한다. 회전성 혈전탄성묘사법을 사용하여 측정한 COVID-19 관련 응고 병증은 섬유소 중합(fibrin polymerization) 증가 및 섬유소 분해(fibrinolysis) 감소로 인한 응고항진부터 응고저하로 인한 출혈까지 다양하게 나타난다. 따라서 회전성 혈전탄성묘사법과 혈장 섬유소원, D-dimer 농도와 같은 표준응고검사를 함께 이용하는 다중 진단 및 모니터링 접근법의 사용이 추천된다. 회전성 혈전탄성묘사법은 환자 개개인의 전체적인 응고 상태에 대한 포괄적 정보를 제공하며 개인 변이를 감지한다. COVID-19와 관련된 응고병증은 매우 역동적인 과정으로, 그 표현형(phenotype)은 감염 과정 중 그리고 항응고요법에 대한 반응으로 변할 수 있다. 기존 연구 결과는 회전성 혈전탄성묘사법과 표준응고검사 분석을 함께 진행하는 것이 COVID-19 환자에서 지혈 문제를 감지하고, 항응고요법을 돕고, 궁극적으로 결과를 개선하는 데 도움이 된다고 보고하고 있다. 그러나 근거-기반 진료지침과 프로토콜을 개발하기 위해서는 앞으로 더 많은 연구가 필요할 것으로 생각된다.

Keywords: Anticoagulants; Blood coagulation disorders; COVID-19; Fibrinolysis; SARS-CoV-2; Thrombelastography; Thrombophilia; Thrombosis.

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Comeback of ketamine: resurfacing facts and dispelling myths

Ketamine의 귀환: 사실의 재조명과 근거없는 믿음의 불식

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Review Article

Korean J Anesthesiol 2021;74(2):103-114
https://doi.org/10.4097/kja.20663
pISSN 2005-6419 • eISSN 2005-7563

Received: December 17, 2020
Revised: January 6, 2021 (1st); January 10, 2021 (2nd)
Accepted: January 10, 2021

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초기에 CI-581로 알려졌던 Ketamine은 phencyclidine의 대체 물질로 1962년에 처음 합성되었으며, 이후로 마취제 및 진통제로 사용되어 왔다. Ketamine은 또한 기관지 확장, 진정, 기억상실 효과가 있으며, 기도 반사와 교감신경계 작용에 영향을 미치지 않는다. Ketamine의 발견 이후로, 특정 환자군에 대한 사용은 많은 논란이 있었다. Ketamine의 잠재적 이득에도 불구하고 지난 50년간 사용에 제한이 있었는데, 이는 각성기 현상(emergence phenomenon), 약물 남용 가능성 및 전신 부작용에 대한 염려 때문이었다. 2012년 이후 세계보건기구(WHO)에서 발간한 Ketamine에 대한 3편의 논평(review)에서 이 약제의 국제적 관리 방안이 논의되었다. 지난 수십 년간 전 세계적으로 연구자들은 이 놀라운 약제를 연구해 왔다. Ketamine의 각성기 현상과 관련된 수많은 믿음과, 외상성 뇌손상 및 개방성 안구손상 환자에서 Ketamine의 사용 금기 사유를 수정할 필요가 있다는 주장이 최근 제기되었다. Ketamine은 입원 전 준비과정, 중환자 관리, 응급의학, 급성 통증 관리 및 국소마취 시 보조제로써 사용이 점차 증가하고 있다. 본 논평은 Ketamine의 다양한 적용에 대하여 현재까지 문헌에 발표된 내용 위주로 고찰하였다.

Keywords: Acute; Antidepressants; Cancer pain; Hallucinations; Intracranial pressure; Intraocular pressure; Ketamine; Pain clinics; Status epilepticus.

KJA
Korean Journal of Anesthesiology

Statistical Round

Korean J Anesthesiol 2021;74(2):115-119
https://doi.org/10.4097/kja.20582
pISSN 2005-6419 • eISSN 2005-7563

Received: October 25, 2020
Revised: December 20, 2020 (1st); January 6, 2021 (2nd); February 9, 2021 (3rd)
Accepted: February 9, 2021

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The principles of presenting statistical results: Table

통계 결과 제시의 원칙: 표

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Korean Journal of Anesthesiology (*KJA*)와 같은 의학 학술지에는 매년 수많은 원고가 투고된다. 하지만, 다양한 원고에서 제시된 다양한 형태의 표로 인해, 논문 심사와 출판과정에 애로를 겪는다. 이는 통계 결과를 표기하는 데 일반적으로 사용되는 서면지침이 없기 때문인 듯하다. 이에, 본 글을 통해 통계 결과를 보고하는 데 흔히 사용되는 여러 표에 대한 작성 방법을 간략하게 설명한다. 이 글이 KJA에 투고하고자 하는 저자들뿐만 아니라 심사자들에게도 지침이 되기를 희망한다.

Keywords: Comparative study; Guideline; Publication formats; Research report; Statistics; Tables.

KJA
Korean Journal of Anesthesiology

Four different methods of measuring cardiac index during cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

용적축소수술과 복강내 온열 항암화학요법 중 심장박출지수 측정의 4가지 방법

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Clinical Research Article

Korean J Anesthesiol 2021;74(2):120-133
https://doi.org/10.4097/kja.20202
pISSN 2005-6419 • eISSN 2005-7563

Received: April 28, 2020
Revised: July 7, 2020 (1st); August 12, 2020 (2nd)
Accepted: August 14, 2020

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This work has been presented in part at International Symposium on Intensive Care and Emergency Care (ISICEM), March 2018, Brussels Meeting Center, Brussels, Belgium.

배경: 용적축소수술(cytoreductive surgery, CRS)과 복강내 온열 항암화학요법(hyperthermic intraperitoneal chemotherapy, HIPEC)은 고위험 광범위 복부 수술에 속한다. 고위험 수술 중 비침습적인 심장박출지수(cardiac index, CI) 측정 방법들이 수술장에서 많이 사용되어 왔다. 저자들은 수술실과 중환자실(ICU)에서 시행한 CRS와 HIPEC 중 4가지 다른 방법(FroTrac, ProAQT, ClearSight, APWA from PICCO)으로 측정한 CI의 정확도를 평가하였으며, 이를 경폐 열희석법(transpulmonary thermodilution, TPTD)과 비교하였다.

방법: CRS-HIPEC이 예정된 25명의 환자를 대상으로, 미리 정의한 9개의 시점 동안 수술실과 ICU에서 동시 혈역학적 측정이 시행되었다. Bland-Altman 도표와 사분면(four-quadrant) 도표, 상호교환성(interchangeability)을 사용하여 CI의 절대적 및 상대적 변화를 분석하였다.

결과: TPTD와 비교하여 평균 불일치(bias)는 ClearSight, ProAQT 및 APWA에서 -0.1 L/min/m^2, FloTrac에서 -0.2 L/min/m^2였다. 모든 CI 측정방법에서 넓은 일치 한계 수준(limits of agreement, LoA)을 보였다. ClearSight, FloTrac, ProAQT 및 APWA의 백분율 오차는 각각 50%, 50%, 54%, 36%였으며, 상호교환성 비율은 각각 36%, 47%, 40%, 72%였다. 임상적으로 유의한 CI 변화를 이용한 일치율(concordance)로 표현된 경향성(trending capabilities)은 각각 85%, 76%, 76%, 66%였으며, 한편 ClearSight, FloTrac, ProAQT 및 APWA의 평균 각 불일치(angular bias) ± 방사상(radial) LoA는 각각 -7° ± 39°, -19° ± 38°, -13° ± 41°, -15° ± 39° 였다. 모든 CI 측정방법에서 낮은 경향성-상호교환성 비율을 보였으며, 각 데이터 쌍은 grey zone에 위치하였다.

결론: CRS-HIPEC 동안 ClearSight, FloTrac 및 ProAQT 시스템은 TPTD와 비교하여 CI를 신뢰할 만한 수준으로 측정하지 못했다. 일치율, 평균 불일치, 방사상 LoA, 상호교환성을 이용하여 시간에 따른 변화 재현성을 모든 도구에서 평가하였으나 만족할 만한 결과를 얻지 못했다.

Keywords: Cardiac output; Comparative study; Hyperthermic intraperitoneal chemotherapy; Laparotomy; Pulse wave analysis; Thermodilution.

KJA
Korean Journal of Anesthesiology

Clinical Research Article

Korean J Anesthesiol 2021;74(2):134-141
https://doi.org/10.4097/kja.20114
pISSN 2005-6419 • eISSN 2005-7563

Received: March 16, 2020
Revised: April 26, 2020 (1st); May 25, 2020 (2nd)
Accepted: June 8, 2020

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Effectiveness of four ultrasonographic parameters as predictors of difficult intubation in patients without anticipated difficult airway

어려운 기도관리가 예상되지 않는 환자에서 어려운 기관내삽관의 예측인자로서 4가지 초음파적 지표의 효용성 연구

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배경: 어려운 기관내삽관(difficult intubation, DI)의 예측은 중요한 과제이며, 아직까지 이를 신뢰성 있게 예측할 만한 단독 임상지표는 없다. 저자들은 DI 예측을 위한 4가지 상기도 초음파 지표의 효용성을 평가하였다. 또한, 이들 초음파 기반 변수들의 조합을 이용한 예측모형의 타당도도 조사하였다.

방법: 본 전향적 이중 맹검 코호트 관찰 연구는 어려운 기도관리가 예측되지 않는 미국 마취과학회(American Society of Anesthesiologists) 신체상태 분류상 I-III으로 분류된 총 1,043명의 수술환자들을 대상으로 하였다. 수술 전 평가에서 혀 두께(tongue thickness, TT), 설골이 보이지 않음(invisibility of hyoid bone, VH), 피부로부터 갑상설골막(thyrohyoid membrane)과 설골(hyoid bone, SH)까지의 전경부 연조직의 두께(SH: soft tissue thickness from skin to hyoid bone, ST: soft tissue thickness from skin to thyrohyoid membrane)를 설하(sublingual) 및 하악하(submandibular) 초음파를 통해 측정되었다. 로지스틱 회귀모형, Youden index, 그리고 수신자 조작 특성(Receiver Operatic Characteristic, ROC) 분석 결과를 보고하였다.

결과: 전체적으로 58명(5.6%)의 환자가 DI로 분류되었다. TT, SH, ST, VH의 DI 예측정확도는 각각 78.4%, 85.0%, 84.7%, 84.9%였다. DI 예측을 위한 TT, SH, ST의 최적값은 > 5.8 cm (민감도: 84.5%, 특이도: 78.1%, AUC: 0.880), > 1.4 cm (민감도: 81%, 특이도: 85.2%, AUC: 0.898) 및 > 2.4 cm (민감도: 75.9%, 특이도: 85.2%, AUC 0.885)였다. VH의 민감도는 72.4%, 특이도는 85.6%였다(AUC: 0.790). 5개 모형의 AUC 값(3개 또는 4개 변수의 조합)의 범위는 0.975-0.992였다. ST 및 VH는 개별 모형의 DI 예측정확도에 유의한 영향을 미치는 것으로 나타났다.

결론: SH의 정확도가 가장 높았으며, 개별 지표들은 타당도 면에서 제한점을 보였다. 결론적으로 4가지 지표 모두를 포함하는 예측모형이 가장 높은 진단적 가치를 제공하였다.

Keywords: Airway management; Diagnostic ultrasound; General anesthesia; Hyoid bone; Intubation; Laryngoscopy; Tongue.

KJA
Korean Journal of Anesthesiology

Validity and reliability of the Korean version of the Quality of Recovery-15 questionnaire

한국어판 Quality of Recovery-15 설문의 타당도 및 신뢰도 평가

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Clinical Research Article

Korean J Anesthesiol 2021;74(2):142-149
https://doi.org/10.4097/kja.20435
pISSN 2005-6419 • eISSN 2005-7563

Received: August 3, 2020
Revised: September 18, 2020 (1st); October 27, 2020 (2nd)
Accepted: October 27, 2020

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배경: Quality of recovery-40 설문(이하 QoR-40)은 수술 후 회복의 질을 평가하기 위해 흔히 사용되는 지표이나, 임상적으로 활용되기에는 다소 문항수가 많다. QoR-40의 짧은 버전인 QoR-15는 많은 언어로 번역되어 타당도가 검증되었으나, 아직 공식적인 한국어판 QoR-15 (QoR-15K)는 확립되지 않았다. 본 연구의 목적은 QoR-15K를 개발하고 타당도를 검증하는 것이다.

방법: 기존에 타당도가 검증된 한국어판 QoR-40 설문을 바탕으로 영어판 원본 QoR-15와 일치하는 총 15개 문항을 선정하여 QoR-15K를 작성하였다. 전신마취 하 수술이 예정된 210명의 환자를 대상으로 하여 분석하였다. 연구대상 환자는 수술 전일, 수술 후 1일째와 2일째에 해당 설문을 완료하였다. 이를 토대로 QoR-15K의 타당도, 신뢰도, 반응도를 평가하였다.

결과: QoR-15K는 회복의 시각통증척도(VAS)에 대해 매우 높은 수렴 타당도를 보였다(ρ = 0.882, $P < 0.001$). QoR-15K과 마취시간, 회복실 기간, 총 병원 재원기간은 유의하게 음의 상관관계를 보였다(각각 ρ = –0.183, –0.151, –0.185). Cronbach's α는 0.909였다. Cohen의 효과 크기와 표준화 반응 평균은 각각 0.819와 0.721였다. 모집율과 완료율은 각각 92.9%, 100%였다. 위의 결과분석은 수술 후 첫날 얻은 결과를 토대로 시행되었다.

결론: 한국어판 QoR-15K의 타당도와 신뢰도는 영어판과 유사하였다. QoR-15K는 국내 환자에서 수술 후 회복의 질 평가에 있어 좋은 도구로 활용될 수 있을 것으로 기대한다.

Keywords: Cross-cultural comparison; Health care; Health status; Quality assurance; Quality of life; Surveys and questionnaires; Translation.

KJA
Korean Journal of Anesthesiology

Effect of preoperative dexmedetomidine nebulization on the hemodynamic response to laryngoscopy and intubation: a randomized control trial

수술 전 dexmedetomidine 분무요법의 후두경 조작 및 삽관에 대한 혈역학적 반응 효과: 무작위 대조군 시험

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Clinical Research Article

Korean J Anesthesiol 2021;74(2):150-157
https://doi.org/10.4097/kja.20153
pISSN 2005-6419 • eISSN 2005-7563

Received: April 7, 2020
Revised: May 18, 2020 (1st); May 19, 2020 (2nd)
Accepted: May 20, 2020

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배경: Dexmedetomidine은 알파-2 작용제로 후두경 검사 조작 시 혈역학적 반응을 감소시키기 위해 사용되어 왔으나, 분무요법은 아직 이용된 바 없다. 저자들은 수술 전 dexmedetomidine 분무요법이 후두경 조작 및 삽관에 대한 혈역학적 반응에 미치는 효과를 평가하고, 수술 중 마취제와 진통제 요구량 및 회복 양상들을 조사하였다.

방법: 기관내 삽관을 필요로 하는 선택적 수술이 예정된 미국 마취과학회 신체 등급 분류 I과 II에 해당하는 총 120명의 성인 환자(모든 성별)를 무작위 배정하여 마취유도 30분전 dexmedetomidine (0.9% 식염수 3-4 ml에 1 μg/kg를 희석) 또는 0.9% 식염수(3-4 ml) 분무를 받도록 하였다. 후두경 조작 후 10분마다 심박수와 비침습적 수축기 혈압을 측정하였다.

결과: 선형 복합 효과 모형을 사용하여 분석한 결과, 후두경 조작 후 dexmedetomidine군에서 식염수군에 비해 심박수 증가가 유의하게 더 낮은 경향을 보였다(P = 0.012). 하지만 양군간에 유의한 수축기혈압의 차이는 없었다(P = 0.904). Propofol의 마취유도 용량(P < 0.001), 수술 중 fentanyl 소비량(P = 0.007), isoflurane 요구량(P = 0.013)은 dexmedetomidine군에서 유의하게 낮았다. 수술 후 2시간내 오심과 구토 및 인후통의 발생에도 차이가 없었다(P = 0.741).

결론: Dexedetomidine (1 μg/kg)의 분무는 후두경 조작 후 수축기 혈압에는 영향을 끼치지 않으면서 심박수 증가를 완화시켰고, 수술 중 마취 및 진통 조절을 위한 약물 소모를 감소시켰다. 또한, 수술 후 초기 오심, 구토, 그리고 인후통에는 효과가 없었으나 부작용 발생을 증가시키지 않았다. Dexmedetomidine 분무 요법은 짧은 수술 시 정맥 주사의 적절한 대안이 될 수 있을 것으로 판단된다.

Keywords: Dexmedetomidine; Hemodynamics; Inhalation; Intravenous anesthetics; Intubation; Laryngoscopy.

KJA
Korean Journal of Anesthesiology

Experimental Research Article

Korean J Anesthesiol 2021;74(2):158-164
https://doi.org/10.4097/kja.20511
pISSN 2005-6419 • eISSN 2005-7563

Intraoperative aerosol box use: does an educational visual aid reduce contamination?

수술 중 에어로졸 상자의 사용: 시각적 보조 교재가 오염을 줄이는가?

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Received: September 14, 2020
Revised: November 2, 2020
Accepted: November 4, 2020

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배경: 에어로졸 상자(aerosol box)는 COVID-19 대유행 동안 에어로졸을 발생시키는 시술 중 바이러스에의 노출을 최소화하고자 빠르게 개발되고 도입되었다. 하지만 사용자들은 이 도구를 어떻게 사용하고 청소하는지 알지 못할 수 있으며, 이로 인해 오히려 환자 및 의료진에게 바이러스 노출을 증가시킬 수 있다. 저자들은 수술 중 오염 및 에어로졸 상자의 오염제거, 그리고 수술 전 시각적 보조 교재의 영향을 평가하였다.

방법: 본 연구는 이중맹검 무작위 배정 연구로 형광 마커로 오염된 에어로졸 상자를 사용한 동일 마취 사례 시뮬레이션에 44명의 마취과 전공의와 교수진이 참여하였다. 연구대상자의 절반은 시뮬레이션 전에 시각적 보조 교재를 숙지했다. 자외선(UV)을 이용하여 10군데의 표준 위치에서 수술 중 오염을 평가하였다. 다음으로 연구대상자들은 다음 환자에 사용을 위해 에어로졸 상자를 청소하도록 지시받았다. 청소 후 자외선을 이용하여 해당 상자의 오염 제거 정도를 평가하였다.

결과: 총 오염 점수의 중간값은 실험군에서 유의하게 감소하였다(5.0 vs. 10.0, $P < 0.001$). 에어로졸 상자의 완전 청소율은 실험군에서 36.4%였으며, 이에 비해 대조군은 4.5%를 보였다($P = 0.009$).

결론: 시각적 보조 교재의 사용은 수술 중 오염을 유의하게 감소시켰으며, 상자의 청소율을 향상시켰다. 이러한 결과에도 불구하고, 임상적으로 유의한 양의 바이러스 노출이 존재할 가능성이 있다. 그러므로 에어로졸 상자의 사용 전에 상자 사용의 위험과 이득에 대한 자세한 평가가 선행되어야 한다. 에어로졸 상자가 사용되는 경우, 의료진에게 최선의 사용법과 청소법을 상기시키기 위한 시각적 보조 교재 사용을 고려해야 한다.

Keywords: Airway management; Anesthesiology; Audiovisual aids; Equipment and supplies; High fidelity simulation training; Infection control.

KJA
Korean Journal of Anesthesiology

Tube-in-tube airway management in a patient with Montgomery T-tube in situ -a case report-

Montgomery T-tube가 있는 환자의 튜브내 튜브 기도 관리

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Case Report

Korean J Anesthesiol 2021;74(2):165-168
https://doi.org/10.4097/kja.20171
pISSN 2005-6419 • eISSN 2005-7563

Received: April 16, 2020
Revised: May 20, 2020 (1st); June 18, 2020 (2nd)
Accepted: June 26, 2020

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배경: Montgomery T-tube (MTT)는 거의 사용되지 않지만 유용한 기도 장치이며, 형태와 구조가 특이하다. MTT를 사용하는 환자가 전신마취와 지속적인 양압환기(continuous positive-pressure ventilation, CPPV)가 필요할 때 기도관리는 마취과 의사에게 매우 어렵다.
증례: MTT를 가지고 있는 48세 74 kg의 남성이 전신마취하에 국소 췌장 절제술을 받을 예정이었다. 저자들은 CPPV를 유지하고 흡입 마취제를 전달하기 위해 구강을 통해 MTT의 기관내 가지안으로 기낭이 있는 기관내 튜브를 삽입하였다. 환자가 마취에서 완전히 회복된 후 기관내 튜브는 성공적으로 제거되었다. 삽관이나 발관 후에도 기관지 부상이나 출혈이 발생하지 않았으며, MTT 위치에는 변화가 없었다.
결론: 구강을 통해 cuffed 기관내관을 MTT의 기관내 가지에 삽입하는 것은 기도 관리를 위한 안전하고 실현 가능한 접근법으로 간주될 수 있다.

Keywords: Airway management; Anesthesia; Anesthetic management; Endotracheal T-tube; Montgomery T-tube; T-shaped airway stent.

KJA
Korean Journal of Anesthesiology

Case Report

Korean J Anesthesiol 2021;74(2):169-174
https://doi.org/10.4097/kja.20204
pISSN 2005-6419 • eISSN 2005-7563

Received: April 29, 2020
Revised: May 28, 2020
Accepted: June 1, 2020

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Infection control of operating room and anesthesia for cesarean section during the COVID-19 outbreak in Daegu, the Republic of Korea -a case series-

대구에서 코로나바이러스감염증-19 유행 기간 중 제왕절개 시 수술실 및 마취 관련 감염관리: 8례의 증례

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배경: 코로나바이러스감염증-19 (COVID-19)는 처음 중국 우한에서 보고된 이후 대한민국으로도 급속히 확산되었다. 국내에서는 COVID-19의 유행을 막고자 전 병원에서 선별검사 가이드라인이 수립되었다. 기존에 COVID-19 확진 산모의 성공적 제왕절개 사례가 1건 보고되었지만, 감염 의심 산모에 대한 진료 가이드라인이 제시된 바는 없다. 대부분의 경우, 제왕절개술은 충분한 감염 평가가 완료되지 않은 상태에서 종종 위급하게 시행된다. 이에 저자들은 COVID-19 감염이 의심되는 제왕절개술 시행 예정인 환자에서 마취 관리 가이드라인을 제시하고자 한다.

증례: 대구에 있는 저자들의 병원은 감염 의심 산모의 출산 및 격리 시설로 국가에서 지정되었다. 저자들은 7명의 감염 의심 산모와 1명의 확진 산모를 대상으로 제왕절개술을 시행하였다.

결론: 본 증례는 COVID-19 의심 산모의 제왕절개술을 할 때 수술실 준비 및 감염으로부터의 수술실의 보호, 수술 중 감염 관리와 마취 관련 감염관리 가이드라인을 제시한다.

Keywords: Cesarean section; COVID-19; Guidelines; Pandemics; Personal protective equipment; Pregnancy; SARS-COV-2.

KJA
Korean Journal of Anesthesiology

Anesthetic concerns during cytoreductive surgery with hyperthermic intraperitoneal chemotherapy

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Editorial

Korean J Anesthesiol 2021;74(2):89-90
https://doi.org/10.4097/kja.21099
pISSN 2005-6419 • eISSN 2005-7563

Received: March 8, 2021
Accepted: March 14, 2021

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Hyperthermic intraperitoneal chemotherapy (HIPEC) is a well-established surgical technique for intraperitoneal administration of chemotherapeutic drugs in patients with primary peritoneal carcinomatosis, or peritoneal metastasis from gynecological or gastrointestinal cancer after cytoreductive surgery (CRS) that involves surgical removal of visible tumors in the abdomen [1]. The goal of HIPEC is to destroy any residual microscopic cancer cells and to prevent recurrence because tumors are more sensitive to cytotoxic drugs during heated chemotherapy [2]. In patients with stage III epithelial ovarian cancer, the addition of HIPEC to intervals of CRS results in longer recurrence-free survival and overall survival than surgical treatment alone [3].

HIPEC is a form of heated chemotherapy that is administered to the abdominal cavity in the operating room under general anesthesia; therefore, the anesthesiologist plays a pivotal role in CRS with HIPEC. Massive fluid shift, blood loss, and temperature imbalance leads to hemodynamic alterations [2], and anesthetic considerations are needed with respect to cardiovascular, respiratory, and renal functions, as well as electrolyte balance and thermoregulation.

During the debulking phase of CRS, the amount of fluid and blood loss is mainly associated with the extent of resection, and, therefore, appropriate fluid management, and transfusion are required. During the HIPEC phase, injection of saline-enriched chemotherapeutic drugs into the abdominal cavity increases intra-abdominal pressure, and this decreases venous return and cardiac output [4]. Adequate administration of crystalloids and colloids is required for adequate organ perfusion and urine output. A previous randomized controlled trial compared standard fluid therapy and goal-directed therapy and found that goal-directed therapy improved postoperative outcomes, including major abdominal and systemic postoperative complications and the length of hospital stay, compared to the standard fluid therapy protocol [5]. Fluid overload and subsequent electrolyte imbalance along with coagulation abnormalities should be properly managed during CRS along with HIPEC.

Invasive hemodynamic monitoring is also recommended because of fluid shift and hyperdynamic circulation during HIPEC. A significant amount of fluid shift and blood loss may occur during CRS. During the HIPEC phase, heated chemotherapy results in vasodilation and hyperdynamic circulation. Vasodilation decreases systemic vascular resistance and mean arterial pressure and increases heart rate and cardiac output. Furthermore, the administration of saline-enriched cytotoxic drugs into the closed abdominal cavity increases intra-abdominal pressure and may further decrease venous return and cardiac output [4]. Invasive monitoring in the form of cardiac output and stroke volume variation is useful during such a hyperdynamic procedure [2].

A systemic review revealed that fluid management protocol guided by an advanced

monitoring system (FloTrac®, LiDCO®, Pulsioflex® or PiCCO®) seems to be related to less postoperative morbidity and mortality following HIPEC [6]. Recently, less invasive methods for the monitoring of cardiac index (CI) have been widely introduced during anesthesia, and four different methods (FroTrac®, ProAQT®, ClearSight®, and arterial pressure waveform analysis from PICCO®) were investigated and compared with transpulmonary thermodilution (TPTD) during CRS with HIPEC [7]. Among these, FloTrac®, ProAQT®, and ClearSight® systems could not reliably measure CI compared to TPTD. Strategy on hemodynamic monitoring and fluid management during HIPEC should be individualized to minimize the postoperative complications.

In addition to hemodynamic management, protective mechanical ventilation is recommended considering cephalad displacement of the diaphragm and the subsequent increase in airway pressure [8]. Fluid management based on hemodynamic monitoring should ensure adequate urine output to prevent acute kidney injury [2]. Electrolyte imbalance and coagulation abnormalities should also be corrected.

CRS with HIPEC is a high-risk surgical procedure that is associated with major hemodynamic and metabolic changes; therefore, a team approach with continuous and vigilant care is required. Reports on anesthetic management till date are insufficient, and guidelines on intraoperative hemodynamic management have not been established. Furthermore, future studies on the impact of hemodynamic management during CRS with HIPEC on postoperative outcomes are needed.

Conflicts of Interest

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

Author Contributions

Jung-Hee Ryu (Conceptualization; Writing – original draft; Writing – review & editing)
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https://doi.org/10.4097/kja.21099

KJA
Korean Journal of Anesthesiology

Review Article

Korean J Anesthesiol 2021;74(2):91-102
https://doi.org/10.4097/kja.21006
pISSN 2005-6419 • eISSN 2005-7563

Received: January 6, 2021
Accepted: January 11, 2021

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Previous presentation in conferences:
This work has been presented in part at The 97th Scientific Meeting of The Korean Society of Anesthesiology, Nov 2020, Grand Hyatt Incheon, Incheon, Korea. Title of the invited lecture: COVID-19 associated Coagulopathy: The Role of Viscoelastic Testing.

The role of rotational thromboelastometry during the COVID-19 pandemic: a narrative review

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The coronavirus disease 2019 (COVID-19) pandemic is currently recognized as a global health crisis. This viral infection is frequently associated with hypercoagulability, with a high incidence of thromboembolic complications that can be fatal. In many situations, the standard coagulation tests (SCT) fail to detect this state of hypercoagulability in patients with COVID-19 since clotting times are either not or only mildly affected. The role of viscoelastic tests such as rotational thromboelastometry (ROTEM®) during this pandemic is explored in this review. COVID-19-associated coagulopathy, as measured using the rotational thromboelastometry parameters, can vary from hypercoagulability due to increased fibrin polymerization and decreased fibrinolysis to bleeding from hypocoagulability. The use of a multimodal diagnostic and monitoring approach, including both rotational thromboelastometry and SCT, such as plasma fibrinogen and D-dimer concentrations, is recommended. Rotational thromboelastometry provides comprehensive information about the full coagulation status of each patient and detects individual variations. Since COVID-19-associated coagulopathy is a very dynamic process, the phenotype can change during the course of infection and in response to anticoagulation therapy. Data from published literature provide evidence that the combination of rotational thromboelastometry and SCT analysis is helpful in detecting hemostasis issues, guiding anticoagulant therapy, and improving outcomes in COVID-19 patients. However, more research is needed to develop evidence-based guidelines and protocols.

Keywords: Anticoagulants; Blood coagulation disorders; COVID-19; Fibrinolysis; SARS-CoV-2; Thrombelastography; Thrombophilia; Thrombosis.

Introduction

The first case of coronavirus disease 2019 (COVID-19) was reported in Wuhan City, China, in December 2019, before it became a global pandemic. The disease is highly contagious, and the clinical picture varies from an asymptomatic course to acute respiratory failure [1]. COVID-19-associated hypercoagulability and subsequent pulmonary thrombosis are among the leading causes of death from COVID-19. This hypercoagulability

can be resistant to standard doses of low molecular weight heparin (LMWH), indicated by low anti-Xa levels (< 0.4 IU/ml), in patients with sub-therapeutic or therapeutic anticoagulation. Furthermore, hypercoagulability in COVID-19 is characterized by high plasma fibrinogen concentrations and elevated D-dimer levels (> 2,500 μg/L). Published data suggest that both hypercoagulability and a significant increase in proinflammatory cytokines (cytokine storm) are the leading causes of multiple organ failure in critically ill COVID-19 patients (immunothrombosis) [2–5]. Moreover, hypercoagulability is initiated by activating proinflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) [6]. The plasma fibrinogen concentration and D-dimer levels subsequently increase. These values exhibit a strong correlation with disease severity and can predict mortality at hospital and intensive care unit (ICU) admission [7]. The presence of other coexisting diseases, such as cardiovascular or cerebral diseases, can also increase the risk for morbidity and mortality [8]. Standard coagulation tests (SCT) of patients with COVID-19 such as platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR) may show normal results despite the presence of hypercoagulability on rotational thromboelastometry and microvascular thrombosis [9–11].

In contrast, viscoelastic tests (VETs) can evaluate the mechanical properties of clot formation and lysis. The most frequently used VETs are thromboelastography (TEG®) and rotational thromboelastometry (ROTEM®). Published literature regarding this pandemic explored the ability of TEG® and ROTEM® to detect COVID-19-associated coagulopathy [12,13]. Increased thrombin generation and clot formation plays an important role in the progression of COVID-19 and can be used to predict the severity and risk of complications [14,15].

Aim and method of the narrative review

This narrative review aimed to identify and discuss the peer-reviewed literature regarding the role of rotational thromboelastometry for COVID-19 patients who experienced coagulopathy. This review provides important information to clinicians and healthcare authorities regarding the possible role of rotational thromboelastometry as a diagnostic and monitoring tool during the current COVID-19 pandemic.

This literature review was approved by the local research and ethics committee on October 18, 2020 (approval no. 2020-10-50) of the College of Medicine, King Faisal University, Al-Ahsa, Hofuf, Kingdom of Saudi Arabia. This review explores and identifies several published studies focusing on the role of rotational thromboelastometry in critically ill patients with COVID-19. Medline, Scopus, PubMed, and Google Scholar were searched for related literature published between January and December 2020. Current peer-reviewed and accepted online ahead of print publications were also included. PubMed was searched using the following keywords, which obtained 24 results: (COVID-19 [Title/Abstract] OR SARS-CoV-2 [Title/Abstract]) AND (ROTEM [Title/Abstract] OR thromboelastometry [Title/Abstract]).

Rotational thromboelastometry

Rotational thromboelastometry (ROTEM®, Tem Innovations, Germany) is a point-of-care device that is capable of evaluating the viscoelastic properties and kinetics of the whole coagulation process, including clot formation and lysis, in vitro. Rotational thromboelastometry can assess both extrinsic and intrinsic coagulation pathways depending on the reagents used [16]. The four principal tests used with ROTEM include EXTEM, INTEM, FIBTEM, and HEPTEM, which assess the extrinsic coagulation pathway, intrinsic coagulation pathway, fibrin contribution to clot firmness, and heparin-like effects, respectively. Rotational thromboelastometry measures the following parameters: CT, CFT, A5, A10, and MCF. CT is the time needed to initiate clot development (until clot firmness = 2 mm). CFT characterizes clot kinetics based on the time needed to increase clot firmness from 2 to 20 mm. MCF is the maximum clot firmness measured in mm achieved during the thromboelastometric measurement. Finally, fibrinolysis is characterized by maximum lysis (ML in %), which is defined as the decrease in clot firmness, expressed in percentage, of MCF during run time. Lysis indexes at 30 (LI30), 45 (LI45), and 60 (LI60) min are defined as the residual clot firmness in percentage of MCF at 30 or 60 min after CT, respectively. To detect hypofibrinolysis/fibrinolysis shutdown, the run time should be at least 60 min in order to achieve LI60. The lysis onset time (LOT in seconds) is defined as the time from CT until the clot firmness amplitude decreases by 15% compared with MCF. LOT is not achieved during a 60-min run time in patients with hypofibrinolysis/fibrinolysis shutdown or prolonged in TPATEM/TPA-test with recombinant tissue plasminogen activator (r-tPA)-challenge in patients with COVID-19. TPATEM/TPA-test is a modified EXTEM test with the addition of r-tPA. Here, r-TPA-doses (Alteplase, Boehringer-Ingelheim, Germany) between 0.125 and 0.625 μg/ml were used for r-tPA-challenge by different investigators. Lysis time (LT in seconds), defined as the time from CT until the clot firmness decreases to 50% (in ClotPro®) or 10% (in ROTEM®) compared with MCF, can also be used to characterize fibrinolysis resistance. Fibrinolysis resistance is characterized by

https://doi.org/10.4097/kja.21006

prolonged LOT, prolonged LT, and increased LI30 in the TPATEM/TPA-test. Fig. 1 illustrates the rotational thromboelastometry parameters and indices mentioned above [16].

Several studies prior to the COVID-19 pandemic demonstrated that an EXTEM or INTEM MCF of > 68 mm (A10 > 61.5 mm) is a strong indicator of hypercoagulability and predictor of thrombosis [17,18]. A FIBTEM MCF value of > 25 mm is associated with a five-fold increased risk of developing thrombosis in cirrhotic patients with hepatocellular carcinoma [19,20]. Hypercoagulability in COVID-19 patients was assessed by rotational thromboelastometry, which is used as a diagnostic tool [21,22]. Hypofibrinolysis/fibrinolysis shutdown in rotational thromboelastometry is diagnosed based on the following criterion: an EXTEM ML of < 3.5% following a 60-min run time, which corresponds to an EXTEM LI60 of > 96.5%. Accordingly, rotational thromboelastometry analysis should run for 65–70 min in COVID-19 patients in order to confirm or exclude hypofibrinolysis/fibrinolysis shutdown [22–24].

COVID-19-associated hypercoagulability in rotational thromboelastometry

Between April and August 2020, several independent research groups (Pavoni et al. [5], Spiezia et al. [25], Collett et al. [26], and Hoechter et al. [27]) reported and confirmed the presence of hypercoagulability after conducting a series of thromboelastometric analyses in COVID-19 patients, and it was associated with an increased risk of thrombosis. Kong et al. [21] described this hypercoagulability as an increase in EXTEM and FIBTEM MCF (Fig. 2). Moreover, Ibañez et al. [28] attributed this hypercoagulability to hypofibrinolysis/fibrinolysis shutdown. Chaudhary et al. [29] suggested that rotational thromboelastometry can monitor the hypercoagulability/hypofibrinolysis status and can be a predictor of thromboembolic complications. In October 2020, Almskog et al. [30] demonstrated that EXTEM and FIBTEM MCF, assessed at hospital admission, could help distinguish hospitalized COVID-19 patients who can be treated at a regular ward from those who will

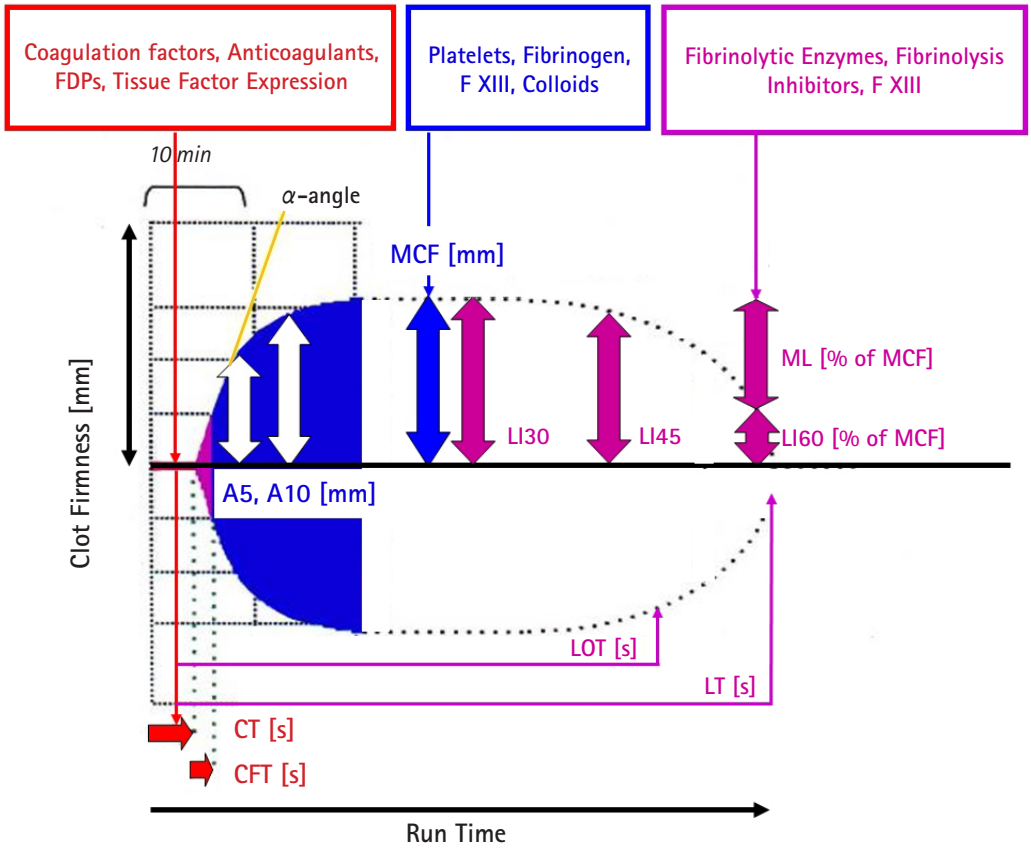

Fig. 1. ROTEM® parameters and indices. A5: clot firmness amplitude 5 min after coagulation time (CT) in mm, A10: clot firmness amplitude 10 min after CT in mm, CFT: clot formation time in seconds (time from 2 to 20 mm clot firmness), CT: coagulation time in seconds (time from test start to 2 mm clot firmness), FDPs: fibrin(ogen) degrading products, F XIII: coagulation factor XIII, LI30: lysis index 30 min after CT in % (residual clot firmness in percentage of MCF), LI45: lysis index 45 min after CT in %, LI60: lysis index 60 min after CT in %, LOT: lysis onset time in seconds (time from CT to 15% fibrinolysis = 85% residual clot firmness compared to MCF), and LT: lysis time in seconds (time from CT to 90% fibrinolysis = 10% residual clot firmness compared to MCF). Courtesy of Klaus Görlinger, Munich, Germany.

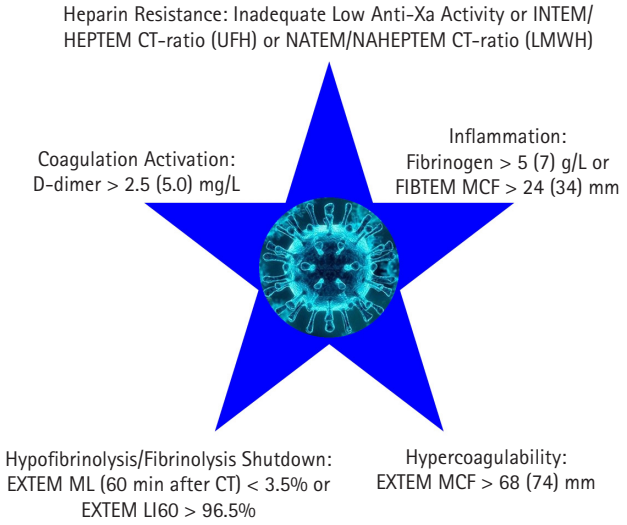

Fig. 2. COVID-19-associated coagulopathy. Diagnostic value of D-dimer, fibrinogen, anti-Xa activity, and rotational thromboelastometry parameters. CT: coagulation time in seconds, EXTEM: ROTEM® test assessing the extrinsic coagulation pathway, FIBTEM: ROTEM® test assessing fibrin contribution to clot firmness, HEPTEM: ROTEM® test assessing the intrinsic coagulation pathway with elimination of heparin-like effects by heparinase, INTEM: ROTEM® test assessing the intrinsic coagulation pathway which is sensitive to heparin-like effects, LI60: lysis index 60 min after CT in % of MCF, LMWH: low molecular weight heparin, MCF: maximum clot firmness in mm, ML: maximum lysis in % of MCF, NAHEPTEM: native ROTEM® test with elimination of heparin-like effects by heparinase, NATEM: native ROTEM® test which is sensitive to LMWH, and UFH: unfractionated heparin. Courtesy of Klaus Görlinger, Munich, Germany.

require treatment at specialized ICUs with the need for mechanical ventilation. They also suggested that this could be used in future triage protocols. Further studies conducted by Spiezia et al. [31], van Veenendaal et al. [32], and Blasi et al. [33] confirmed that these rotational thromboelastometry findings provide supportive evidence to indicate that hypercoagulability in EXTEM, INTEM, and FIBTEM were associated with a more severe COVID-19. Roh et al. [34] also suggested that the significant increase in fibrinogen plasma concentrations and FIBTEM MCF indicates the severity of COVID-19 and can be used for risk stratification for thrombosis, respiratory failure, and mortality. In fact, an ongoing multinational (11 countries), multicenter (16 hospitals) observational trial is aimed at assessing the value of rotational thromboelastometry and SCTs in predicting the need for hospital resources, patients' course, and outcomes in 500 hospitalized patients with COVID-19 (ROHOCO study; DRKS00023934) [22].

COVID-19-associated hypofibrinolysis/fibrinolysis shutdown in rotational thromboelastometry

The failure of LMWH or unfractionated heparin (UFH) to reduce the incidence of thrombosis was reported by Creel-Bulos et al. [24] and was attributed to the presence of hypofibrinolysis/fibrinolysis shutdown, characterized by an EXTEM ML value of < 3.5%, which corresponds to an EXTEM LI60 value of > 96.5%. Here, either 8 of 9 (89%) patients with venous thrombosis met the diagnostic criteria for hypofibrinolysis/fibrinolysis shutdown, or 8 out of 11 (73%) patients with hypofibrinolysis/fibrinolysis shutdown developed thrombosis. Meanwhile, only 1 out of 14 (7%) patients without hypofibrinolysis/fibrinolysis shutdown developed thrombosis. The cut-off value for the hypofibrinolysis/fibrinolysis shutdown reported by Creel-Bulos et al. [24] is in line with those for hypofibrinolysis/fibrinolysis shutdown published by Adamzik et al. [35] and Schmitt et al. [36] for bacterial sepsis and Gomez-Builes et al. [23] and Stettler et al. [37] for trauma patients.

COVID-19-associated fibrinolysis resistance in rotational thromboelastometry

Weiss et al. [38] and Nougier et al. [39] demonstrated that clots from some critically ill COVID-19 patients were resistant to r-tPA challenge in rotational thromboelastometry (TPATEM = EXTEM with 0.125–0.625 μg/ml r-tPA (Alteplase, Boehringer-Ingelheim, Germany) despite the high D-dimer plasma concentrations. Fibrinolysis resistance was defined as a delay in the lysis onset time (LOT in seconds) or an increased LI30 in % of MCF after an in vitro r-tPA challenge (Fig. 3). Here, healthy controls showed a LI30 of 1.8 ± 3.2%; non-ICU COVID-19 patients, 18 ± 35%; ICU COVID-19 patients, 63 ± 39%; and ICU COVID-19 patients with thrombosis, 82 ± 26% (P = 0.003). A TPATEM assay with 0.125 μg/ml r-tPA has been validated on ROTEM® *delta* [40]; however, a CE-marked TPA-test can only be performed using the ClotPro® device, a modification of ROTEM® [41]. In COVID-19 patients with thrombosis, LT was significantly prolonged in the TPATEM/TPA-test. Whether detection of fibrinolysis resistance provides additional clinically relevant information compared with the detection of hypofibrinolysis/fibrinolysis shutdown remains unknown and requires further investigation.

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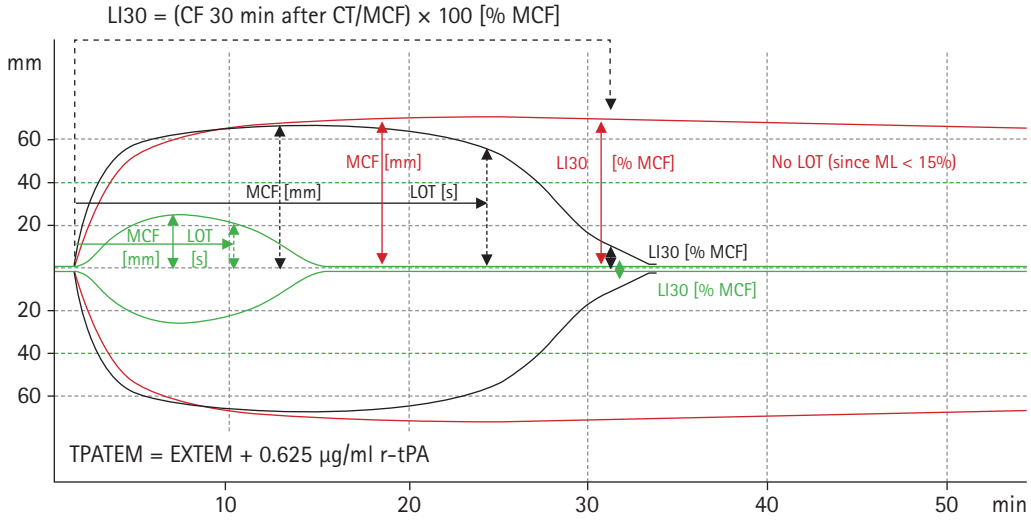

Fig. 3. TPATEM/TPA-test findings in COVID-19 patients. Representative TPATEM curves from a healthy donor (green curve), a COVID-19 patient without thrombosis (black curve), and a COVID-19 patient with thrombosis (red curve). In COVID-19 patients, LOT and LT are prolonged, and MCF and LI30 are increased compared with those in healthy controls after r-tPA challenge (TPATEM = EXTEM + 0.625 µg/ml r-tPA). CF: clot firmness in mm, CT: coagulation time in seconds, EXTEM: ROTEM® test assessing the extrinsic coagulation pathway, LI30: lysis index 30 min after CT in % of MCF, LOT: lysis onset time in seconds, MCF: maximum clot firmness in mm, ML: maximum lysis in % of MCF, and r-tPA: recombinant tissue plasminogen activator. Courtesy of Klaus Görlinger, Munich, Germany.

High D-dimer levels combined with hypofibrinolysis/fibrinolysis shutdown as a strong predictor of thrombosis in COVID-19 patients

The combination of high D-dimer levels and hypofibrinolysis/fibrinolysis shutdown in VET showed the best predictive value for venous thromboembolism (VTE), thrombotic stroke, and renal failure with the need for dialysis in COVID-19 patients [42,43]. Here, Wright et al. [42] demonstrated that the receiver operating characteristics area under the curve (ROC AUC) values for predicting VTE were 0.742 (95% CI, 0.581, 0.903; P = 0.022) for TEG® lysis 30 (TEG® LY30 in % = decrease of clot firmness amplitude in percentage of maximum amplitude [MA] at 30 min after MA) and 0.582 (95% CI, 0.372, 0.792; P = 0.440) for D-dimer. The ROC AUC values for predicting renal failure with the need for dialysis were 0.799 (95% CI, 0.610, 0.949; P = 0.005) for D-dimer and 0.606 (95% CI, 0.414, 0.797; P = 0.292) for TEG® LY30. Combined analysis revealed the VTE, thrombotic stroke, and renal failure incidence rates of 5%, 7%, and 14%, respectively, with the need for dialysis in COVID-19 patients with a D-dimer concentration of ≤ 2,600 FEU and TEG® lysis 30 of > 0% (TEG® LY30 is defined as the reduction in clot firmness amplitude in percentage of [MA] 30 min after MA). If the D-dimer concentration was higher than 2,600 FEU or the TEG® LY30 was 0%, the incidence rates of VTE, thrombotic stroke, and renal failure with the need for dialysis increased to 30%, 10%, and 30%, respectively. If the D-dimer concentrations were higher than 2,600 FEU and the LY30 was 0%, the incidence rates of VTE, thrombotic stroke, and renal failure with the need for dialysis increased to 50% (P = 0.008), 30% (P = 0.274), and 80% (P = 0.004), respectively. These results are in line with the data published recently by Kruse et al. [43]. Here, EXTEM ML was inversely (ROC AUC, 0.8 [95% CI, 0.7, 0.9]; P = 0.002) and D-dimer concentration was directly (ROC AUC, 0.78 [95% CI, 0.6, 0.9]; P < 0.001) associated with an increased risk of VTE complications. The combination of EXTEM ML values and D-dimer concentrations showed high sensitivity and specificity for VTE risk prediction (D-dimer [mg/L] – EXTEM ML [%] cut-off, 3.7; ROC AUC, 0.92 [95% CI, 0.8, 1.0]; P < 0.001; sensitivity, 94%, specificity > 90%). Accordingly, the combination of hypofibrinolysis/fibrinolysis shutdown and increased D-dimer levels is actually the best predictor for VTE, thrombotic stroke, and renal failure with the need for dialysis in critically ill COVID-19 patients. Primarily, this combination resulted in some confusion since increased D-dimer levels have been misinterpreted as a biomarker of increased fibrinolysis [28]. However, both Almskog et al. [30] and Madathil et al. [44] reported that only 0.02%–0.2% of the fibrinogen mass was cleaved to D-dimers in COVID-19. Accordingly, increased D-dimer concentration in COVID-19 patients reflect an increased fibrin deposition but not an increased breakdown of fibrin (fibrinolysis). Finally, the combination of increased fibrin deposition in the microcirculation combined with hypofibrinolysis results in multiple organ failure (lungs, kidney, and brain).

Potential implications of hypofibrinolysis/fibrinolysis shutdown for the therapy of COVID-19-associated coagulopathy

These data suggest that COVID-19 patients with respiratory failure (PaO_2/FiO_2 < 150 mmHg for more than 4 h despite optimum mechanical ventilation and prone positioning) who experienced hypercoagulability and hypofibrinolysis/fibrinolysis shutdown might benefit from sub-therapeutic/therapeutic anticoagulation and/or additional thrombolytic therapy with r-tPA (Alteplase, Boehringer-Ingelheim, Germany) [34,45–49]. A recent case series showed that r-tPA therapy can improve oxygenation and may improve survival in this specific patient population [50–53].

The required r-tPA-dose can vary from patient to patient. Therefore, monitoring the effect of thrombolytic therapy in COVID-19 patients by rotational thromboelastometry is recommended [50,53]. Here, rotational thromboelastometry is not only important in selecting the COVID-19 patient population who might benefit from thrombolytic therapy, but it can also detect the patient population with a higher risk of developing bleeding complications under thrombolytic therapy. Symptomatic intracerebral hemorrhage usually occurs within 24–36 h after thrombolytic infusion and remains one of the most feared complications of thrombolytic therapy. Campello et al. [54] demonstrated that a baseline FIBTEM MCF of < 13.5 mm is an important biomarker that can be easily obtained to predict which patients have a higher risk of developing hemorrhagic events after r-tPA therapy (sensitivity: 94% and specificity: 80%). Furthermore, bleeders showed higher EXTEM ML after r-tPA infusion and borderline hyperfibrinolysis (median [Q1, Q3], 14% [10%, 18%] versus 6% [5%, 8.5%]; P = 0.007). Accordingly, thrombolytic therapy might be harmful in patients with advanced stages of COVID-19, where the hemostatic status changed from hyper- to hypocoagulability and from hypo- to hyperfibrinolysis in case of disseminated intravascular coagulation (DIC) [55]. An ongoing phase IIa randomized controlled trial is aimed at evaluating the efficacy and safety of different doses of Alteplase (50–100 mg IV) for respiratory failure in patients with COVID-19 (STARS trial) [56]. In this trial, heparin infusion was administered following thrombolytic therapy for therapeutic anticoagulation.

Inhalation therapy with thrombolytic agents in severe COVID-19 patients

Furthermore, nebulizer r-tPA may provide a targeted approach in COVID-19 patients to degrade fibrin and improve oxygenation with limited bleeding risk in critically ill patients [57]. The administration of thrombolytic drugs by inhalation might improve alveolar ventilation by resolving fibrin-containing exudates in the pulmonary alveolar space and dissolving fibrin thrombi at the microcirculatory level near the alveoli. Inhalation therapy with tPA is reported to be effective for various cases of acute respiratory distress syndrome (ARDS) or plastic bronchitis. Actually, a phase II clinical trial of r-tPA inhalation is currently underway (PLATyPuS; Alteplase, NCT02315898). Other studies reported promising results of plasminogen inhalation in COVID-19 patients [58]. If r-tPA is not available, nebulization of streptokinase can be used as an alternative method. Abdelaal Ahmed Mahmoud et al. [59] performed a randomized controlled trial comparing nebulized streptokinase with nebulized heparin and the standard of care in patients with severe ARDS; (PaO_2/FiO_2 < 100 mmHg) nonresponsive to recruitment maneuvers and prone positioning. Streptokinase (250,000 IU/4 h by nebulizer, with a total daily dose of 1,500,000 IU) or heparin (dose of 10,000 IU/4 h by nebulizer, with a total daily dose of 60,000 IU UFH) prepared in 3 ml volume of distilled water and nebulized for a period of 15 min every 4 h was administered. Nebulized streptokinase resulted in an improvement in oxygenation (increased PaO_2/FiO_2), decreased $PaCO_2$ (P < 0.001), improved lung compliance, reduced plateau pressure, and decreased ICU mortality compared with nebulized heparin and standard of care therapy [59].

COVID-19, heparin resistance, and anticoagulation monitoring with rotational thromboelastometry

Heparin resistance can be defined as a decrease in the heparin dose-response curve. It can also be defined as the need for more than 35,000 IU UFH per 24 h to prolong the aPTT or activated clotting time to its therapeutic range [60,61]. An antithrombin activity of less than 60%, age above 65 years, increased factor VIII and fibrinogen levels, and platelet level of > 300,000/μl were the predictors of heparin resistance [62]. Although antithrombin activity rarely drops below 60% in COVID-19 patients, increased age, factor VIII and fibrinogen levels, and high platelet counts commonly occur in those with severe COVID-19 [25,27,63,64].

LMWH (e.g., enoxaparin, 20–30 mg subcutaneously (SC) once a day) is used as a thromboprophylactic treatment in COVID-19 patients with low thrombotic risk and fibrinogen plasma concentrations of < 500 mg/dl provided that an anti-Xa activity target of 0.1–0.4. IU/ml is achieved 2–4 h after SC injection. For sub-therapeutic or therapeutic anticoagulation in COVID-19 patients with moderate to high risk of VTE, 0.5 to 1 mg/kg enoxaparin SC twice

https://doi.org/10.4097/kja.21006

per day can be used if the anti-Xa activity targets of 0.4–0.6 IU/ml and 0.6–1.0 IU/ml are achieved 2–4 hours after SC injection. In critically ill COVID-19 patients who require vasopressor therapy, SC injection of LMWH might be inappropriate as the vasopressor can lead to peripheral vasoconstriction and reduced resorption of the drug. Here, IV infusion of UFH or LMWH can be used as an alternative treatment. However, the effect might be limited by heparin resistance; the anti-Xa activity targets for sub-therapeutic (200 IU/kg/24 h) and therapeutic anticoagulation (400 IU/kg/24 h) with UFH are 0.15–0.30 IU/ml and 0.3–0.7 IU/ml, respectively.

To monitor the effect of heparin anticoagulation or to diagnose heparin resistance with rotational thromboelastometry, it is important to consider that INTEM is not highly sensitive to the effect of LMWH. The INTEM/HEPTEM CT-ratio correlates well with anti-Xa activity for UFH (r = 0.72 compared to 0.36 for aPTT) [65]. The native rotational thromboelastometry test (NATEM) is more sensitive to LMWH, and the NATEM/NAHEPTEM CT-ratio (NAHEPTEM = native test with heparinase) correlates well with the anti-Xa activity calibrated for LMWH [unpublished data].

The direct factor Xa inhibitor apixaban can be used thromboprophylaxis or alternative anticoagulation in patients with COVID-19 who developed heparin resistance and in whom oral administration is preferred [66–69]. Notably, the plasma concentrations of direct oral anticoagulant (DOAC) can increase substantially if DOACs are used in combination with antiviral drugs in COVID-19 patients [70]. Therefore, these combinations should be avoided or DOAC concentrations should be monitored. To monitor the effect of apixaban with rotational thromboelastometry, modified assays with lower tissue factor concentrations are needed [71,72].

In critically ill patients with high VTE risk and fibrinogen plasma concentrations of > 500 mg/dl, the off-label use of argatroban can be implemented as an alternative anticoagulation particularly in patients with heparin resistance [60]. Argatroban is a direct thrombin inhibitor approved for thromboprophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia. The argatroban plasma concentrations needed for therapeutic anticoagulation range from 0.2 IU/ml to 0.5 IU/ml of anti-IIa activity. Here, EXTEM CT correlated better with argatroban plasma concentrations than aPTT (r = 0.71; P < 0.001 and r = 0.214; P = 0.117, respectively) [73,74]. Furthermore, the importance of VET in patients treated with direct thrombin inhibitors was highlighted by Ranucci et al. [75] and Maier et al. [76]. They pointed out that fibrinogen plasma concentration assessed using the Clauss method is not reliable if direct thrombin inhibitors have been used and results in falsely low values. Therefore, they recommend using FIBTEM and TEG® functional fibrinogen measurements to assess the fibrinogen plasma concentration in these patients and to determine the appropriate argatroban or bivalirudin dosage [75,76].

Bleeding in patients with COVID-19

In hospitalized COVID-19 patients receiving standard-dose thromboprophylaxis, Al-Samkari et al. [77] reported an overall and major bleeding rate of 4.8% (95% CI, 2.9, 7.3) and 2.3% (95% CI, 1.0, 4.2), respectively. Similar results were reported by Jiménez et al. [78]. In this systematic review, the pooled incidence of VTE was 17.0% (95% CI, 13.4, 20.9), 12.1% (95% CI, 8.4, 16.4) for deep vein thrombosis, 7.1% (95% CI, 5.3, 9.1) for pulmonary embolism, 7.8% (95% CI, 2.6, 15.3) for bleeding, and 3.9% (95% CI, 1.2, 7.9) for major bleeding. The highest estimated pooled incidence of bleeding was reported in patients receiving intermediate-dose or full-dose anticoagulation (21.4%).

Patients with COVID-19 have an increased risk of developing thrombosis, and mortality can be reduced in hospitalized patients by providing thromboprophylaxis [48,68,79,80]. On the contrary, patients receiving therapeutic anticoagulation have an increased incidence of major bleeding (11% versus 4%; P = 0.04) and significantly higher mortality (41.6% versus 15.3%; P < 0.001) compared with those receiving pharmacological thromboprophylaxis [81]. After conducting a multivariate logistic regression analysis, therapeutic anticoagulation was still associated with increased mortality, with an odds ratio of 6.16 (95% CI, 2.96, 12.83; P < 0.001). Major bleeding and central nervous system bleeding were associated with increased mortality (40% versus 21.5%; P = 0.054 and 100% versus 21.9%; P = 0.001, respectively), while gastrointestinal bleeding was not associated with increased mortality (16.7% versus 22.7%; P = 1.000). Dogra et al. [82] reported 33 COVID-19-positive patients with intracerebral hemorrhage (ICH). Almost all patients with ICH received either therapeutic anticoagulation (66.7%) or a prophylactic dose (9.1%) prior to ICH discovery. Accordingly, the risk of ICH should be considered when developing an anticoagulation regimen for patients with COVID-19. Usman et al. [83] reported a case series of COVID-19 patients treated with veno-venous extracorporeal membrane oxygenation (ECMO). Four of ten patients had hemorrhagic stroke, three of whom died. Schmidt et al. [84] confirmed a major bleeding incidence of 42%, a hemorrhagic stroke incidence of 5%, and a mortality rate of 36% in COVID-19 patients treated with ECMO. Accordingly, close monitoring of all hematologic parameters, including VET and personalized antithrombotic therapy, is

recommended in patients with severe COVID-19, particularly during ECMO support [29]. The degree of anticoagulation can be assessed based on the anti-Xa activity or INTEM/HEPTEM CT-ratio for UFH, anti-Xa activity or NATEM/NAHEPTEM CT-ratio for LMWH, and anti-IIa activity, EXTEM CT, or ECATEM/ECA-test CT for IV direct thrombin inhibitors such as argatroban and bivalirudin [65,73,74,85–90].

Furthermore, the hemostatic phenotype of COVID-19 patients may change from hyper- to hypocoagulability and from hypo-to hyperfibrinolysis during advanced stages of COVID-19 in case of DIC [21,55]. The combination of rotational thromboelastometry and SCT enables the monitoring of these dynamic changes in COVID-19-associated coagulopathy and its corresponding therapy.

Conclusion

A multimodal diagnostic approach that includes SCT, such as fibrinogen plasma concentration and D-dimers, as well as rotational thromboelastometry, is required for the detection, monitoring, and management of COVID-19-associated coagulopathy. Fibrinogen plasma concentrations, D-dimer levels, and FIBTEM clot firmness play an important role in the risk stratification, prediction of the level of care needed during hospitalization, and determination of outcomes in hospitalized COVID-19 patients. SCTs such as aPTT and PT/INR may fail to detect hypercoagulability. In contrast, the combination of increased D-dimer levels and the hypofibrinolysis/fibrinolysis shutdown detected by rotational thromboelastometry is actually the best predictor for thromboembolic complications in COVID-19 patients. Rotational thromboelastometry should be utilized to guide personalized management and monitor individual responses to treatment. Therefore, there is an urgent need to develop rotational thromboelastometry-guided protocols and algorithms for the management of COVID-19-associated coagulopathy.

Conflicts of Interest

Klaus Gorlinger is working as the Medical Director of Tem Innovations GmbH, Munich, Germany, since July 2012. All other authors declared no conflict of interest relevant to this manuscript.

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https://doi.org/10.4097/kja.21006

KJA
Korean Journal of Anesthesiology

Comeback of ketamine: resurfacing facts and dispelling myths

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Review Article

Korean J Anesthesiol 2021;74(2):103-114
https://doi.org/10.4097/kja.20663
pISSN 2005-6419 • eISSN 2005-7563

Received: December 17, 2020
Revised: January 6, 2021 (1st); January 10, 2021 (2nd)
Accepted: January 10, 2021

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Initially known as CI-581, ketamine was first synthesized in 1962 as a replacement from phencyclidine. It has since been used as an anesthetic and analgesic. In addition, it has bronchodilating, sedative, and amnestic properties, preserving airway reflexes and sympathetic nervous system tone. Since the discovery of ketamine, it has been a major topic of discussion due to controversies regarding its usage in particular sets of patients. In the past 50 years, despite its potential benefits, it is not commonly used because of concerns of "emergence phenomenon," its use as a substance of abuse, and its systemic side effects. Since 2012, three World Health Organization reviews on ketamine have addressed its international control. Researchers have been studying this wonder drug for a decade worldwide. Many myths of ketamine regarding emergence phenomenon and its use in traumatic brain injury and open eye injury have been disproved in recent times. It is becoming popular in pre-hospital settings, critical care, emergency medicine, low-dose acute pain services, and adjuvant in regional anesthesia techniques. This review highlights the current consensus on the various applications of ketamine in the literature.

Keywords: Acute; Antidepressants; Cancer pain; Hallucinations; Intracranial pressure; Intraocular pressure; Ketamine; Pain clinics; Status epilepticus.

Introduction

Ketamine is a versatile drug with a unique profile, permitting its worldwide usage in many situations. Its variable dosing regimens make it a wonderful agent for anesthesia induction at high dosages with preservation of protective reflexes, and a potent analgesic in low-dose infusions. With the advent of newer and considerably safer drugs and because of its problems of abuse, ketamine use has reduced. Recently, researchers worldwide have gained interest in ketamine, and studies have been conducted on this agent and are included in this review.

This article highlights the controversies related to psychosomatic issues caused by ketamine use. The authors also discuss the evidence and consensus regarding its use in patients with raised intracranial and intraocular pressures in acute and chronic pain services and critical settings.

Discovery of ketamine and its timeline

1962: Calvin Stevens at Parke Davis laboratory synthesized a compound known as CL 581 from phencyclidine, which he later named ketamine.

1964: Its first use as anesthetic on prisoners in Michigan state prison by Dr. Corssen

1968: After Food and Drug Administration (FDA) approval, ketamine anesthesia was

first used on American soldiers during the Vietnam War.

1970-80: Recreational use of ketamine became popular worldwide.

Early 1980s: Emergence phenomenon led to increasing illicit use and withdrawal from mainstream anesthetic use in humans.

2000: Antidepressant effects of ketamine used in resistant cases by Dr. Berman at Yale University.

2002: Continuous infusions became popular for intractable complex regional pain syndrome by Drs. Harbert and Correl at Yale University.

2013: Moved from Schedule H to Schedule X drug to prevent its use per Drugs and Cosmetics Act

2014: Effect of ketamine on suicidal ideation by Dr. Price at Yale University and as treatment of posttraumatic stress disorder

2015: Large scale persistent network reconfiguration demonstration by Dr. Yang

Pharmacology

Ketamine is a phencyclidine derivative and a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist that blocks the phencyclidine sites on NMDA receptors mostly present in the cerebral cortex, thalamus, limbus, and spinal cord. This in turn leads to neuronal depolarization (Fig. 1). Its analgesic action is mainly due to its effects on opioid receptors. Added to the regular intravenous route, it can also be administered intramuscularly, intranasally, and interosseously.

It is highly lipid soluble and has a low protein binding capacity. It is metabolized primarily in the liver via hydroxylation and N-demethylation into Nor-ketamine, which is 30% as potent as ketamine with weak analgesic properties.

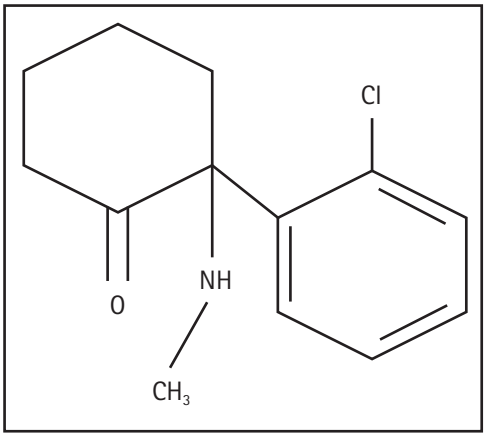

Fig. 1. Structure of ketamine: The chiral center of the cyclohexanone ring results in S-(+) and R-(-) isomers.

Systemic effects: what anesthesiologists should know

Cardiovascular

In patients with normal autonomic activity, it has a central sympathomimetic action leading to tachycardia, hypertension, and increased cardiac output. This is because it is an agent of choice for inductions in acute hypovolemic shock, whereas it is to be avoided in patients with coronary artery diseases. In patients with depleted catecholamines, such as in chronic shock and critically ill patients, it has a negative inotropic effect, which further accentuates shock-like states. If the autonomic activity is normal, sympathomimetic effects overrides negative inotropic action [1].

Respiratory

It preserves the airway tone and laryngo-pharyngeal reflex and causes bronchodilation. However, airway reflexes are very unpredictable in infants [2]. Intravenous ketamine use in large boluses could lead to transient apnea, as it may have a slight respiratory depressant effect and decrease the stimulant action of hypercarbia [3].

Miscellaneous

Ketamine also affects the metabolic and endocrine systems. It increases blood glucose, plasma cortisol, and prolactin levels [1]. It also leads to excessive salivation; thus, some clinicians advocate the routine use of an antisialagogue.

Since its discovery, ketamine has remained controversial because of associated dogmas. We wish to disprove the associated myths and establish evidence-based facts.

Consensus on ketamine use: what does the evidence say?

Ketamine in traumatic brain injury

Elevated intracranial pressure (ICP) with ketamine is one of the biggest controversies regarding the use of ketamine in patients with a head injury. It is a notion that ketamine can cause a rise in ICP through sympathetic stimulation, potentially exacerbating the condition. However, when ketamine is used with a γ-aminobutyric acid (GABA) agonist, this rise in ICP may not occur [4]. Furthermore, by increasing cerebral perfusion, ketamine may benefit patients with neurological injury. A thorough literature

https://doi.org/10.4097/kja.20663

search found a series of six studies published in the 1970s that reported an association between ketamine and increased ICP. Moreover, these studies were case reports and small case-control studies. These publications were confounded by patients with abnormal cerebrospinal fluid pathways, which included patients with aqueductal stenosis and obstructive hydrocephalus [5]. None of these studies have directly evaluated the effect of ketamine in patients with traumatic brain injuries (TBIs). Unfortunately, the myth that ketamine was contraindicated in TBIs has persisted until recently when large-scale studies showed conflicting results. A recent study has directly studied the effects of ketamine on ICP in patients with TBI and showed that ketamine is one of the best agents to facilitate airway management in patients with a head injury [6]. A large systematic review based on Cochrane methodology with Oxford level 2b, GRADE C evidence also supports that ketamine does not increase ICP in sedated and ventilated patients with severe TBI, and ketamine may lower the ICP in some patients [7]. In patients with TBI, it is important to maintain the mean arterial pressure, prevent hypoxia and hyperventilation, and mitigate increases in ICP, and ketamine helps fulfill these conditions. Ketamine retains the patient's respiratory drive, does not decrease the blood pressure, yields no increase in ICP, and allows for an additional advantage over other sedation medications and behavioral control without apnea [8]. Recent publication has provided evidence for the role of ketamine in neuroprotection [9]. In addition, ketamine can be administered intramuscularly or through the intranasal route, and therefore, it can be used easily in emergency settings [10]. Lastly, ketamine has a high therapeutic index that allows flexibility in dosing, which is necessary to obtain an accurate body weight [11].

Consensus: Ketamine can safely be used in patients with TBI as no large trials have proven that it increases the ICP in such patients; rather it provides hemodynamic stability in such patients [4,6–9].

Ketamine in patients with raised intraocular pressure

The initial work on ketamine and its effects on intraocular pressure (IOP) was performed by Corssen and Hoy in 1967, who described an increase in IOP; however, the study had several limitations [12]. The study included patients of different ages undergoing general anesthesia for various surgeries. They included only 15 pediatric patients, many of whom had incomplete data. The pre-medications used in the study were not standardized and included agents not generally used in the pediatric age group for this purpose (e.g., barbiturates). The investigators studied the patients for 3 min after drug administration, a time point that alone is not appropriate for the pharmacokinetics of this drug. In almost half of the subjects, the measurements either did not change or decrease in one or both eyes. A lesser proportion of IOP elevation was noted in pediatric cases, and these subjects yielded a pooled mean increase of less than 3 mmHg from control readings. A landmark study by Drayna et al. [13] proved that at dosages ≤ 4 mg/kg, there are no clinically meaningful associations of ketamine with IOP. Recently, a systematic review comprising nine studies including 293 patients also suggested that the administration of ketamine to pediatric patients during ocular tonometry has little or no effect on IOP. Two out of the nine studies mentioned a slight rise in IOP if ketamine doses were more than 4 mg/kg [14]. Further studies are warranted to determine whether ketamine can be used safely for procedural sedation when elevated IOP or globe injury is a concern.

Consensus: Available literature suggest that ketamine influences the IOP in a dose-dependent manner. Generally, doses less than 4 mg/kg do not lead to an increase in IOP and at times decreases it, but most analyses have a low level of evidence and further large trials are needed to validate it the dose dependent influence of ketamine on IOP.

Ketamine in acute pain services

The analgesic characteristics of ketamine are primarily established via NMDA receptors located in the central nervous system [15] and to some extent through opioid receptors [16]. The American Society of Regional Anesthesia and the American Society of Anesthesiologists have published an entire consensus on the role of ketamine in acute pain management. They have supported the use of ketamine for acute pain in a variety of contexts, including as a stand-alone treatment, as an adjunct to opioids and especially in opioid-tolerant patients. They have recommended that ketamine bolus doses should not exceed 0.35 mg/kg and infusions for acute pain should not exceed 1 mg/kg/h in settings where there is no intensive monitoring [17]. Ketamine's adverse effects will prevent some patients from tolerating higher doses in acute pain settings, and unlike in chronic pain therapy, lower doses (i.e., 0.1–0.5 mg/kg/h) may be needed to achieve an adequate balance of analgesia and adverse effects (grade C recommendation, moderate level of certainty). Consensus guidelines also state that clinicians should exclude or limit ketamine use in patients with commonly considered contraindications. These include severe hepatic dysfunction (cirrhosis) [18] and high-risk coronary artery disease [19]. A recent meta-analysis also reported that patients receiving continuous sub-anesthetic ketamine experienced considerably less pain than those treated with traditional opioid regimens [20].

Another Cochrane systematic review of 37 randomized controlled trials (RCTs) also concluded that sub-anesthetic doses of ketamine are effective in reducing morphine requirements in the first 24 h after surgery, and it also reduces postoperative nausea and vomiting, which is the main problem with opioids, the most commonly used formulations for postoperative analgesia [21]. It has been studied not only for intravenous use in perioperative analgesia but also by various other routes. Feltracco et al. [22] showed that epidural infusion of sub-anesthetic doses of S(+)-ketamine during thoracic surgery provides better postoperative analgesia than epidural ropivacaine. Preemptive intranasal ketamine (1.5 mg/kg) enhances postoperative analgesia after endoscopic nasal surgery [23]. Ketamine spray (0.5 mg/kg) in the tonsillar fossa is effective for post-tonsillectomy pain control in children [24]. A recent RCT evaluating low-dose S(+)-ketamine in target-controlled intravenous anesthesia with remifentanil and propofol for open gynecological surgery concluded that there was no effect on the 24-h cumulative morphine consumption with S(+)-ketamine; however, there was a delayed emergence from general anesthesia reported with S(+)-ketamine [25].

Consensus: The application of ketamine at sub-anesthetic doses in the perioperative setting has been associated with reduced pain scores, opioid requirements, and postoperative nausea and vomiting, without any considerable side effects. Moreover, good results have been established using ketamine for surgery patients with high levels of postoperative pain. The level of evidence is still poor to recommend it as a sole agent for perioperative infusions for analgesia, although a good level of evidence is present for its use as an adjuvant.

Ketamine use in chronic pain

Noncancer pain

The action of ketamine on opiate tolerance and hyperalgesia combined with its direct analgesic activity has prompted its increasing use in chronic pain states [8]. IV ketamine has also been evaluated in phantom limb pain, and a study reported that infusion of 300 μg/kg in 60 mL solution over 3 h led to complete remission [26]. Low-dose intranasal S(+)-ketamine is beneficial for the ad hoc treatment of breakthrough pain in patients with neuropathic pain [27]. Oral ketamine has a poor safety profile and its efficacy in chronic pain management discourages its use, but its use may be limited as an add-on therapy in patients with complex chronic pain when other therapeutic options have failed [28]. However, the long-term effectiveness of ketamine in treating chronic pain remains controversial, as studies often demonstrate contradicting results. A recent meta-analysis comprising six clinical trials in which ketamine was compared with a placebo during chronic non-cancer pain found moderate evidence suggesting the efficacy of ketamine during chronic pain. However, it was found that ketamine increased the incidence of psychedelic manifestations in comparison to placebo. Further studies are warranted in this regard so as to determine optimal administration regimes of this agent during this condition [29]. Studies conducted by Connolly et al. [30] (meta-analysis of six studies in 2015), Maher et al. [31] (review of 11 RCTs in 2017), and Michelet et al. [32] (review of six RCTs in 2018) suggest that there is no high-quality evidence available evaluating the efficacy of ketamine for complex regional pain syndrome and all manuscripts examined in this review were of moderate-to-low quality.

Cancer pain

Ketamine is now considered to be an essential adjuvant analgesic for refractory cancer pain, and it is on the World Health Organization list of essential drugs for patients who no longer respond to high doses of opioids or have predictable breakthrough pains [33]. Nowadays, ketamine is regarded as an essential adjuvant drug in palliative care in many countries. It can be administered in various regimens through oral, intravenous, intrathecal, subcutaneous, and topical routes of administration [34]. A recently published Cochrane systematic review studying ketamine as an adjuvant to refractory cancer pain concluded that the current evidence is insufficient to assess the benefits and adverse effects of ketamine as an adjuvant to opioids. Furthermore, dose escalation to as high as 500 mg did not lead to any added clinical advantage and rather may have serious adverse events [35]. However, a 2012 Cochrane review on the use of ketamine in cancer pain found two RCTs that suggest the use of ketamine as an adjunct to morphine because it improves the effectiveness of morphine in cancer pain. This review included 32 case reports, of which 28 reported excellent pain relief with ketamine. The adverse effects commonly reported were sedation and hallucinations, although they were not severe [35]. One dose-escalation, double-blind, randomized, placebo-controlled phase III trial including 185 participants, in which ketamine or the placebo was delivered subcutaneously over 3 to 5 days, concluded that ketamine does not have a net clinical benefit when used as an adjunct to opioids and standard co-analgesics in cancer pain [36]. A literature search found four RCTs that examined the benefit of oral, subcutaneous, or intravenous ketamine in opioid refractory cancer pain, and none showed clinically relevant benefits in relieving pain or reducing opioid consumption [37].

Consensus: We found a moderate level of evidence suggesting the use of ketamine in chronic non-cancer pain, whereas most

https://doi.org/10.4097/kja.20663

RCTs present a low level of evidence for its use in cancer pain. However, a large number of open label studies and retrospective case series advocate its use [34–37].

Ketamine as an antidepressant and role in cognition and schizophrenia

Ketamine has been proven to be an extremely effective treatment for major depression, bipolar disorder, and suicidal behavior. Resistance to regular antidepressants is a growing concern in patients with manic depressive disorder. The slow onset and moderate degrees of receptor occupancy by ketamine could largely be used to avoid the anesthesia effect, dissociation, and psychotomimetic reactions [38]. Ketamine works incredibly fast, relieving depression in less than 2 h, which is unlike conventional anti-depressants that generally take weeks to work [39,40]. A systematic review also showed ketamine to be a rapid and effective treatment option for depression, reducing suicidal ideation, with minimal short-term side effects [41]. In 2018, Chen et al. [42] found that 0.5 mg/kg dose of ketamine infusion was beneficial for the cognitive function of patients with resistant depression.

Ketamine is a racemic mixture with equal parts of R(-)-ketamine and S(+)-ketamine. Of the two, S(+)-ketamine was developed as an antidepressant agent owing to its higher affinity for NMDA receptors. On March 5, 2019, S(+)-ketamine nasal spray was approved by the US FDA for the same purpose [43].

Although the efficacy of ketamine has also been shown in depressed patients with a history of psychotic symptoms, its administration in patients with psychotic disorders has largely been neglected due to its potential to exacerbate dissociative or psychotic symptoms [44].

A study by Duman and Li [45] showed that a single injection of ketamine increased prefrontal synaptogenesis and reversed stress-induced atrophy. This is consistent with findings that mice carrying a mutant form of glycogen synthase kinase 3, an enzyme involved in synaptic plasticity, are unresponsive to ketamine [46].

Research on ketamine is still preliminary, and many facets remain obscured. For instance, there is no consensus regarding its effects on controlled long-term use. Most studies have been conducted on drug abusers in a correlational manner, and thus generalization to "physically healthy" human population is difficult. As most studies enrolled many disproportionately young patients, it is questionable whether results can be translated to more vulnerable depressed populations (e.g., elderly patients and patients with cardio-vascular impairments) [47].

Other uses of ketamine with moderate level of evidence

In pediatrics

(1) Premedication: Ketamine can be administered orally (5–8 mg/kg), intramuscular (4–6 mg/kg), or IV (1–2 mg/kg) routes. The advantages include its analgesic properties and the ability to cause sedation without respiratory depression [48]. Because of its rapid onset of action, ketamine has been used as an IM induction drug in children and patients with intellectual disabilities [49]. Intranasal ketamine is widely studied for procedural sedation. A recent publication reviewed 11 studies and suggested that intranasal ketamine at doses up to 10 mg/kg appears to be safe in children with adequate analgesia at doses as low as 0.5 mg/kg. They also concluded that the most common adverse effect of intranasal ketamine was vomiting, reported in ten studies at doses of at least 1 mg/kg. Although studies on children suggested that adequate sedation can be achieved safely with an intranasal route, evidence is limited and the overall quality of evidence is low, necessitating the need for larger high-quality trials [50]. It is used for sedation or general anesthesia for pediatric procedures such as cardiac catheterization, radiation therapy, radiological studies such as magnetic resonance imaging, dressing changes, and dental work [51]. Combination of low doses of ketamine and propofol provides effective and safe sedation-analgesia in pediatric emergency short surgical procedures and in adults undergoing colonoscopy and short gynecological procedures [52–54].

(2) Caudal epidural block: A quantitative systematic review of RCTs on adding ketamine to pediatric caudal anesthesia concluded that ketamine prolonged analgesia with few side effects compared with local anesthetic alone [55]. Another meta-analysis stated that caudal ketamine in pediatric patients was associated with decreased post-operative pain and non-opioid analgesic requirements [56]. In 2018, Aliena et al. [57] compared the postoperative analgesic effect of caudal bupivacaine with and without ketamine in pediatric sub-umbilical surgeries and found that caudal administration of ketamine 0.5 mg/kg along with 0.75 ml/kg 0.25% bupivacaine significantly prolonged the duration of postoperative analgesia in children more than plain bupivacaine, without any significant adverse reactions.

Ketamine as an adjuvant and its role in overcoming the pitfalls of dexmedetomidine

Adjuvants used with ketamine to averse its undesirable effects are known, but very recently, there is an increasing amount of evidence suggesting its utility as an adjuvant to averse the effects of sedatives such as dexmedetomidine. In 2012, Tobias [58] in his

review highlighted that dexmedetomidine is generally effective for sedation during noninvasive procedures but there is enough literature available challenging its efficacy as a sole agent for painful procedures. Its disadvantages include its long onset time, limited analgesic effect, and undesirable hemodynamic perturbations such as bradycardia and hypotension. Tobias categorically mentioned many robust trials where adding low-dose ketamine to dexmedetomidine led to satisfactory outcomes in invasive procedures in both adults and children. He suggested that when used together, ketamine prevents bradycardia and hypotension, which has been reported with dexmedetomidine alone, and also hastens the onset. Char et al. [59] clearly stated that dexmedetomidine alone is inadequate to provide adequate sedation for either pediatric intensive care management or procedural sedation. It also has an adverse effect on the conduction system, leading to hemodynamic instability. They observed a decrease in heart rate after dexmedetomidine administration, which returned to baseline after co-administration of ketamine (mean difference between baseline and after ketamine 6.5 bpm; 95% CI, 11.2 to 1.8; P = 0.005). In 2020, a double-blind randomized RCT concluded that adding ketamine to dexmedetomidine led to good postoperative analgesia, decreased postoperative opioid requirements, and led to smooth recovery after functional endoscopic sinus surgery [60]. Sinha et al. [61] compared combination of dexmedetomidine and ketamine with dexmedetomidine alone for awake fiberoptic nasotracheal intubation and concluded that the addition of low-dose ketamine (15 mg as a bolus of 5 ml, followed by continuous infusion at 20 mg/h) further enhanced hemodynamic stability and provided better sedation than dexmedetomidine alone. Kim et al. [62] and Chun et al. [63] in their respective studies have found that a combination of ketamine and dexmedetomidine led to shorter procedural time, improved sedation quality, and quicker onset of sedation with fewer incidences of desaturation. Qiao et al. [64] reported a lower rate of successful venous cannulation in children with dexmedetomidine alone (47%), whereas it was 80% when ketamine was added (P = 0.006) [64].

In critical care medicine

Ketamine used in patients in a critical care unit provides combined sedation and analgesia, has favorable effects on hemodynamics, and can treat persistent bronchospasm. A recently published multi-centric retrospective study evaluated the use of ketamine infusions in 390 adult intensive care unit (ICU) patients and suggested that there is no consensus regarding the indication, dose, or dose units associated with ketamine. Hemodynamic changes are common and start occurring as early as 4 h after the infusion; however, other adverse effects appear to be minimal [65]. In 2015, Umunna et al. [66] also suggested that ketamine is a good sedative agent along with its low incidence of adverse effects; thus, it may be a reasonable alternative for patients requiring mechanical ventilation. In septic patients with cardiovascular instability, ketamine reduces inotropic support and exerts a protective anti-inflammatory effect against the sepsis process because of its cardiovascular stimulatory effects [67].

Overall, very little research is available on its use in critical care settings and its efficacy in the emergency department and anesthesia practice has been extrapolated to its applicability in ICUs.

Other uses of ketamine with low level of evidence

Alcohol withdrawal

Ketamine offers a plausible pharmacologic mechanism for use in the setting of severe alcohol withdrawal as both ketamine and alcohol antagonize the NMDA receptor. The authors of a retrospective study assessed the effect of ketamine infusion added to the usual therapy with benzodiazepines titrated to symptoms on requirements for benzodiazepines in patients admitted with delirium tremens and found that the rate of endotracheal intubation and mean duration of ICU stay were drastically reduced [68]. However, another retrospective analysis noted that benzodiazepine doses drastically decreased after initiation of a ketamine infusion. In addition, better symptom control was achieved with a new regimen, which had no adverse neurological outcomes or hemodynamic perturbations [69].

Unfortunately, very limited literature is available for ketamine use in alcohol withdrawal, and all studies were retrospective, open-label studies involving the simultaneous use of numerous different agents. None of these studies proved anything about the use of ketamine infusions for alcohol withdrawal

Status epilepticus

Super-refractory status epilepticus (SRSE) is defined as status epilepticus (SE) continuing after 24 h of anesthetic infusion or recurring after discontinuation of the anesthetic infusion. Typically, SE is treated with a combination of benzodiazepines and specific antiepileptics, quickly escalating to anesthetic infusions (most commonly propofol). Prolonged SE and SRSE are associated with a downregulation of GABA-A receptors and an upregulation of NMDA receptors, placing ketamine as a therapeutic adjunct, especially due to concerns about the adverse effects of prolonged propofol infusions, such as hyperlipidemia and propofol infusion syndrome. There are no randomized trials comparing ketamine to other agents in SRSE. Sabharwal et al. [70] studied patients, most of whom were on both propofol and ketamine infusions, in

https://doi.org/10.4097/kja.20663

a neurocritical care setting. They concluded that 1.5–10.5 mg/kg/h is the recommended dose of ketamine infusions and should be combined with a 1.5–8 mg/kg/h dose of propofol infusion. A case audit involving several countries revealed that ketamine was considered only for the most severe cases of SE very late in the course of the disease [71]. More recent experiences with ketamine and the possibility for a neuroprotective effect support the early administration (duration of SE < 3 days) rather than the late rescue [72,73]. An Italian group reported their experience with children on a protocol that used IV ketamine for refractory SE upfront added to other antiepileptics. They found that in instances in which ketamine was used as the sole anesthetic agent for refractory SE, there was the added benefit of avoiding endotracheal intubation [74]. This experience has not been replicated in adults but is intriguing. In 2015, Shrestha et al. [75] also concluded that ketamine can be a safe, effective, readily available, and economic therapeutic agent for the management of SRSE in patients with hemodynamic instability.

Unfortunately, no RCT is available to test its safety and efficacy in patients with SE. Most of the available studies are either case reports or series with a low level of evidence.

Some other clinical uses of ketamine available in literature

Most of these clinical applications have just been mentioned in case reports with no randomized trials. Large multi-centric studies are needed to recommend its routine use.

Cardiopulmonary bypass (CPB) surgery

Several opportunities remain for ketamine to be studied in cardiac surgery patients. The current literature supports the idea that ketamine attenuates the inflammatory response to cardiac surgery with CPB. Whether this consistently leads to improved clinical outcomes remains unclear. It also has a potential use in the post-cardiac surgery ICU because of its excellent hemodynamic profile, minimal respiratory depression, and potent analgesic properties. However, at this time, there is a paucity of studies to support its use in this setting. Mogahd et al. [76] compared the safety and efficacy of ketamine-dexmedetomidine (KD) with that of ketamine-propofol (KP) combinations for sedation in patients after coronary artery bypass graft surgery and concluded that KD provided a short duration of mechanical ventilation with less fentanyl dose requirement in comparison with KP, whereas hemodynamic stability and length of the ICU stay were the same for both regimens. Future studies comparing ketamine to other commonly accepted sedative regimens, such as propofol and dexmedetomidine, are critically needed [77]. Some authors have reported that a single dose of ketamine 0.5 mg/kg administered upon induction was associated with lower serum levels of C-reactive protein and lower incidence of delirium and cognitive dysfunction after cardiac surgery with CPB. This is because of the neuroprotective and anti-inflammatory effects of ketamine [78].

Electroconvulsive therapy

Given the need for anesthesia during electroconvulsive therapy (ECT) and the excitement about ketamine's acute effects in reducing depressive symptoms, combining the two therapies seems to be a logical next step. A study showed that S(+)-ketamine administered for ECT decreased the number of ECT sessions, produced lower depression severity scores, and higher cognitive ratings [79]. A study showed that the ketamine-propofol combination (ketofol) can be an alternative strategy to enhance the seizure quality and clinical efficiency of ECT [80,81]. Shams and El-Masry [82] compared KD with KP in the ECT procedure and concluded that KD had an effective anti-depression effect and resulted in less agitation and more patient satisfaction than KP.

However, the research on ketamine use in ECT has been disappointing [83]. The clinical enthusiasm is tempered by concerns that ketamine's antidepressant activity is short-lived and by the uncertainty regarding the long-term safety in repeated administrations, with unknown risks for long-term cognitive side effects, psychotic symptoms, and substance abuse [84].

Sore throat

Ketamine gargles have been shown to reduce the incidence of postoperative sore throat and hoarseness of voice after endotracheal intubation under general anesthesia [85–88].

Ketamine and emergence reactions

Most anesthesiologists are apprehensive of hallucinations, delirium, and nightmares that patients experience while awakening, and these clusters of symptoms are categorized as the "reemergence phenomenon." Several receptors as well as neurochemical mechanisms have been hypothesized to be implicated in the occurrence of the emergence phenomena (EP) such as NMDA, opiates, dopamine, and acetylcholine. Hence, a wide variety of drugs belonging to different classes are being tested to prevent or treat symptoms of the EP with some success.

The 37th expert committee on drug dependence released a review report, which also states that these symptoms were reduced by the concurrent use of benzodiazepines, putting the patient in a low-stimulus environment and providing information on the possible emergence reactions preoperatively.

A RCT was conducted in 2011 on 200 patients who received ketamine for procedural sedation. The authors concluded that 23% of patients experienced a reemergence phenomenon with ketamine, whereas only 8% of patients exhibited such symptoms when 0.03 mg/kg of midazolam was administered [89]. Another cross-sectional observational study conducted by Lohit et al. [90] also concluded that the perioperative administration of midazolam with ketamine was effective in controlling EP, leading to a smooth postsurgical recovery. Another recent RCT published in 2019 also concluded that premedication with either midazolam 0.05 mg/kg or haloperidol 5 mg intravenously significantly reduces ketamine-induced recovery agitation while delaying recovery [91].

Ketamine uropathy

Ketamine uropathy describes the effects of ketamine on the urinary system. It is a misnomer to use ketamine cystitis or ketamine bladder syndrome as while the bladder is often most severely affected, the whole urinary tract may be damaged. A 2019 study from Taiwan found that 84% of the 106 ketamine users had shown lower urinary tract symptoms (LUTS), and in most of these cases, LUTS appeared at a mean of 24 months after its daily use [92]. The largest study assessed symptoms in 1,056 male users and noted a prevalence of 76%. Again, they found a significant correlation between higher age (> 30 years), longer duration of use (> 24 months), and the co-use of other illicit drugs with symptom severity [93]. Chang et al. [94] in their study reported moderate-to-severe LUTS including frequency, urgency, dysuria, and hematuria when the mean daily consumption of ketamine was 3.2 ± 2.0 g and they also reported that the mean interval from consumption to the development of LUTS was 12.7 months (range, 2–36 months).

The authors could not find any large RCT on ketamine uropathy, but all available literature clearly stated that the long-term continuous use of ketamine (most commonly as recreational agent) leads to LUTS, which are mostly dose- and duration-dependent. However, most of these symptoms are reversible after the discontinuation of ketamine.

Conclusion

Ketamine's role in the operating room as an anesthetic, sedative, amnestic, and analgesic agent has been well established since its discovery. A moderate level of evidence is available to prove its role in TBI patients, acute pain services, chronic non-cancer pain, and as an antidepressant. A low level of evidence is available for its role in patients with raised IOP (dose < 4 mg/kg), cancer pain management, and critical care settings. Most of its adverse reactions are minor, and the incidence of emergence reaction has been reported in most of the available literature but can be easily managed with the concurrent use of benzodiazepines.

Currently, there are several ongoing trials despite the increasing addiction burden in the Western society. However, various policies, legislations, and support groups are coming up to fight against the addiction problems with ketamine, popularly known as the "super K." In the era of evidence-based medicine, the so-called "super K" can be a boon to medical science if we leave our age-old fears of conquering the heights. This drug is both good and bad. Now, the challenge is to find the pious and fight the evil.

Conflicts of Interest

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

Author Contributions

Abhijit Kumar (Conceptualization; Data curation; Formal analysis; Software; Visualization; Writing – original draft)
Amit Kohli (Conceptualization; Data curation; Formal analysis; Software; Visualization; Writing – original draft; Writing – review & editing)

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https://doi.org/10.4097/kja.20663

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https://doi.org/10.4097/kja.20663

KJA
Korean Journal of Anesthesiology

The principles of presenting statistical results: Table

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Statistical Round

Korean J Anesthesiol 2021;74(2):115-119
https://doi.org/10.4097/kja.20582
pISSN 2005-6419 • eISSN 2005-7563

Received: October 25, 2020
Revised: December 20, 2020 (1st); January 6, 2021 (2nd); February 9, 2021 (3rd)
Accepted: February 9, 2021

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General medical journals such as the *Korean Journal of Anesthesiology* (*KJA*) receive numerous manuscripts every year. However, reviewers have noticed that the tables presented in various manuscripts have great diversity in their appearance, resulting in difficulties in the review and publication process. It might be due to the lack of clear written instructions regarding reporting of statistical results for authors. Therefore, the present article aims to briefly outline reporting methods for several table types, which are commonly used to present statistical results. We hope this article will serve as a guideline for reviewers as well as for authors, who wish to submit a manuscript to the KJA.

Keywords: Comparative study; Guideline; Publication formats; Research report; Statistics; Tables.

Introduction

It has been encouraging to see the growing number of outstanding article submissions and publications in the *Korean Journal of Anesthesiology* (*KJA*) over the years. Unfortunately, however, the diversity of result presentation format, alongside the number of manuscripts, has resulted in confusion not only in the review and publication process but also in delivering appropriate information to the readers. Presenting results derived using similar statistical methods in a prescribed tabular format recommended by the journal will not only simplify the review and publication process but also help with readers' understanding of the published content.

General methods of presenting easy-to-read results can be found in the previous article [1]. In this article, we present specific examples of the appropriate application of the Instruction for Authors of KJA[1)] to the tabular results for various analysis methods commonly used in research.

Common statistical tests and tables

Various types of tables are used to clearly present various forms of research results. Even if presented independently, tables must contain the essential elements needed to

convey the necessary information. For instance, the title must contain sufficient description of the content, while the body and footnotes of the table must describe in detail the statistical method and results of the analysis.

The following are the examples of typical tabular results commonly submitted to this journal. The data used in the examples were generated randomly, unless otherwise indicated, and do not reflect results of a specific study, i.e., the presented results have no clinical significance.

Common guidelines

Statistic provided in all the tables follow the guidelines on the representation of significant figures and statistics in the Instructions for authors provided by the KJA. There must be no blank spaces in the table and estimate, sample size (n), and the statistical method used must be appropriately included when presenting results using statistical analysis. Quantitative data can be expressed as a representative value and its distribution, such as 'mean ± standard deviation' or 'median (first quartile, third quartile). Qualitative data can be expressed as 'frequency (percent, %)', et al. For statistical analyses involving variable transformation that changes the shape of the distribution (i.e., log transformation), statistic reflective of the original value should be used. An inverse statistic may also be expressed if needed. Description of the transformation method and transformed values must accompany variable transformation. For more information on data transformation, refer to Lee's article [2].

Based on the statistic derived from the sample data of the study, the population parameters are estimated. It is recommended to display a confidence interval (i.e., 95% CI) that is an interval estimator along with point estimators such as mean, median, proportion, coefficient, et al. The previously derived estimates are described together with the hypothesis test results. P value must be described in three decimal places, and a test statistic should be presented in detail so that statistical inference can be made. Presenting the effect size, if possible, can aid the interpretation of statistical results.

An explanation of the abbreviations must be included in the footnote even if an explanation is provided in the text so that the table can be interpreted independently. The unit of measure of each variable must be accurately described, and the number of samples should be presented in the title or alongside the variable.

One sample comparison

In one sample comparisons, the data of the experimental sample are compared to a specific reference value. The example in Table 1 is a comparison between the arterial pressures of the experimental sample with the reference value of 60 mmHg. Based on the distribution of experimental data, a parametric or non-parametric method of statistical analysis was applied, along with the difference between the reference value and that of the experimental sample and its 95% CI.

In the case of categorical data, proportions, etc. can be compared. One sample proportion test can be performed to compare the response rate with the reference value, and when the response rate is close to 0% or 100%, an exact binomial test is sometimes performed. The comparison results are described in Table 2 along with the 95% CI of the response rate.

Comparison of two independent samples

Table 3 presents the results of comparing the mean arterial pressure and heart rate after endotracheal intubation when two types of endotracheal intubation devices were used. A parametric or non-parametric method of statistical analysis is applied depending on the distribution of the experimental data. The statistical method used is described in the table along with a representative value suitable for the distribution. To facilitate the interpretation of the results, the difference between the two groups is presented and the corresponding P value is presented to three decimal places.

Table 1. Example of One Sample Comparison with Reference Value

Variables	Results	Reference value	Difference (95% CI)	P value
MBP (mmHg, n = 30)*	70.0 ± 5.0	60	10.0 (8.0, 12.0)	< 0.001†
MBP (mmHg, n = 28)‡	70 (64.0, 75.0)	60	10.0 (8.0, 12.0)	< 0.001†

Values are presented as mean ± SD or median (Q1, Q3). MBP: mean blood pressure. *One-sample t-test, †Two-sided P value < 0.05, ‡Wilcoxon's signed rank test. These values, including P values, are presented according to the Instructions for Authors of Korean Journal of Anesthesiology for notation below the decimal point.

[1] https://ekja.org/authors/authors.php

https://doi.org/10.4097/kja.20582

Table 2. Example of One Sample Test of Proportions

Variables	Positive response	Reference probability	Response rate (95% CI)	P value
PONV (n = 25)*	9	0.20	0.36 (0.18, 0.57)	0.080
Itching sense (n = 64)†	5	0.02	0.08 (0.03, 0.17)	0.009‡

PONV: postoperative nausea and vomiting, *One sample proportion test with continuity correction, †Exact binomial test, ‡Two-sided P value < 0.05. These values, including P values, are presented according to the Instructions for Authors of Korean Journal of Anesthesiology for notation below the decimal point.

Table 3. Example of Independent Two Sample Comparison

Variables	Group S (n = 49)	Group P (n = 53)	Difference (95% CI)	P value
MBP (mmHg)*	72.3 ± 14.3	73.1 ± 14.9	−0.8 (−6.5, 4.9)	0.781
Heart rate†	89.0 (75.0, 103.0)	82.0 (72.0, 93.0)	7.0 (0, 14.0)	0.062

Values are presented as mean ± SD or median (Q1, Q3). MBP: mean blood pressure. *Independent two sample t-test, †Mann-Whitney U test. These values, including P values, are presented according to the Instructions for Authors of Korean Journal of Anesthesiology for notation below the decimal point.

Table 4. Example of Dependent Two Samples Comparison

Underlying factors	MBP		Mean difference (95% CI)	P value
	Pre-treatment	Post-treatment		
Hypertension (n = 20)*	74.0 ± 13.9	70.9 ± 13.6	3.1 (0.4, 5.8)	0.026†
BMI > 30 kg/m^2 (n = 25)‡	75.4 (66.8, 81.5)	73.9 (65.0, 84.5)	1.5 (-1.0, 4.0)	0.228

Values are presented as mean ± SD or median (Q1, Q3). BMI: body mass index, MBP: mean blood pressure. *Paired t-test, †Two-sided P value < 0.05, ‡Wilcoxon's signed rank test. These values, including P values, are presented according to the Instructions for Authors of Korean Journal of Anesthesiology for notation below the decimal point.

Table 5. Example of Three Independent Samples Comparison

Variables	Control group (n = 30)	ITM group (n = 30)	QLB group (n = 30)	P value
Morphine requirement (mg)*	61.0 ± 12.9	42.8 ± 10.4	18.2 ± 9.6	< 0.001†
Time to first morphine dose (h)‡	2 (0.5, 4)	8 (3, 24)	17 (6, 36)	0.002†

Values are presented as mean ± SD or median (Q1, Q3). ITM: intrathecal morphine, QLB: quadratus lumborum block. P values indicate the statistical inference result of overall comparisons. *One-way analysis of variance with Tukey's method, †Two-sided P value < 0.05, ‡Kruskal-Wallis H test with Dunn's procedure. These values, including P values, are presented according to the Instructions for Authors of Korean Journal of Anesthesiology for notation below the decimal point. Excerpt from Salama ER [3] results showing representative values and P value as examples of comparison of three independent samples.

Comparison of matched pairs

Table 4 presents data from a study measuring mean blood pressure before and after the administration of a drug. The table presents results of administering the drug in a sample of hypertensive patients and a sample of patients with a body mass index over 30 kg/m^2. The number of patients in each sample has been presented and the mean or median blood pressure was used as the representative value according to the distribution of measurements. A paired t-test was used to perform a paired comparison using the difference in pre- and post-treatment values for each patient. The statistically estimated differences are presented alongside the its 95% CI. The statistical method and P value is also clearly presented.

Comparison of three or more independent samples

Results from a study on pain control following a Cesarean section are presented in Table 5 [3]. The administered dose of morphine and time taken until the first dose was compared between a control group that received normal saline, a group that received intrathecal morphine and a group that received a quadratus lumborum block. Morphine requirement with a normal distribution was expressed as 'mean ± standard deviation', while the time taken until the first dose was expressed as a 'median (Q1, Q3)' value as it did not satisfy the normal distribution assumption. An accurate P value, up to 3 decimal places, and the number of samples in each group are presented, while a detailed description of the statistical method including the multiple comparison method for

Table 6. Example of Categorical Data Comparison

Variables	Group N (n = 49)	Group C (n = 53)	P value
Successful tracheal intubation*	44 (89.8)	32 (60.4)	0.001†
Sore throat at 1 h‡	11 (22.4)	20 (37.8)	0.144
Vocal cord paralysis‡	1 (2.0)	2 (3.8)	> 0.999

Values are presented as frequency (%). *Chi-squared test, †Two-sided P value < 0.05, ‡Fisher's exact test. These values, including P values, are presented according to the Instructions for Authors of Korean Journal of Anesthesiology for notation below the decimal point.

post hoc analysis is provided.

Categorical data comparison

Table 6 presents results of an investigation analyzing the occurrence of successful endotracheal intubation, sore throat 1 hour following tracheal extubation, and post-surgical vocal cord paralysis in two groups treated with an existing versus newly developed endotracheal tube. Results were reported as the frequency of occurrence and relative frequency and the statistical method and P value are clearly presented.

Logistic regression analysis

The dependent variable is a nominal scale. This analysis method is widely used when selecting a meaningful variable among various explanatory variables and results are presented in terms of odds ratio, etc. Parts of results of a study published in the KJA is presented in Table 7 [4]. The study analyzed the risk factors of post-anesthesia emergence agitation in the recovery room. Variables with three or more components were converted into insignificant dummy variables to estimate the odds ratio. The table presents the odds ratio of referenced components and those converted into dummy variables alongside the 95% CI. A detailed description of the statistical methods used to select variables in the logistic regression analysis is also included.

Conclusion

This article examined the principles of presenting the statistical results in clinical studies as a table. We hope to see manuscript submissions with standardized tables reflective of the provided framework. Such standardized format will help facilitate the submission and review process for both authors and reviewers.

Table 7. Risk Factors of Emergence Agitation in the PACU (n = 158) [4]

Variables	Odds ratio (95% CI)	P value*
Marital status		
Divorced	Reference	
Single	0.16 (0.04, 0.64)	0.009†
Married	0.16 (0.04, 0.62)	0.008†
Pre-existing ND	6.78 (1.36, 33.80)	0.020†
Gynecological surgery	0.29 (0.12, 0.71)	0.007†
Thoracic surgery	0.23 (0.07, 0.80)	0.021†
IO bleeding	1.00 (1.00, 1.00)	0.047†
IO morphine administration	1.15 (1.03, 1.28)	0.015†
Analgesic drugs in PACU	2.99 (1.56, 5.73)	0.001†

The odds ratio of Marital status is estimated with non-weighted dummified variables. IO: intraoperative, ND: neurologic disorders, PACU: post-anesthesia care unit, *Backward binary stepwise logistic regression, †Two-sided P value < 0.05. These values, including P values, are presented according to the Instructions for Authors of Korean Journal of Anesthesiology for notation below the decimal point.

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Conflicts of Interest

All authors are Statistical Round Board Members in KJA.

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https://doi.org/10.4097/kja.20582

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KJA
Korean Journal of Anesthesiology

Clinical Research Article

Korean J Anesthesiol 2021;74(2):120-133
https://doi.org/10.4097/kja.20202
pISSN 2005-6419 • eISSN 2005-7563

Received: April 28, 2020
Revised: July 7, 2020 (1st); August 12, 2020 (2nd)
Accepted: August 14, 2020

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Previous presentation in conferences:
This work has been presented in part at International Symposium on Intensive Care and Emergency Care (ISICEM), March 2018, Brussels Meeting Center, Brussels, Belgium.

Four different methods of measuring cardiac index during cytoreductive surgery and hyperthermic intraperitoneal chemotherapy

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Background: Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) are high-risk extensive abdominal surgery. During high-risk surgery, less invasive methods for cardiac index (CI) measurement have been widely used in operating theater. We investigated the accuracy of CI derived from different methods (FroTrac, ProAQT, ClearSight, and arterial pressure waveform analysis [APWA], from PICCO) and compared them to transpulmonary thermodilution (TPTD) during CRS and HIPEC in the operative room and intensive care unit (ICU).

Methods: Twenty-five patients scheduled for CRS-HIPEC were enrolled. During nine predefined time-points, simultaneous hemodynamic measurements were performed in the operating room and ICU. Absolute and relative changes of CI were analyzed using a Bland-Altman plot, four-quadrant plot, and interchangeability.

Results: The mean bias was −0.1 L/min/m^2 for ClearSight, ProAQT, and APWA and was −0.2 L/min/m^2 for FloTrac compared with TPTD. All devices had large limits of agreement (LoA). The percentage of errors and interchangeabilities for ClearSight, FloTrac, ProAQT, and APWA were 50%, 50%, 54%, 36% and 36%, 47%, 40%, 72%, respectively. Trending capabilities expressed as concordance using clinically significant CI changes were −7° ± 39°, −19° ± 38°, −13° ± 41°, and −15° ± 39°. Interchangeability in trending showed low percentages of interchangeable and gray zone data pairs for all devices.

Conclusions: During CRS-HIPEC, ClearSight, FloTrac and ProAQT systems were not able to reliably measure CI compared to TPTD. Reproducibility of changes over time using concordance, angular bias, radial LoA, and interchangeability in trending of all devices was unsatisfactory.

Keywords: Cardiac output; Comparative study; Hyperthermic intraperitoneal chemotherapy; Laparotomy; Pulse wave analysis; Thermodilution.

Introduction

Hemodynamic monitoring is an essential part of patient care in the operating room (OR) and in the intensive care unit (ICU). Many hemodynamic measuring devices are available, with each having their own limitations [1–3]. In recent years, the use of invasive hemodynamic measuring devices has declined, as they have been linked to complications and the benefit for the patients is unclear [4]. Instead, there has been an increased focus on development of less invasive hemodynamic monitoring devices. In the perioperative period [5,6] hemodynamic measurements are used to minimize perioperative-related

complications [7,8]. The use of these devices in critically ill patients is still a subject of debate [5,9]. Most new non-invasive devices are validated under stable ICU conditions. However, clinical conditions vary considerably in most studies, with both reference technique and clinical setting influencing the results [10].

In patients undergoing high risk surgery, goal directed therapy (GDT) using specific hemodynamic goals improves patient outcomes [11,12]. Cardiac index (CI) is often an element within the treatment algorithm and can be measured using many devices [3,8,12]. Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) are high risk extensive abdominal surgery having a curative intent. After extensive resections which can even be multi-organ resections in some cases, intravenous chemotherapy is followed by intraabdominal perfusion of chemotherapy at 42–43°C. This procedure is known to cause extensive fluid shifts [13] and inflammation [14] with periods of hemodynamic instability. Advanced hemodynamic monitoring is used to tailor hemodynamic therapy [13], but complications can occur [4]. We evaluated three different methods to measure CI with variable levels of invasiveness and compared them to transpulmonary thermodilution (TPTD), which is the standard measuring device during this extensive surgical procedure. Two devices, the FloTrac, Edwards Lifesciences, CA, USA, and ProAQT system, Pulsion Medical Systems, Germany; Maquet Getinge Group, Sweden, use waveform analysis. The ClearSight system, EV1000 Clinical Monitor Platform, Edwards Lifesciences, CA, USA, uses volume clamp method. All were tested during different stages of this operation. CI obtained using arterial pressure waveform analysis (APWA) by the PiCCO™ system (Pulsion Medical Systems, Germany; Maquet Getinge Group, Sweden) was also compared to TPTD to analyze drift. The accuracy of CI measurements and the reproducibility of CI changes over time using these devices were compared to TPTD measurements. The goal of the study was to investigate if one of the less invasive devices could replace TPTD measurements in the OR or in the ICU, thereby increasing patient safety in the future.

Materials and Methods

Study design

This prospective and observational clinical cohort study was approved by the Medical Ethics Review Board of Arnhem-Nijmegen, the Netherlands, under the Number 2015-1793 (Dr. M. J. J. Prick, 21-05-2015). This study was registered at www.trialregister.nl, under a national trial registry number of NTR5249. The study was conducted between November 2015 and June 2017 at the Radboud University Medical Center, Nijmegen, The Netherlands according to the Declaration of Helsinki 2013 and following the ICH guidelines for Good Clinical Practice. After obtaining written informed consent, 25 patients older than 18 years who were scheduled for a CRS-HIPEC procedure were included. The study was performed in the OR and ICU of a university teaching hospital, Radboud University Medical Center, the Netherlands.

The exclusion criteria were patients with known valvular heart disease (severe tricuspid or aortic valve insufficiency), cardiac arrhythmias, or severe peripheral vascular disease as well as those who did not give informed consent. This study did not modify the standard perioperative or intensive care provided during and after the CRS-HIPEC procedure.

Anesthetic management

Standard patient monitoring, including continuous electrocardiogram, oxygen saturation and non-invasive blood pressure monitoring, were applied to all patients. All patients were given general anesthesia, supplemented with a thoracic epidural analgesia at T8–T10. Postoperative analgesic regimen consisted of patient controlled analgesia using ropivacaine with sufentanil 2 mg/1 μg/ml. Continues infusion varied according to analgesic effect between 8–10 ml/h. Patient bolus was set at 2 ml with 20 minutes lock out time. The epidural could be used in the peri-operative period, this was left to the discretion of the anesthesiologist. After orotracheal intubation mechanical ventilation with tidal volumes of 6–8 ml/kg was initiated. FiO_2 and positive end-expiratory pressure were adjusted to maintain a peripheral oxygen saturation above 94%. Respiratory rate was adjusted to maintain $PaCO_2$ between 35–40 mmHg. General anesthesia was maintained using isoflurane. Multimodal anesthesia/analgesia was administered using S-ketamine (10 mg loading dose followed by 10 mg/h), dexamethasone 8 mg intravenously, and magnesium chloride (30 mg/kg loading dose in 30 min followed by 500 mg/h) [15–17]. After induction of general anesthesia, ultrasound-guided insertion (Sonosite, X-porte, USA) of the PiCCO catheter in the right femoral artery (Pulsion, ref. PV2015L20-A) and a central venous catheter (Vygon multicath 3+, ref. 6209.251) in the right internal jugular vein were performed. One hour before the end of the CRS period, folic acid and systemic 5-fluorouracil were administered to all patients receiving oxiplatin as abdominal perfusion chemotherapy [9]. The data from the PiCCO system was used by the attending anesthesiologist to guide hemodynamic management. At the end of surgery, the patients remained intubated and were transferred to the ICU.

Body temperature was obtained from the thermistor in the

TPTD system.

Brief description of techniques

Transpulmonary thermodilution measurement by the PiCCO® system (Pulsion Medical Systems, Germany; Maquet Getinge Group, Sweden)

TPTD measurements using the PiCCO system is an invasive technique that uses intermittent bolus injection of cold saline through a central line above the diaphragm and a femoral arterial catheter with a thermistor tip to measure the thermodilution curve. Measurements were performed using the IntelliVue MX800 or IntelliVue MP70 monitor (Philips, The Netherlands, software version J.10.52). This method provides the following variables: CI, global end-diastolic volume, intra thoracic blood volume, extravascular lung water, global ejection fraction and pulmonary vascular permeability index [18]. Intermittent bolus measurements are averaged and with this mean CI, pulse contour analysis of the PiCCO system (APWA) is (re)calibrated. The method is comparable with pulmonary artery catheter-derived measurements, which makes it a good reference technique when assessing new hemodynamic measuring devices [19].

Non-invasive ClearSight™ system

The ClearSight™ system (EV1000 Clinical Monitor Platform, Edwards Lifesciences, software version 1.8, USA) is an auto-calibrated measurement device that measures finger arterial blood pressure waveform using the volume clamp method and is automatically calibrated using the Physical method. The finger pressure waveform is transformed into a reconstructed brachial blood pressure waveform. The exact algorithm is explained elsewhere [20]. In summary, after applying a (size-specific) cuff to the finger, the arterial blood pressure waveform is obtained by the pressure in the cuff. An infrared transmission plethysmograph is used to measure the finger artery's diameter, which is used to keep the blood volume in the finger artery at a constant level [21]. By using the proprietary CO-Trek algorithm for pulse contour analysis on these non-invasively obtained arterial blood pressure waveforms, continuous cardiac output measurements are estimated.

FloTrac/Vigileo™ system (Edwards Lifesciences, USA)

The FloTrac/Vigileo™ system is an auto-calibrated system that has updated its algorithm over the last few years [9]. The fourth-generation algorithm (Version 4.00) was developed to improve the performance of the system during rapid vascular tone changes. The system calculates Cardiac Output (CO) as follows: CO = PR × SD (blood pressure [bp]) × χ, where PR = pulse rate, SD [bp] = standard deviation of the arterial pressure, and χ = auto-calibration factor that is part of a proprietary algorithm and incorporates the assessment of vascular tone based on waveform morphology analysis and patient characteristics. Initially, χ was recalculated every minute. With the fourth-generation FloTrac algorithm, a new component called Kfast was developed, which is inversely proportional to pressure and is added to χ, with the new component calculated every 20 seconds. Thus, CO = PR × SD [bp] × K4 × Kfast using the latest algorithm [22].

PulsioFlex-ProAQT® system (Pulsion Medical Systems, Germany; Maquet Getinge Group, software V4.0.0.7 A, Sweden) The Professional Arterial FlowTrending device (ProAQT) uses auto-calibrated pulse contour analysis. A special sensor is connected to an existing arterial catheter to provide beat-to-beat CI monitoring. The initial CI is automatically determined using patient characteristics and waveform analysis sampling at 250 Hz [23]. The statistical approach for autocalibration is the result of an analysis of a comprehensive database. The value of CI results from both the previous autocalibration and the pulse contour analysis that has run afterward. Hereafter, continuous cardiac indices are estimated using the known PiCCO algorithm. Calibrating with an externally-derived CI is possible at any time.

Protocol

Patient and surgical characteristics were recorded. Age, height, weight, and gender were entered in all monitors. All monitor devices were set up according to the operational manual provided by the manufacturer. All pressure transducers, including the ClearSight Heart Reference Sensor, were zeroed to the level of the right atrium. The FloTrac and ProAQT system were both connected to the already in situ PiCCO arterial catheter. All clocks were synchronized. Simultaneous CI measurements were performed at nine predetermined time-points (T_1–T_9):

- T_1 = after induction of general anesthesia but before surgical incision
- T_2 = 30 minutes after the start of CRS
- T_3 = 30 minutes before the end of CRS (in consultation with the surgeon or halfway iv chemotherapy)
- T_4 = after CRS, before the start of the HIPEC procedure
- T_5 = halfway through HIPEC
- T_6 = after the end of chemotherapy perfusion
- T_7 = at the end of surgery but still in the OR
- T_8 = approximately 6 hours postoperatively in the ICU
- T_9 = approximately 12 hours postoperatively in the ICU

https://doi.org/10.4097/kja.20202

Each TPTD measurement was performed in sets of three to five bolus injections of 20 ml of iced isotonic saline through the central venous catheter irrespective of the ventilator cycle. The mean value was recorded as TPTD CI. All individual bolus measurements were stored and used for the analysis of the precision of the reference method. APWA was also compared to TPTD to analyze drift. All devices provide continuous CI measurements, so we simultaneously used three minutes at the start of each of TPTD measurements to calculate the mean CI of all devices at each time-point. The mean values of these three-minute time frames were recorded and stored for analysis. All measurements were performed by a dedicated research group.

Statistical analysis and data storage

Statistical analyses were performed using IBM SPSS Statistics for Windows (Version 25.0, IBM Corp.) and GraphPad Prism (Version 5.03, GraphPad Software Inc.), figures were produced by SPSS and Microsoft Excel (2007, Version 12.0.6776.5000 SP3, Microsoft Corp.), and data were collected using Microsoft Access (2007, Version 12.0.6735.5000 SP3, Microsoft Corp.). $P < 0.05$ was considered statistically significant. Patient characteristics are presented as mean (SD) or median [range] where appropriate.

Agreement and thus interchangeability of the test devices with TPTD was examined with Bland-Altman analysis corrected for repeated measurements [24,25] and according to previously published statistical suggestions [26–28]. Agreement was calculated using mean CI, and presented as bias and limits of agreement (LoA) with 95% confidence intervals (95% CI). A percentage of error (PE) of less than 30% was considered clinically acceptable [24–28]. The precision of the less invasive hemodynamic devices was calculated as the repeatability coefficient (RC, %) using raw CI data collected in the three minutes. The precision of the TPTD measurement was calculated using the 3–5 individual measurements per time-point [28]. Proportional error (i.e. error dependent on the magnitude of the measurement) was assessed with linear regression analysis [24]. Systemic vascular resistance index (SVRI) was calculated from

$$(SVRI = \frac{mean\ arterial\ pressure\text{-}central\ venous\ pressure}{TPTD\text{-}CI} \times 80\ \text{dyne.s/cm}^5\text{m}^2).$$

Trending abilities were assessed using a four-quadrant plot [29,30] and a polar plot [26,30]. Trend interchangeability was assessed within these plots and expressed as a number (percentage) using the method suggested by Fisher et al. [31]. Trend interchangeability was considered to be excellent (≥ 95%), good (≥ 90%) [32], poor (75%–90%), or not clinically relevant (< 75%) according to its value. Trending ability was good when angular bias was within ± 5° and radial LoA was between ± 30°. To decrease statistical noise delta (Δ), CI < 10% was excluded in the polar plot analysis [26]. The precision of all devices was calculated using 2 × coefficient of variation [33]. All selected data were secured in a Castor electronic clinical research form (Castor EDC, CIWIT B.V., www.castoredc.com), and were independently reviewed for consistency, accuracy, and errors by an external auditor.

Sample size calculation

Sample size and posthoc power analyses were calculated according to Zou [34]. The presumed bias was 0 L/min/m^2, the expected mean CI 3 L/min/m^2, and the expected PE 30% [33], resulting in an expected LoA of 0.9 L/min/m^2 (30% × 3.00 L/min /m^2). Considering a clinical acceptable LoA of 0.6 L/min/m^2 with the desired power of 0.80, this resulted in 130 paired measurements [35]. Anticipating the possible loss of measurements in patients who would be inoperable (20%), we included 25 patients, thus anticipating 225 paired measurements per test device.

Power analysis

Using the ICU measurements and an inoperable rate of 16%, we obtained 170 to 195 paired measurements per device instead of the required 130 for an expected power of 0.80. Using a LoA of 1.6 L/min/m^2 and bias of −0.1 L/min/m^2, these additional measurements increased the power to detect LoA of 0.6 L/min/m^2 to 1.00. The data would allow us to correctly reject the null hypothesis with a power of 0.80 (or type 2 error rate of 0.20) when the expected LoA would be at least 1.2 L/min/m^2.

Results

Twenty-five patients were included in the study, their characteristics summarized in Table 1. Individual patient data are listed in Table 2. Four patients had extensive disease, thus disqualifying them for the actual HIPEC. They were extubated at the end of the procedure and not admitted to the ICU; only their existing data was included in the analysis. Monitor-derived data were analyzed with one-way analysis of variance, as differences in CI measured with the test devices were normally distributed according to the D'Agostino and Pearson test ($P = 0.489$, $P = 0.204$, $P = 0.522$ for ClearSight, FloTrac, and ProAQT CI).

TPTD vs. ClearSight™

TPTD CI ranged from 1.7 to 7 L/min/m^2 while ClearSight CI ranged from 1.5 to 7.8 L/min/m^2. In total, 171 paired measure-

Table 1. Patient Characteristics

Patient factor	
Age (yr)	60.5 ± 13.2
Height (cm)	173.2 ± 8.6
Weight (kg)	83.4 ± 15.7
Gender (M/F)	15/10
Body mass index (kg/m^2)	27.8 ± 4.6
ASA PS (I/II)	2/23
Duration of surgery (min)	390 (310, 458)
CRS phase (T_1–T_4)	235 (151, 310)
HIPEC phase (T_4–T_6)	121 (72, 141)
Post-HIPEC phase (T_6–T_7)	38 (20, 56)
Chemotherapeutic agent	
Mitomycin	5
Cisplatin	1
Oxaliplatin	15
None	4
Norepinephrine dose (μg)	2018 (772, 8932)
Fluid balance (L)	
Fluid administration	4.9 (1.9, 20.1)
Measured fluid loss	−2.0 (−15.4, −0.3)
Fluid balance	2.5 (−0.1, 13.3)

Values are presented as mean ± SD, median (Q1, Q3), or number of patients. Four patients were considered inoperable and did not receive HIPEC treatment. Cumulative norepinephrine dose and fluid balance are taken into account from the start of surgery to T_7. ASA PS: American Society of Anesthesiologists physical status, CRS: cytoreductive surgery, HIPEC: hyperthermic intraperitoneal chemotherapy.

ments were obtained for both devices. The mean bias was −0.1 (95% CI: −0.3, 0.0) L/min/m^2, LoA ± 1.6 (95% CI: 1.4, 1.8) L/min/m^2, and PE was 50% (95% CI: 44%, 57%). The interchangeability rate was 36%.

Trending analysis showed 65% uninterpretable data pairs of measurements and 13% interchangeability. Considering the repeatability of each measurement, 32% of pairs were uninterpretable and 8% were interchangeable. Using only clinically significant CI values, the chance of concordance was 85%. Polar plot analysis showed a mean angular bias of −7° and a radial LoA of ± 39° (95% CI: 34, 43°).

TPTD vs. FloTrac/Vigileo™

TPTD CI ranged from 1.7 to 7.2 L/min/m^2, while FloTrac CI ranged from 1.6 to 5.6 L/min/m^2. In total, 198 paired measurements were obtained. The mean bias was −0.2 (95% CI: −0.3, −0.1) L/min/m^2 with a LoA of ± 1.6 (95% CI: 1.4, 1.8) L/min/m^2 and a PE of 50% (95% CI: 45%, 58%). The interchangeability rate was 47%.

Table 2. Individual Patient Characteristics

Patient no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Age (yr)	48	62	47	64	60	69	50	68	72	75	48	75	78	66	75	49	73	28	40	60	45	55	77	60	68
Height (cm)	168	179	184	160	164	185	178	167	185	163	178	167	164	173	168	171	169	171	162	163	185	180	185	185	175
Weight (kg)	89	107	81	78	104	100	78	90	97	64	74	79	75	100	62	72	66	52	71	73	83	103	91	114	82
Gender (M/F)	F	M	M	F	F	M	M	F	M	F	F	M	M	M	M	M	F	F	F	F	M	M	M	M	M
BMI (kg/m^2)	32	33	24	30	39	29	25	32	28	24	23	28	28	33	22	24	23	18	27	27	24	32	27	33	27
ASA PS	2	2	2	2	2	2	2	2	2	2	1	2	2	2	2	1	2	2	2	2	2	2	2	2	2
Duration of surgery (min)	440	513	281	342	189	222	541	183	461	484	388	199	472	194	169	686	550	291	313	321	430	455	388	207	401
Abdominal chemo agent	mito	ox	ox	ox	ox	ox	ox	ox	cis	ox	ox	-	ox	-	-	mito	ox	mito	mito	ox	mito	ox	ox	-	ox
CRS phase (min)	237	310	194	204	106	102	377	116	242	312	272	-	304	-	-	499	353	134	151	142	222	322	235	-	199
HIPEC phase (min)	145	122	70	110	72	80	154	55	137	162	72	-	72	-	-	141	148	122	121	124	203	69	91	-	96
Post HIPEC phase (min)	57	91	24	21	15	41	12	12	79	14	46	-	74	-	-	55	21	20	38	56	10	38	50	-	70
Vasopressor dose (μg)	3312	7092	1513	1307	794	1303	2869	772	3985	2615	2839	969	4814	1776	878	5008	8932	1632	1365	1652	2018	4983	6427	1875	3442
Fluid administration (ml)	6500	11950	3000	4300	3007	1893	10402	2850	4874	6730	5600	3262	4344	2240	2750	15270	20087	4928	3928	3840	6775	7322	6041	3168	6286
Fluid loss (ml)	2375	4290	1165	850	960	320	4160	435	2360	2705	1250	1330	1455	280	1000	15400	6790	2970	2685	2025	3425	3805	2435	1180	1966
Fluid balance (ml)	4125	7660	1835	3450	2047	1573	6242	2415	2514	4025	4350	1932	2889	1960	1750	-130	13297	1958	1243	1815	3350	3517	3606	1988	4320

Patient No. of 12, 14, 15, 24 were considered inoperable and did not receive HIPEC treatment. BMI: body mass index, ASA PS: American Society of Anesthesiologists physical status, CRS: cytoreductive surgery, mito: mitomycin, ox: oxaliplatin, cis: cisplatin, HIPEC: hyperthermic intraperitoneal chemotherapy.

https://doi.org/10.4097/kja.20202

Trending analysis showed 68% uninterpretable data pairs and 9% interchangeability. Considering the repeatability of each measurement, 33% of pairs were uninterpretable and 7% were interchangeable. After the exclusion of clinically insignificant CI changes, concordance was found to be 76%. Polar plot analysis showed a mean angular bias of -19° and a radial LoA of ± 38° (95% CI: 32, 41°).

TPTD vs. PulsioFlex-ProAQT®

TPTD CI ranged from 1.7 to 7.2 L/min/m^2, while ProAQT CI ranged from 1.5 to 7.8 L/min/m^2. A total of 178 paired measurements were obtained with a mean bias of −0.1 (95% CI: −0.2, 0.0) L/min/m^2, a LoA of ± 1.7 (95% CI: 1.5, 2.0) L/min/m^2, and a PE of 54% (95% CI: 47%, 61%). The interchangeability rate was 40%.

The trending analysis showed 70% uninterpretable data pairs and 11% interchangeability. Considering the repeatability of each measurement, 33% of pairs were uninterpretable and 13% were interchangeable. Analyzing clinically significant changes gave a concordance of 76%. Polar plot analysis showed a mean angular bias of -13° with a radial LoA of ±41° (95% CI: 34, 43°).

TPTD PiCCO™ vs. APWA PiCCO™

TPTD CI ranged from 1.7 to 7.2 L/min/m^2, while APWA CI ranged from 1.5 to 7.0 L/min/m^2. In total, 171 paired measurements were obtained for both methods. The mean bias was −0.1 (95% CI: −0.2, 0.1) L/min/m^2, LoA was ± 1.2 (95% CI: 1.1, 1.4) L/min/m^2, and PE was 36% (95% CI: 32%, 41%). The interchangeability rate was 72%.

Trending analysis showed 74% uninterpretable data pairs and 6% interchangeability. Considering the repeatability of each measurement, 36% of pairs were uninterpretable and 4% were interchangeable. Analyzing clinically significant CI changes, the concordance was found to be 66%. Polar plot analysis showed a mean angular bias of -15° with a radial LoA of ±39° (95% CI: 37, 40°).

The graphical representation of the results is presented in Figs. 1, 2, and 3, respectively, as follows: Bland Altman analysis (including interchangeability), correlation analysis, and the four-quadrant plot (including interchangeability). Fig. 4 shows interchangeability in trending of all devices. In all graphs, the number of orange (possibly interchangeable) and green (interchangeable) data pairs are more or less equal. This in contrast with the blue (uninterpretable) and red (not interchangeable) data pairs. Using the actual RC for each point reveals additional interchangeable pairs, which were otherwise classified as uninterpretable. Results from all devices at individual time-points are shown in Table 3. There were no significant differences between the devices themselves nor among different time-points. All had minimal bias but large LoAs, thus resulting in high PEs.

During the HIPEC procedure, the intraabdominal temperature remained between 42–43°C for all patients. As a result, blood temperature significantly increased during this phase compared to pre-HIPEC blood temperature ($P < 0.05$). The SVRI during the CRS phase (T_2–T_4) was significantly lower ($P < 0.05$) compared to T_1. During this procedure, there were significant changes in the SVRI. During the HIPEC phase (T_5–T_6), SVRI was significantly lower compared to the CRS ($P < 0.05$) and T_1 phases ($P < 0.001$). There was also a significant difference in SVRI between CRS and HIPEC phases ($P < 0.05$).

The precision of the reference method TPTD, which was expressed as the repeatability coefficient, was 10%. The repeatability coefficients of Clearsight, FloTrac/Vigileo, ProAQT, and APWA were 8%, 9%, 10%, and 10%, respectively. This respectively corresponds to 0.4 (95% CI: 0.3, 0.4), 0.4 (95% CI: 0.3, 0.4), 0.4 (95% CI: 0.4, 0.5) and 0.5 (95% CI: 0.4, 0.5) L/min/m^2. Bias was dependent on the magnitude of CI in ClearSight and APWA (0.22 and 0.14 L/min/m^2 per L/min/m^2, respectively, zero bias at 3.7 L/min/m^2), but proportional LoAs were present in all devices (0.17, 0.30, 0.21 and 0.10 L/min/m^2 per L/min/m^2) for Clearsight, FloTrac/Vigileo, ProAQT and APWA, respectively. The estimated LoAs were 1.5, 1.4, 1.6 and 0.9 L/min/m^2 for Clearsight, FloTrac/Vigileo, ProAQT, and APWA, respectively. Bias in APWA CI was not dependent on time since last TPTD bolus calibration (linear regression, $R^2 = 0.002$; Pearson's $r = -0.043$, $P = 0.603$; Spearman's $\rho = 0.032$, $P = 0.704$).

Discussion

In this perioperative validation study, we compared CI measurements using less invasive hemodynamic monitoring devices, namely ClearSight, FloTrac and ProQAT, to that of TPTD measurements during CRS-HIPEC operations. Our data show a negligible bias for all studied devices but a large LoA.

Interchangeability rates, which are objective measurements of a device's performance compared to a reference device as described by Lorne et al. [27], were well below clinically relevant levels. Using the measurement error of each individual pair of measurements, and thus a nonconstant repeatability coefficient, worsened the interchangeability rates in all test devices. We could not determine the cut off for 95% interchangeability in any of the devices because the inclusion rate was well below 95% within any subrange, which underlines the lack of interchangeability.

Considering the reproducibility of changes over time during

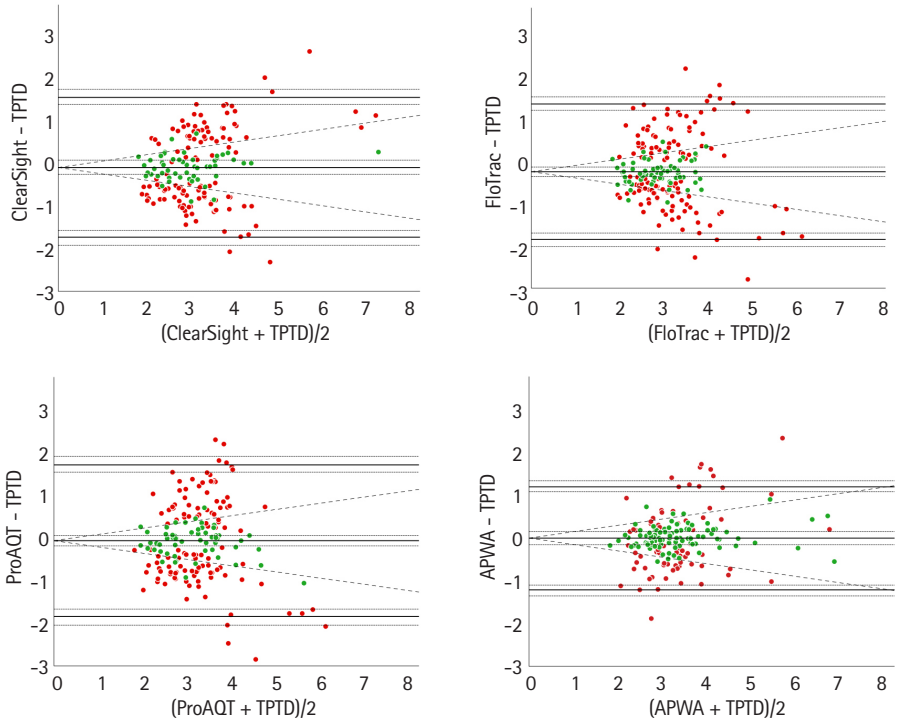

Fig. 1. Bland-Altmann plot of all devices vs. TPTD. Bland-Altman plot showing the agreement between ClearSight, FloTrac, ProAQT, APWA, and TPTD, respectively. All data are expressed as CI (L/min/m^2). Solid lines indicate systematic bias ± limits of agreement (LoA). Dotted lines indicate the 95% CI around the bias and limit of agreement. Dashed lines indicate the inclusion zone using the repeatability coefficient of the thermodilution measurements. Green or red color: inclusion or exclusion of the data point using the repeatability coefficient of each data pair instead of using the overall inclusion zone. AWPA: arterial pressure wave analysis, TPTD: transpulmonary thermodilution, CI: cardiac index.

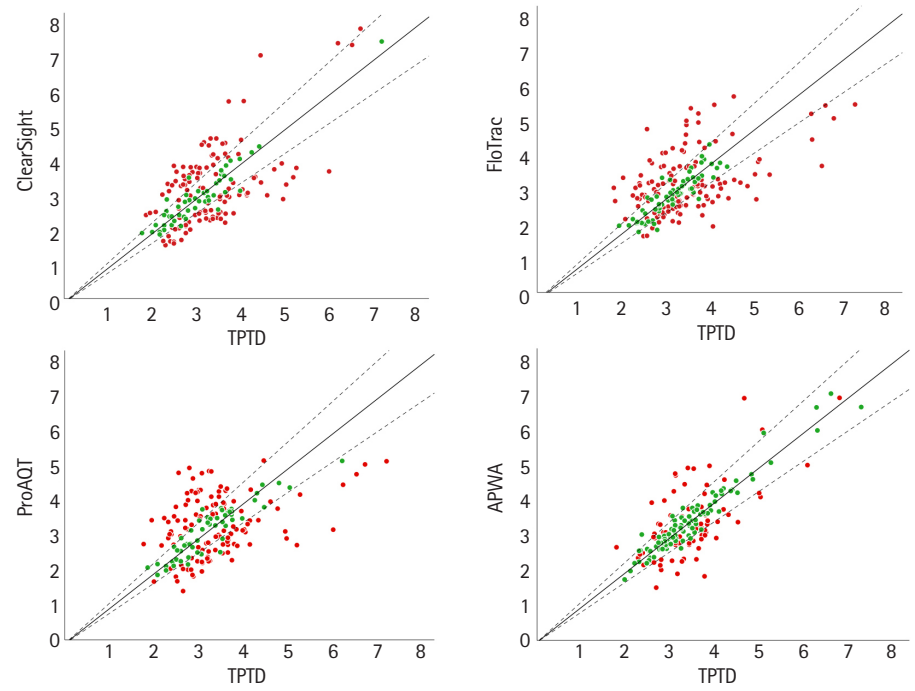

Fig. 2. Correlation plot of all devices vs. TPTD. Correlation plot of ClearSight, FloTrac, ProAQT, and AWPA vs. TPTD. All data are expressed as CI (L/min/m^2). Clearsight R^2 = 0.48; FloTrac R^2 = 0.32; ProAQT R^2 = 0.24; APWA R^2 = 0.68 compared with TPTD. Solid lines indicate the line of identity considering systematic bias. Dashed lines indicate the inclusion zone using the mean repeatability coefficient of the test device and the reference device. Green or red color: inclusion or exclusion of the data point using the repeatability coefficient of each measurement instead of using the overall inclusion zone. TPTD: transpulmonary thermodilution, AWPA: arterial pressure wave analysis, CI: cardiac index.

https://doi.org/10.4097/kja.20202

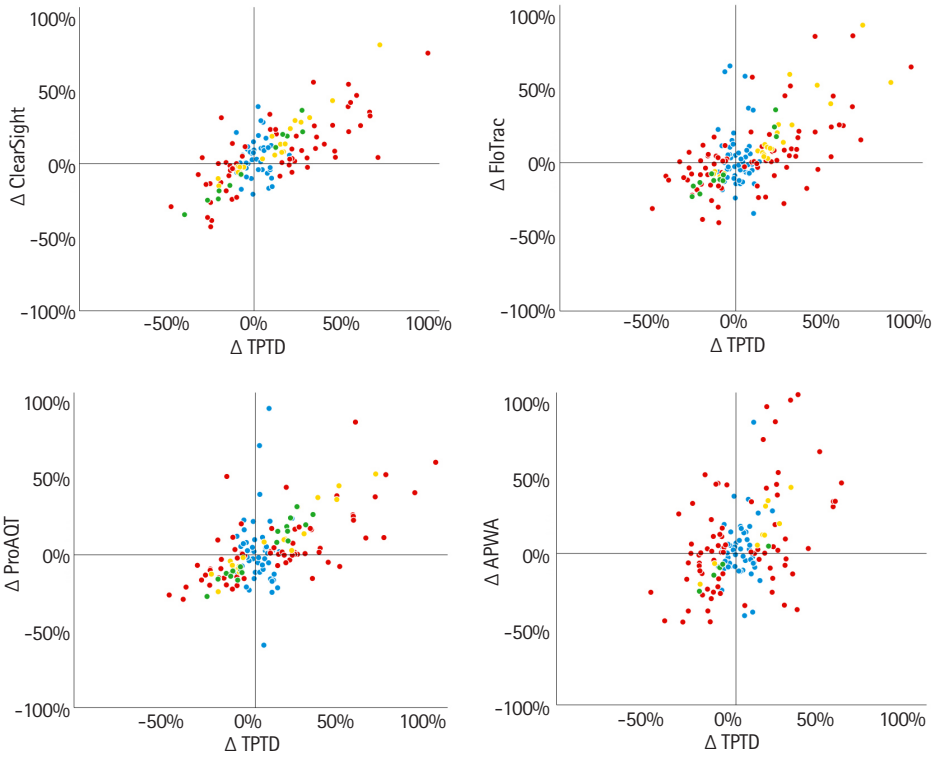

Fig. 3. Four-quadrant plot of all devices vs. TPTD Four-quadrant plot of the trending ability of ClearSight, FloTrac, ProAQT, and APWA vs. TPTD. The percentual increase or decrease from the preceding measurement is plotted as Δ%. Additionally, each data point is classified according to its interchangeability. Blue = uninterpretable change; red = test device and thermodilution measurements are not interchangeable; orange = 'gray zone' where test device and thermodilution could be interchangeable; and green = test device and thermodilution seem interchangeable. TPTD: transpulmonary thermodilution, AWPA: arterial pressure wave analysis.

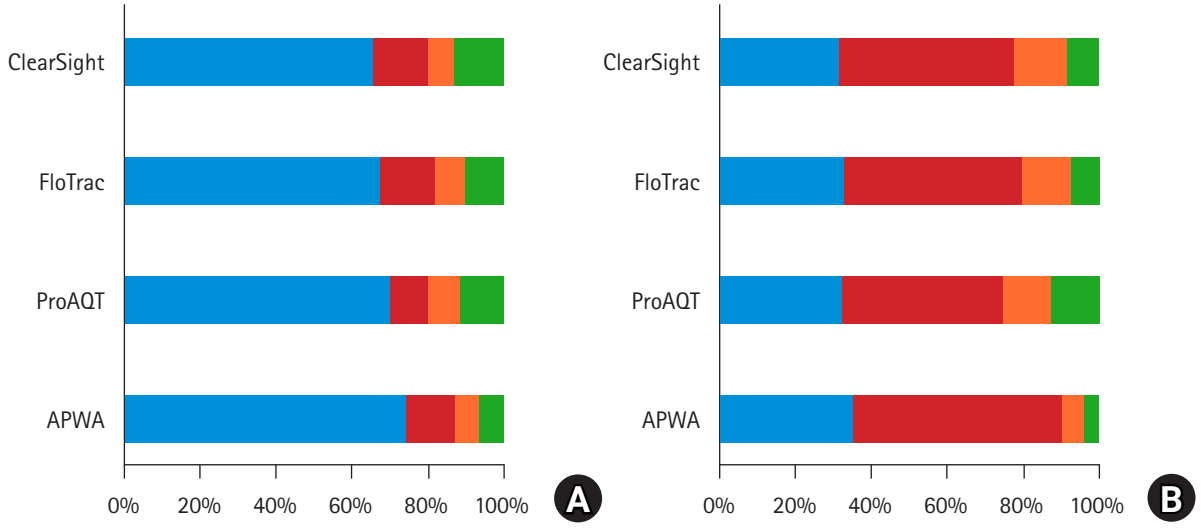

Fig. 4. Summary of trending analysis. The proportion of data points from Fig. 3 being classified as uninterpretable (blue), as not interchangeable (red), in the 'gray zone' of possible interchangeability (orange), and as interchangeable (green) are summarized per test device according to Fischer et al. [31]. Fig 4A left: Data points are classified using the mean repeatability coefficient of the thermodilution measurements. This results in 66, 68, 70, and 74% uninterpretable pairs, and in 13, 9, 11, 6% interchangeable pairs for ClearSight, FloTrac, ProAQT, and APWA, respectively. Fig 4B (right): Data points are classified using the repeatability coefficient of the thermodilution measurements for each data point. This results in 32%, 33%, 32%, and 36% uninterpretable pairs; and in 8%, 7%, 13%, and 3% interchangeable pairs for ClearSight, FloTrac, ProAQT and APWA, respectively. Blue = uninterpretable data points; red = test device and thermodilution measurements are not interchangeable; orange = 'gray zone' where test device and thermodilution could be interchangeable; and green = test device and thermodilution seem interchangeable. AWPA: arterial pressure waveform analysis.

Table 3. Bland-Altman Analyses per Time-point

	T_1	T_2	T_3	T_4	T_5	T_6	T_7	T_8	T_9	Overall
Blood temperature (°C)	35.8 (35.6, 36.0)	35.7 (35.5, 35.9)	35.8 (35.5, 36.0)	35.9 (35.6, 36.1)	37.5* (37.3, 37.8)	37.0* (36.6, 37.4)	36.5* (36.3, 36.8)	37.2* (36.8, 37.6)	37.2* (37.0, 37.5)	
Systemic vascular resistance index (dyne·sec/cm^5·m^2)	2168 (1901, 2434)	1664* (1460, 1867)	1729* (1559, 1899)	1805 (1546, 2064)	1468† (1312, 1625)	1474† (1340, 1607)	1508* (1383, 1633)	1841 (1638, 2043)	1598* (1425, 1771)	
Bias (L/min/m^2)										
ClearSight	−0.1 (−0.5, 0.3)	−0.2 (−0.6, 0.2)	−0.3 (−0.7, 0.2)	0.1 (−0.5, 0.6)	0.0 (−0.7, 0.7)	−0.1 (−0.6, 0.5)	−0.2 (−0.6, 0.1)	0.1 (−0.4, 0.5)	−0.2 (−0.5, 0.2)	−0.1 (−0.3, 0.0)
FloTrac	−0.1 (−0.3, 0.1)	−0.1 (−0.4, 0.3)	0.0 (−0.3, 0.4)	0.1 (−0.3, 0.5)	−0.3 (−0.7, 0.1)	−0.5 (−0.8, −0.1)	−0.5 (−0.9, −0.2)	−0.2 (−0.5, 0.1)	−0.6 (−0.9, −0.3)	−0.2 (−0.3, −0.1)
ProAQT	0.3 (0.0, 0.6)	−0.1 (−0.4, 0.3)	−0.3 (−0.6, 0.0)	−0.1 (−0.4, 0.3)	−0.5 (−0.9, −0.1)	−0.4 (−0.7, 0.0)	−0.4 (−0.8, −0.1)	0.4 (0.0, 0.9)	0.4 (0.1, 0.8)	−0.1 (−0.2, 0.0)
APWA		−0.2 (−0.6, 0.1)	−0.1 (−0.6, 0.4)	−0.2 (−0.6, 0.3)	−0.2 (−0.7, 0.3)	0.1 (−0.3, 0.5)	0.0 (−0.4, 0.4)	0.2 (−0.2, 0.6)	0.0 (−0.5, 0.5)	−0.1 (−0.2, 0.1)
TPTD	0.0 (−0.2, 0.2)	0.0 (−0.3, 0.3)	0.0 (−0.4, 0.4)	0.0 (−0.4, 0.4)	0.0 (−0.4, 0.4)	0.0 (−0.4, 0.4)	0.0 (−0.4, 0.4)	0.0 (−0.3, 0.3)	0.0 (−0.4, 0.4)	0.0 (−0.1, 0.1)
Limits of agreement (L/min/m^2)										
ClearSight	±1.5 (1.1, 2.1)	±2.0 (1.5, 2.8)	±1.6 (1.2, 2.3)	±1.7 (1.3, 2.4)	±1.8 (1.3, 2.6)	±1.7 (1.3, 2.4)	±1.8 (1.3, 2.6)	±1.4 (1.0, 2.5)	±1.7 (1.2, 2.8)	±1.6 (1.5, 1.8)
FloTrac	±1.1 (0.8, 1.5)	±1.8 (1.4, 2.5)	±1.7 (1.3, 2.4)	±1.9 (1.5, 2.7)	±1.4 (1.1, 2.0)	±1.6 (1.2, 2.2)	±1.8 (1.3, 2.5)	±1.4 (1.0, 2.0)	±1.8 (1.3, 2.7)	±1.6 (1.5, 1.8)
ProAQT	±1.2 (0.9, 1.8)	±1.8 (1.4, 2.5)	±2.0 (1.5, 2.8)	±1.5 (1.1, 2.1)	±1.5 (1.1, 2.2)	±1.8 (1.3, 2.5)	±2.0 (1.5, 2.7)	±1.7 (1.2, 2.7)	±1.9 (1.3, 3.0)	±1.8 (1.6, 2.0)
APWA		±1.3 (1.0, 1.8)	±1.4 (1.1, 1.9)	±1.0 (0.7, 1.4)	±1.4 (1.1, 2.0)	±1.1 (0.9, 1.6)	±0.9 (0.7, 1.3)	±1.0 (0.7, 1.5)	±1.4 (1.1, 2.1)	±1.2 (1.1, 1.3)
TPTD	±0.4 (0.3, 0.6)	±0.5 (0.4, 0.7)	±0.5 (0.4, 0.7)	±0.5 (0.4, 0.8)	±0.6 (0.4, 0.8)	±0.5 (0.4, 0.7)	±0.5 (0.4, 0.6)	±0.4 (0.3, 0.5)	±0.5 (0.4, 0.8)	±0.4 (0.4, 0.4)
Repeatability coefficient (L/min/m^2)										
ClearSight	0.4 (0.3, 0.6)	0.5 (0.4, 0.7)	0.4 (0.3, 0.5)	0.3 (0.2, 0.4)	0.2 (0.2, 0.3)	0.3 (0.3, 0.5)	0.2 (0.2, 0.3)	0.5 (0.3, 0.8)	0.5 (0.3, 0.8)	0.4 (0.3, 0.4)
FloTrac	0.3 (0.3, 0.5)	0.3 (0.3, 0.5)	0.3 (0.2, 0.4)	0.5 (0.4, 0.7)	0.2 (0.2, 0.3)	0.5 (0.3, 0.6)	0.6 (0.5, 0.8)	0.4 (0.3, 0.5)	0.3 (0.2, 0.4)	0.4 (0.3, 0.4)
ProAQT	0.5 (0.4, 0.8)	0.5 (0.4, 0.7)	0.5 (0.4, 0.7)	0.4 (0.3, 0.6)	0.2 (0.1, 0.3)	0.5 (0.3, 0.6)	0.3 (0.2, 0.5)	0.6 (0.4, 0.9)	0.5 (0.4, 0.9)	0.4 (0.4, 0.5)
APWA		0.5 (0.3, 0.6)	0.4 (0.3, 0.5)	0.5 (0.4, 0.8)	0.4 (0.3, 0.6)	0.4 (0.3, 0.6)	0.5 (0.4, 0.8)	0.4 (0.3, 0.6)	0.6 (0.5, 0.9)	0.5 (0.4, 0.5)
TPTD	0.4 (0.3, 0.6)	0.5 (0.4, 0.7)	0.5 (0.4, 0.7)	0.6 (0.4, 0.8)	0.6 (0.4, 0.8)	0.5 (0.4, 0.7)	0.5 (0.4, 0.7)	0.4 (0.3, 0.6)	0.6 (0.4, 0.9)	0.5 (0.4, 0.5)
Percentage error (%)										
ClearSight	58 (43, 84)	60 (46, 84)	52 (40, 72)	52 (39, 74)	51 (38, 76)	50 (37, 71)	53 (39, 77)	45 (30, 77)	49 (34, 77)	50 (45, 56)
FloTrac	42 (33, 58)	53 (40, 75)	53 (40, 74)	59 (45, 84)	43 (32, 62)	48 (37, 68)	55 (42, 78)	43 (32, 62)	54 (39, 79)	50 (46, 56)
ProAQT	45 (33, 65)	53 (40, 74)	63 (48, 88)	45 (34, 66)	47 (34, 68)	54 (41, 76)	59 (45, 83)	49 (34, 77)	50 (35, 79)	54 (49, 60)
APWA		39 (29, 54)	44 (33, 60)	31 (23, 44)	43 (32, 61)	32 (24, 45)	28 (21, 39)	30 (22, 44)	40 (29, 59)	36 (32, 40)
TPTD	17 (13, 23)	14 (11, 20)	15 (12, 21)	17 (13, 24)	16 (12, 23)	15 (11, 21)	13 (10, 18)	11 (8, 16)	15 (11, 21)	12 (11, 13)

Values are presented as mean (95% CI). Bland-Altman analysis at each predefined time-point (T_1-T_9). Bland-Altman analysis at each predefined time-point as follows: T_1: after induction of general anesthesia but before surgical incision, T_2: 30 minutes after the start of cytoreductive surgery (CRS), T_3: 30 minutes before the end of CRS (in consultation with the surgeon or halfway iv chemotherapy), T_4: after CRS, before the start of the hyperthermic intraperitoneal chemotherapy (HIPEC) procedure, T_5: halfway through HIPEC, T_6: after the end of chemotherapy perfusion, T_7: at the end of surgery but still in the operating room, T_8: approximately six hours postoperatively in the intensive care unit (ICU), T_9: approximately 12 hours postoperatively in the ICU. LoA: limits of agreement, RC: repeatability coefficient, PE: percentage error, APWA: arterial pressure waveform analysis by PiCCO, TPTD: transpulmonary thermodilution. The temperature during T_5-T_9 are significantly higher compared to T_1-T_4, *$P < 0.05$. Systemic vascular resistance index at T_1 is significantly higher compared to T_2-T_3, and T_9, *$P < 0.05$ and T_1 vs $T_{5\text{-}6}$, †$P < 0.001$.

https://doi.org/10.4097/kja.20202

this extensive surgical procedure, all devices had a concordance of < 92%. Only ClearSight had a concordance of 85%, which was closest to moderate trending. All devices showed systematic errors, with mean angular bias found to be between −7° and −19°. The radial LoA of all devices were outside the acceptable range, and varied from ± 38° and ± 41°.

Interchangeability in trending was defined using the measurement error of both the test device and the reference device. Uninterpretable pairs resulted from a statistically negligible change in the reference CI because of overlapping errors of two consecutive measurements, leading to > 60% of measurement pairs being uninterpretable. The proportion of either uninterpretable pairs (high) and interchangeable pairs (very low) was consistent with the results of Fischer et al. [31]. Using a nonconstant repeatability coefficient derived from the measurement error of each single measurement in both the test device and the reference device, both the proportion of uninterpretable pairs and the proportion of interchangeable pairs decreased. This is usually caused by a smaller individual repeatability coefficient (Table 3) and thus a smaller measurement error, which results in a larger number of statistically significant changes. The smaller individual repeatability coefficients may or may not change the classifications of not-interchangeable (red), possibly interchangeable (orange), or interchangeable (green). We also analyzed the repeatability of the devices, which showed an inverse proportional relation with the magnitude of the CI. This may justify the use of the measurement error of each CI measurement instead of using just one global repeatability coefficient. Trend interchangeability was low for all devices during this clinical procedure. The hemodynamic conditions of patients in previous studies varied from being stable post cardiac surgery [9,21,22,36] to developing sepsis or septic shock [9,21,37,38]. If validated in the OR, it often concerned liver surgery [9,37,38], and rarely, general surgery [39]. Most of these studies did not reach the criteria for interchangeability [23,36–41]. The trending ability of the devices in these studies varied and often showed conflicting results between the analyses used [21–23,37–41]. Overall, the results support moderate trending at best [21,22,38,39,41]. Our results conducted in the OR and ICU were comparable with literature [9,21–23,36–41].

All devices showed minimal bias at any time-point but a large LoA. These results were comparable to results seen during sepsis or septic shock [9,21,37,38] or liver surgery [9,37,38] and recognized for a decrease in vascular tone. Indeed, during CRS-HIPEC, the vascular tone significantly decreased (Table 3), which is also illustrated by the percentage of error of the APWA CI of 36%. These changes were unexpected during abdominal surgery. Our tested devices have shown to be sensitive to changes in vascular tone [22,37,40]. The aforementioned PE in combination with the short recalibration times (mean recalibration time was 63 min, SD 59 min) illustrate the complexity of hemodynamic monitoring in this patient population.

Many factors influence vascular tone during extensive surgical procedures, including the administration of general anesthesia, epidural analgesia, magnesium chloride infusion [17], as well as the patient's immune response/inflammation [14,42]. Fluid administration and inotrope and/or vasopressor therapy counteract hypotension. During this extensive surgery we found an increase in CI (+8%; 95% CI: 1%, 14%) and a decrease in SVRI (−17%; 95% CI: −27%, −9%) despite increasing norepinephrine dosages (+65%; 95% CI: 37%, 93%) and rate of fluid administration (+148%; 95% CI: −12%, 310%). These data do resemble the hemodynamic changes that take place during sepsis episodes, in which we know less invasive devices are less accurate [3,9,21,37–39]. After the initiation of hyperthermic treatment, there was a significant reduction of SVRI (Table 3), which required an increase in vasopressor support. Although GDT studies have been published using different devices [12], the exact position with regards to the use of GDT remains unclear [43]. Results found in our study could have occurred in other studies involving liver surgery [9,37,38] and extensive surgical procedures [12,43], which likely negatively influenced the results.

Our recalibration moments were predefined and not influenced by the clinical situation. Time since the last calibration did not influence the bias between TPTD and APWA. To improve pulse contour-derived continuous cardiac index accuracy and precision, frequent recalibration is advised especially in hemodynamic challenging conditions. When to recalibrate remains unclear [44,45], Huber and colleagues advised that recalibration be initiated based on changes in APWA CI compared to the prior TPTD calibration [46].

Best TPTD measurement is achieved by creating a maximum temperature difference between the blood and injectate [47], with the maximal delta temperature measured at the thermistor tip. The accuracy of the measurements is not affected as long as the delta temperature is higher than > 0.3°C (verbal communication Pulsion/Getinge). We used a maximal amount of iced saline (20 ml) during the entire procedure. During HIPEC, the abdominal temperature was kept between 42–43°C, thus causing an expected rise in intravascular temperature (Table 3). The combination of high blood temperature and ice water provided the best condition for a good measurement [47]. Injecting iced saline during TPTD measurements did not alter abdominal temperature. Thus, there was no negative effect with regards to therapeutic effects during the HIPEC procedure.

Our study is a validation of extensive abdominal surgery and intensive care. In 25 patients and at nine predetermined timepoints, we obtained 718 paired measurements. This number exceeds that in most validation studies [21–23,39,41,45,48]. We were able to calculate the precision of the measurements and the precision of the agreement of all measuring devices as advised by Hapfelmeier et al. [28]. This allowed us to conclude that the unacceptably high LoA and PE found in the present study were not attributable to a large variation in the measurements [33]. We combined old [24,25,33] and new [27,28] analyses for absolute values comparison. For the trending analysis, we also combined old and new values, combining the use of a four-quadrant plot [29,30], polar plot analysis [26], and interchangeability in trending [31], thus making the results robust.

Although visually inspected, theoretical under- or over dampening of the arterial waveform could have occurred during hemodynamic measurements. We did not use the pulmonary artery catheter as a reference technique due to its complications and lack of benefit with its use. We instead replaced it with TPTD [2,4]. The anesthesia protocol was not standardized to the fullest extent possible. As most of our anesthetics influence vascular tone, this could have influenced our results. Bias and precision of the tested devices (including the reference method) used have shown to be sensitive to changes in vascular tone [37–41,44–46,48]. The data from the TPTD measurement was used by the attending anesthesiologist to guide hemodynamic management. Different interpretations of these measurements could have led to different subsequent actions concerning fluid management and inotrope/vasopressor therapy. We think these inconsistencies were mitigated by the heterogeneity of the CRS-HIPEC.

Our study was also limited by the devices which we have used in this validation study combined with the selected CRS-HIPEC procedure. The generalization of these results could be questionable. However, extensive surgical procedures are performed on a large scale, and thus, results from T_1–T_4 apply to extensive abdominal surgery. Twenty-five patients were included and 718 paired measurements were taken. Although this could still be seen as a small cohort, power calculation found this to be enough.

During the HIPEC phase, blood temperature increased to a maximum mean temperature of 37.5°C (T_5), with the intraperitoneal temperature being 42–43°C All hemodynamic measurements were performed at "normal" blood temperatures (Table 3). However, one could argue that changes in temperature could have influenced our hemodynamic measurements in some way.

The ClearSight, FloTrac, and ProAQT systems were not able to reliably measure cardiac output compared to TPTD with the PiCCO system during CRS-HIPEC, with these devices having large limits of agreement and unacceptably high percentage errors. Reproducibility of changes over time using concordance, angular bias, radial LoA, and interchangeability in trending of all devices was unsatisfactory.

Acknowledgements

We thank the members of the HEMOHIP team (Dennis van Aalst, Chiel Baert, Lonneke Baggen, Martin Bucx, Hettie Custers, Mark Hoytink, Margien Jacobs, Koert Kersten, Jörg Mühling, Ruud van der Putten, Marlou Swenne, and Dominique Willems) for providing care for the study patients and facilitating the data acquisition as well as Ewald Bronkhorst, statistical and methodological consultant, for his advice and assistance for the conduct of statistical analyses.

Funding Statement

Clinical monitors were provided by Edwards Lifesciences and Pulsion Medical systems for the duration of the study, while disposables were purchased by the researchers. Further support was provided solely by institutional and/or departmental sources.

Conflicts of Interest

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

Author Contributions

Amon Heijne (Conceptualization; Data curation; Formal analysis; Methodology; Resources; Visualization; Writing – original draft; Writing – review & editing)
Piet Krijtenburg (Conceptualization; Data curation; Investigation; Methodology; Validation; Writing – original draft; Writing – review & editing)
Andre Bremers (Data curation; Investigation; Resources; Supervision; Validation; Writing – original draft; Writing – review & editing)
Gert Jan Scheffer (Conceptualization; Investigation; Supervision; Writing – original draft; Writing – review & editing)
Ignacio Malagon (Conceptualization; Methodology; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing)
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https://doi.org/10.4097/kja.20202

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https://doi.org/10.4097/kja.20202

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KJA
Korean Journal of Anesthesiology

Effectiveness of four ultrasonographic parameters as predictors of difficult intubation in patients without anticipated difficult airway

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Clinical Research Article

Korean J Anesthesiol 2021;74(2):134-141
https://doi.org/10.4097/kja.20114
pISSN 2005-6419 • eISSN 2005-7563

Received: March 16, 2020
Revised: April 26, 2020 (1st); May 25, 2020 (2nd)
Accepted: June 8, 2020

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Background: Predicting difficult intubation (DI) is a key challenge, as no single clinical predictor is sufficiently valid to predict the outcome. We evaluated the effectiveness of four upper airway ultrasonographic parameters in predicting DI. The validity of the models using combinations of ultrasonography-based parameters was also investigated.

Methods: This prospective, observational, double-blinded cohort trial enrolled 1,043 surgical patients classified as American Society of Anesthesiologists physical status I–III without anticipated difficult airway. Preoperatively, their tongue thickness (TT), invisibility of hyoid bone (VH), and anterior neck soft tissue thickness from the skin to thyrohyoid membrane (ST) and hyoid bone (SH) were measured by sublingual and submandibular ultrasonography. The logistic regression, Youden index, and receiver operator characteristic analysis results were reported.

Results: Overall, 58 (5.6%) patients were classified as DI. The TT, SH, ST, and VH had accuracies of 78.4%, 85.0%, 84.7%, and 84.9%, respectively. The optimal values of TT, SH, and ST for predicting DI were > 5.8 cm (sensitivity: 84.5%, specificity: 78.1%, AUC: 0.880), > 1.4 cm (sensitivity: 81%, specificity: 85.2%, AUC: 0.898), and > 2.4 cm (sensitivity: 75.9%, specificity: 85.2%, AUC: 0.885), respectively. VH had a sensitivity and specificity of 72.4% and 85.6% (AUC: 0.790). The AUC values of the five models (with combinations of three or four parameters) ranged from 0.975–0.992. ST and VH had a significant impact on the individual models.

Conclusions: SH had the best accuracy. Individual parameters showed limited validity. The model including all four parameters offered the best diagnostic value.

Keywords: Airway management; Diagnostic ultrasound; General anesthesia; Hyoid bone; Intubation; Laryngoscopy; Tongue.

Introduction

Securing the airway is a vital component in the clinical practice of anesthesia. Difficult intubation (DI) is prone to potential complications, ranging from minimal airway edema to life-threatening events. Predicting DI during the preoperative assessment is a key challenge, as no single clinical predictor is sufficiently valid for predicting the outcomes. Various imaging techniques have been under consideration for evaluation of the airways, but each has specific limitations, such as radiation exposure, high cost, and procedure time, etc.

Ultrasonography is a non-invasive and quick bedside tool that allows easy visualization of the neck anatomy and assessment of the airway [1,2]. Various ultrasonography-related

parameters such as tongue thickness (TT), the invisibility of hyoid bone (VH), mandible condylar mobility, and anterior neck soft tissue thickness from the skin to the thyrohyoid membrane (ST) and the hyoid bone (SH), respectively, have the potential of predicting difficult airway. The current literature is, however, limited to small studies, restricted further by the low incidence of DI [3–5]. Thus, the validity of ultrasonography-based parameters in predicting DI requires further exploration. We hypothesized that upper airway ultrasonographic parameters including TT, SH, ST, and VH would reliably predict DI during preoperative assessment in patients without anticipated difficult airway. We preferred these parameters considering the ease and rapidity in locating their anatomical landmarks to allow precise measurements, their potential ability to predict DI, and the limited role of clinical screening in their evaluation. Our primary aim was to evaluate the effectiveness of aforesaid ultrasonographic parameters in predicting DI by comparing them between the DI and easy intubation (EI) groups. We also analyzed the validity of various models with combined ultrasonography-based parameters in predicting DI.

Materials and Methods

After obtaining institutional ethical approval (AIIMS/IEC/18/85) and written informed consent, patients of both sexes classified as American Society of Anesthesiologists physical status I–III, aged 18 to 60 years, undergoing tracheal intubation for surgery under general anesthesia, were included in this prospective, observational, cohort study conducted between August 2018 to July 2019 (Indian Clinical Trial Registry No: CTRI/2018/07/014786). This clinical research was done following the ethical principles for medical research involving human subjects in accordance with the Helsinki Declaration 2013. An experienced investigator conducted a difficult airway assessment during the preoperative visit. Those with upper airway anatomical anomaly, trauma, or tumor; history of a difficult airway; and difficult airway on pre-anesthetic check-up and those requiring deviation in the study protocol were excluded. A modified Mallampati test (MMP) grade of 3 or 4, small thyromental distance (< 6.5 cm), and small inter-incisor distance (< 3 cm) indicate the presence of difficult airway.

All enrolled patients underwent a duly explained ultrasonographic examination (Logic eR7, GE Medical Systems Co. Ltd., China) of the upper airway in the pre-operative room. A skilled investigator (≥ 5 years of experience in airway ultrasonography) performed the procedure and recorded the measurements. For sublingual ultrasonography, patients were positioned in the sitting, neutral head position [4]. A curved ultrasound probe (4.2–10.0 MHz in a sterile cover) was placed intra-orally under the patient's tongue in a longitudinal orientation (perpendicular to the face) and advanced backwards as far as the patient felt comfortable (Fig. 1A). The hyoid bone was noted in the obtained image (Fig. 1D). For submandibular ultrasonography, all patients were asked to remain in a supine and extended neck posture, to keep their mouth closed, and to remain quiet, with the tip of tongue relaxed and just touching the incisors [6]. A curvilinear ultrasound

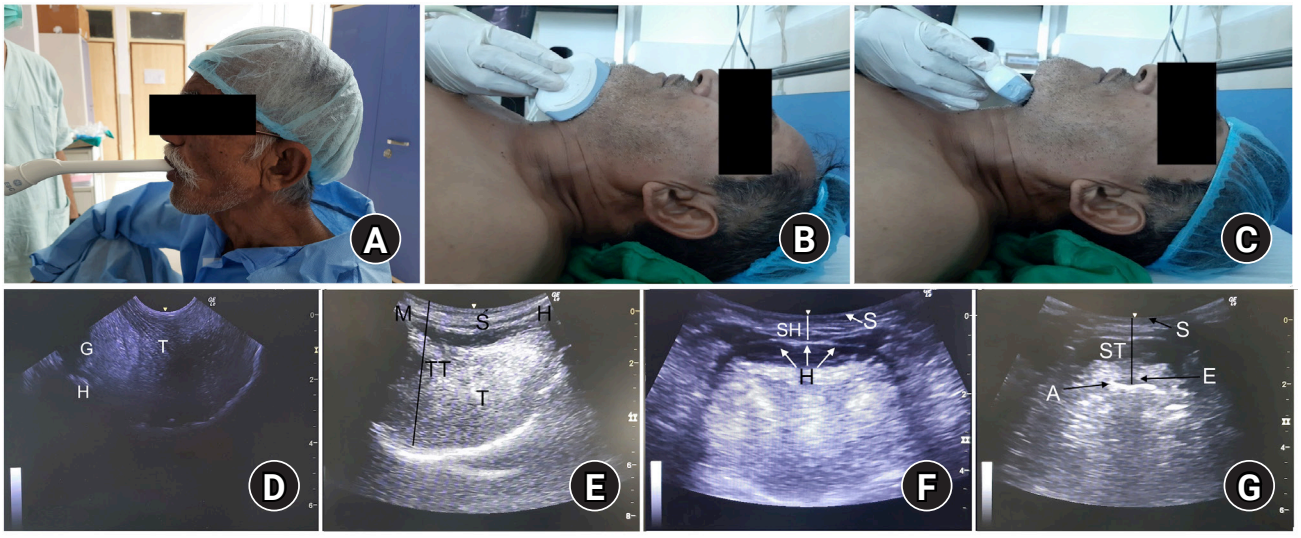

Fig. 1. Schematic diagram showing the position of ultrasound probe and the corresponding images of upper airway. (A) Probe placed intraorally under the patient's tongue, (B) positioned beneath the mentum along the mid-sagittal plane, and (C) rotated 90° in the same position. Ultrasonography image showing (D) visibility of hyoid bone, (E) measurement of TT, (F) measurement of SH, and (G) measurement of ST. A: air-membrane interface, E: epiglottis, G: geniohyoid, H: hyoid, M: mentum, S: skin, SH: soft tissue thickness from skin to hyoid bone, ST: soft tissue thickness from skin to thyrohyoid membrane, T: tongue, TT: tongue thickness.

probe (2–5 MHz) was positioned beneath the mentum along the mid-sagittal plane, adjusted to obtain a clear image of the tongue contour (Fig. 1B). The maximum vertical length from the tongue surface to the submental skin was noted and defined as TT (Fig. 1E). In the same position, the transducer was rotated to 90° and SH and ST, were measured (Figs. 1C, 1F and 1G).

Thereafter, the patients were moved to the operation theatre, and standard monitors were applied. After adequate pre-oxygenation, general anesthesia was induced with propofol (1–2 mg/kg IV), midazolam (0.05 mg/kg IV), fentanyl (0.004 mg/kg IV), and vecuronium (0.1 mg/kg IV). After 3 minutes of mask ventilation, an experienced investigator (≥ 5 years of experience in intubation procedure) performed the laryngoscopy (Macintosh blade size 3 or 4) in the sniffing position. To facilitate laryngeal view, external laryngeal manipulation was allowed, and intubation was attempted. In case of failed attempts, standard protocols were followed as per unanticipated DI guidelines [7]. 'DI' was defined as the placement of the endotracheal tube by using conventional laryngoscopy that required > 2 attempts, lasted > 10 min, or required alternate methods [7]. The 'time taken for intubation' was defined as the time point from initiation of the first direct laryngoscopy attempt to confirmation of successful endotracheal intubation by continuous waveform capnography. The difficult airway cart included intubating stylet (IS), McCoy blade (MB), intubating laryngeal mask airway (ILMA), video laryngoscope (VL), light wand (LW), fiberoptic bronchoscope, and percutaneous cricothyroidotomy. The endpoint of the study was tracheal intubation, based on which all the included patients were categorized as EI or DI.

Clinical airway assessment data and ultrasonography-based data were categorized according to the group for statistical analysis and interpretation. The investigator who performed the ultrasonographic examination was blinded to the preoperative airway assessment data, intubation procedure, and group allocation. Another investigator carried out the preoperative airway assessment, intubation procedure and group allocation, but was blinded to ultrasonographic parameters. Another investigator blinded to study protocols performed the data analysis.

Statistical analysis

The sample size was calculated using the sample size calculator of the University of California, San Francisco, US [8]. Taking an alpha error of 5%, power of 80%, the incidence of unanticipated DI as 5% (a weighted average of data from the literature [1–9.5%]), the sample size was calculated as 1,030 (EI: 978, DI: 52), considering an effect size of 0.8 (estimated from initial pilot observations) for the primary outcome [3,9]. Statistical analysis was performed using MedCalc software version 19.0.7 (Acacialaan, Belgium). The results were presented as descriptive statistics, summarized as mean (SD) or number (percentage). Data were analyzed by logistic regression, receiver operator characteristic (ROC) curve, and Youden index to calculate the diagnostic validity profile of the outcome variables. The continuous variables were compared by unpaired student t-test. The categorical variables were compared by Chi-square test/Fisher's exact test. A $P < 0.05$ was considered significant.

Results

We assessed 1,252 patients for eligibility, of which 1,043 were included in the study (no dropouts). The demographic profile was comparable among the groups (Table 1). In all, 985 patients were classified as EI, as 58 patients as DI (Fig. 2). The EI group had significantly lower MMP grade than the DI group. On direct laryngoscopy, the EI group had a Cormack-Lehane (CL) grade of 1 or 2, while DI group had a CL grade of 2 or 3 with some grade 4 cases as well, which varied significantly on intergroup comparison (Table 1). Further, 802 patients could be intubated in the first attempt, while the remaining required repeat attempts or alternate methods, such as IS+MB in 27 patients, ILMA in 24 patients, VL in 10 patients, and LW in one patient, with success rates of 96.3%, 91.6%, 90%, and 100%, respectively.

The means of the upper airway ultrasonography-based parameters TT, SH, and ST were significantly greater in the DI group than in the EI group ($P < 0.001$, respectively) (Table 2). The VH was 14.4% in the EI group versus 72.4% in the DI group ($P < 0.001$). For validity analysis, an ROC curve was plotted for each ultrasonographic parameter. The optimal criterion for TT to predict DI was found to be > 5.8 cm (sensitivity: 84.5%, specificity: 78.1%) with an area under the curve (AUC) of 0.880. For SH, the optimal value was > 1.4 cm (sensitivity: 81%, specificity: 85.2%), with an AUC of 0.898; for ST, it was > 2.4 cm (sensitivity: 75.9%, specificity: 85.2%), with an AUC of 0.885. The sensitivity and specificity for VH were 72.4% and 85.6%, respectively, with an AUC of 0.790 (Table 2). We also plotted a graph to determine the changes in sensitivity and specificity for each threshold value of TT, SH, and ST. An increase in TT, SH, and ST thresholds led to an increase in the specificity but a decrease in the sensitivity for identifying DI (Fig. 3). The TT, SH, ST, and VH had the accuracies of 78.4%, 85.0%, 84.7%, and 84.9%, respectively. On univariate analysis, the odds ratio (OR) for TT was 1.06, indicating a 6% increase in the log-odds of DI per millimeter increase in TT. Similarly, the ORs for SH, ST, and VH were 1.07, 1.10, and 15.58, re-

https://doi.org/10.4097/kja.20114

Table 1. Characteristics of Included Patients

Variable	Easy intubation (n = 985)	Difficult intubation (n = 58)	P value
Age (yr)	41.2 ± 13.0	39.1 ± 12.9	0.247
Weight (kg)	60.5 ± 12.7	60.0 ± 11.2	0.763
Male	349 (35.4)	15 (25.9)	0.157
MMP			
Grade 1	720 (73.1)	27 (46.5)	< 0.001
Grade 2	265 (26.9)	31(53.4)	< 0.001
CL			
Grade 1	715 (72.6)	-	< 0.001
Grade 2	267 (27.1)	26 (44.8)	< 0.001
Grade 3	3 (0.3)	27 (46.5)	< 0.001
Grade 4	-	5 (8.6)	< 0.001
Number of intubation attempts			
1	802 (81.4)	0	-
2	183 (18.6)	0	-
3	0	54 (93.1)	-
4	0	4 (6.9)	
Average time taken for intubation (s)	54.5 ± 6.3	287.1 ± 20.4	< 0.001

Values are presented as mean ± SD or number (%). MMP: Modified Mallampati, CL: Cormack-Lehane. A P value < 0.05 was considered to be statistically significant.

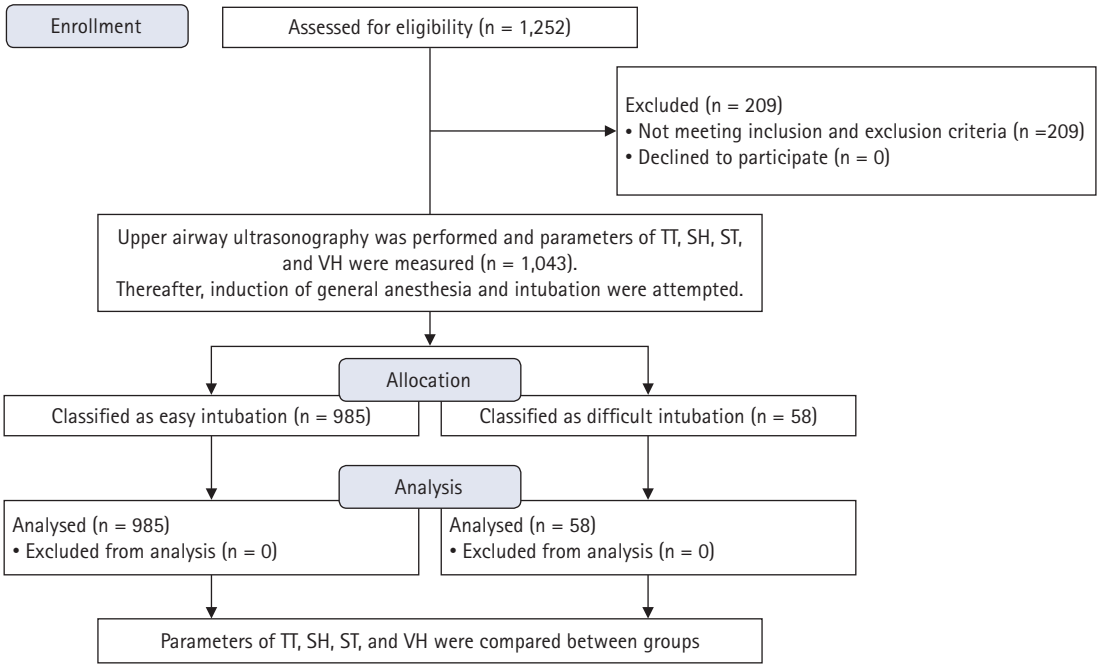

Fig. 2. CONSORT flowchart of patient selection. TT: tongue thickness, SH: anterior neck soft tissue thickness from skin to hyoid bone, ST: anterior neck soft tissue thickness from skin to thyrohyoid membrane, VH: invisibility of hyoid bone.

spectively. A wide CI (8.52, 28.47) was observed for VH, indicating a low level of precision (Table 2). A subgroup analysis was also performed to compare the ultrasonographic parameters in those with CL grade 2 and a similar difference was observed between the ultrasonographic parameters.

The validity of five models based on combined ultrasonography-based parameters was also assessed through multiple logistic regression-derived ROC analysis (Table 3, Fig. 4). 'Model 1', which included all the four ultrasonographic parameters, had the highest accuracy with an AUC of 0.992. 'Model 2', which included TT, SH,

Table 2. Diagnostic Validity Profile of Ultrasonographic Parameters in Predicting Difficult Intubation

Variable	EI (n = 985)	DI (n = 58)	OC	SE	SP	Accuracy % (95% CI)	OR (95% CI)	AUC	P value
TT (cm)	5.6 ± 0.2	6.1 ± 0.3	> 5.8	0.845	0.781	78.4 (75.8, 80.9)	1.06 (1.04, 1.07)	0.88	< 0.001
SH (cm)	1.3 ± 0.2	1.6 ± 0.2	> 1.4	0.81	0.852	85 (82.6, 87.1)	1.07 (1.06, 1.09)	0.898	< 0.001
ST (cm)	2.2 ± 0.2	2.5 ± 0.2	> 2.4	0.759	0.852	84.7 (82.3, 86.8)	1.1 (1.08, 1.12)	0.885	< 0.001
VH	142 (14.4)	42 (72.4)	-	0.724	0.856	84.9 (82.5, 87.0)	15.58 (8.52, 28.47)	0.79	< 0.001

Values are presented as mean ± SD or number (%). EI: easy intubation group, DI: difficult intubation group, OC: optimal criterion, SE: sensitivity, SP: specificity, OR: odds ratio, AUC: area under curve, TT: tongue thickness, SH: anterior neck soft tissue thickness from skin to hyoid bone, ST: anterior neck soft tissue thickness from skin to thyrohyoid membrane, VH: invisibility of hyoid bone. A P value < 0.05 was considered to be statistically significant.

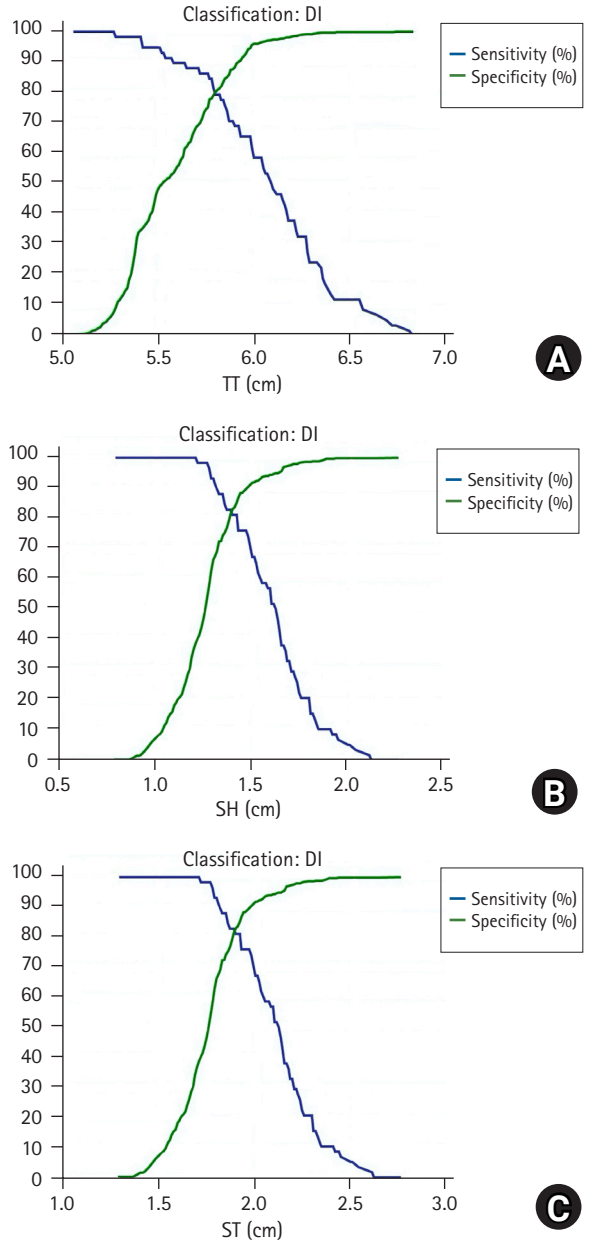

Fig. 3. Sensitivity and specificity profile for predicting difficult intubation at different values of ultrasonographic parameters. (A) tongue thickness (TT), (B) anterior neck soft tissue thickness from skin to hyoid bone (SH), (C) anterior neck soft tissue thickness from skin to thyrohyoid membrane (ST).

and ST, and 'Model 4', with TT, ST, and VH, had an AUC of 0.981. 'Model 3', which included SH, ST, and VH, had an AUC of 0.975. 'Model 5', which included TT, SH, and VH, had an AUC of 0.978. On evaluating the relative contribution of each parameter, VH had the largest OR, though a wide CI was observed for the OR values of VH. ST was the second variable to have a strong impact on the diagnostic validity of the models (Table 3).

Discussion

This study demonstrated the ability of individual upper airway ultrasonography-based parameters and of models using a combination of these paraments in predicting DI. All the upper-airway ultrasonographic parameters varied significantly between the EI and DI groups. The SH parameter had the highest accuracy, while the TT was least accurate in predicting DI. Among the five models, 'Model 1' with all the four ultrasonographic parameters had the highest validity in terms of the AUC.

For optimal viewing of the glottis during direct laryngoscopy, the soft tissues in the neck need to be mobilized adequately. Adhikari et al. [10] evaluated the anterior neck soft tissue thickness at different ultrasonographic planes and observed that ST and SH correlated strongly with difficult laryngoscopy. We used similar levels for predicting DI and obtained a threshold limit of 1.4 cm for SH and 2.4 cm for ST. Wu et al. [11] found an SH cut-off of 1.28 cm while Adhikari et al. [10] obtained an ST limit of 2.8 cm, for predicting difficult laryngoscopy. Yadav et al. [5] reported cut off values of 0.66 and 2.03 cm, respectively, for SH and ST. It appears that different cut-off targets are required for predicting difficult laryngoscopy and intubation. The small sample sizes in the above studies could have attributed to such variation.

Previous studies have correlated increased TT to difficult laryngoscopy [5,6]. However, the measurements varied significantly according to the anatomic level of the ultrasonographic scans. We measured the TT in the mid-sagittal plane to obtain values of the thickest portion of entire tongue contour. The ROC analysis showed that TT > 5.8 cm predicted risk of DI with a sensitivity of

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Table 3. Diagnostic Validity Profile of Different Models in Predicting Difficult Intubation by Combining Ultrasonographic Parameters

Variable	Ultrasonographic parameters	OR (95% CI)	AUC (95% CI)	P value
Model 1	TT	1.06 (1.04, 1.08)	0.992 (0.984, 0.996)	< 0.001
	SH	1.07 (1.04, 1.10)		
	ST	1.11 (1.07, 1.14)		
	VH	21.25 (6.72, 67.20)		
Model 2	TT	1.05 (1.04, 1.07)	0.981 (0.971, 0.988)	< 0.001
	SH	1.07 (1.04, 1.09)		
	ST	1.11 (1.08, 1.14)		
Model 3	SH	1.08 (1.06, 1.10)	0.975 (0.964, 0.984)	< 0.001
	ST	1.10 (1.07, 1.12)		
	VH	23.64 (9.17, 60.10)		
Model 4	TT	1.06 (1.04, 1.08)	0.981 (0.970, 0.988)	< 0.001
	ST	1.11 (1.08, 1.15)		
	VH	18.02 (6.91, 47.03)		
Model 5	TT	1.05 (1.03, 1.06)	0.978 (0.967, 0.986)	< 0.001
	SH	1.07 (1.05, 1.09)		
	VH	21.13 (8.57, 52.09)		

OR: odds ratio, AUC: area under curve, TT: tongue thickness, SH: anterior neck soft tissue thickness from skin to hyoid bone, ST: anterior neck soft tissue thickness from skin to thyrohyoid membrane, VH: invisibility of hyoid bone. A P value < 0.05 was considered to be statistically significant.

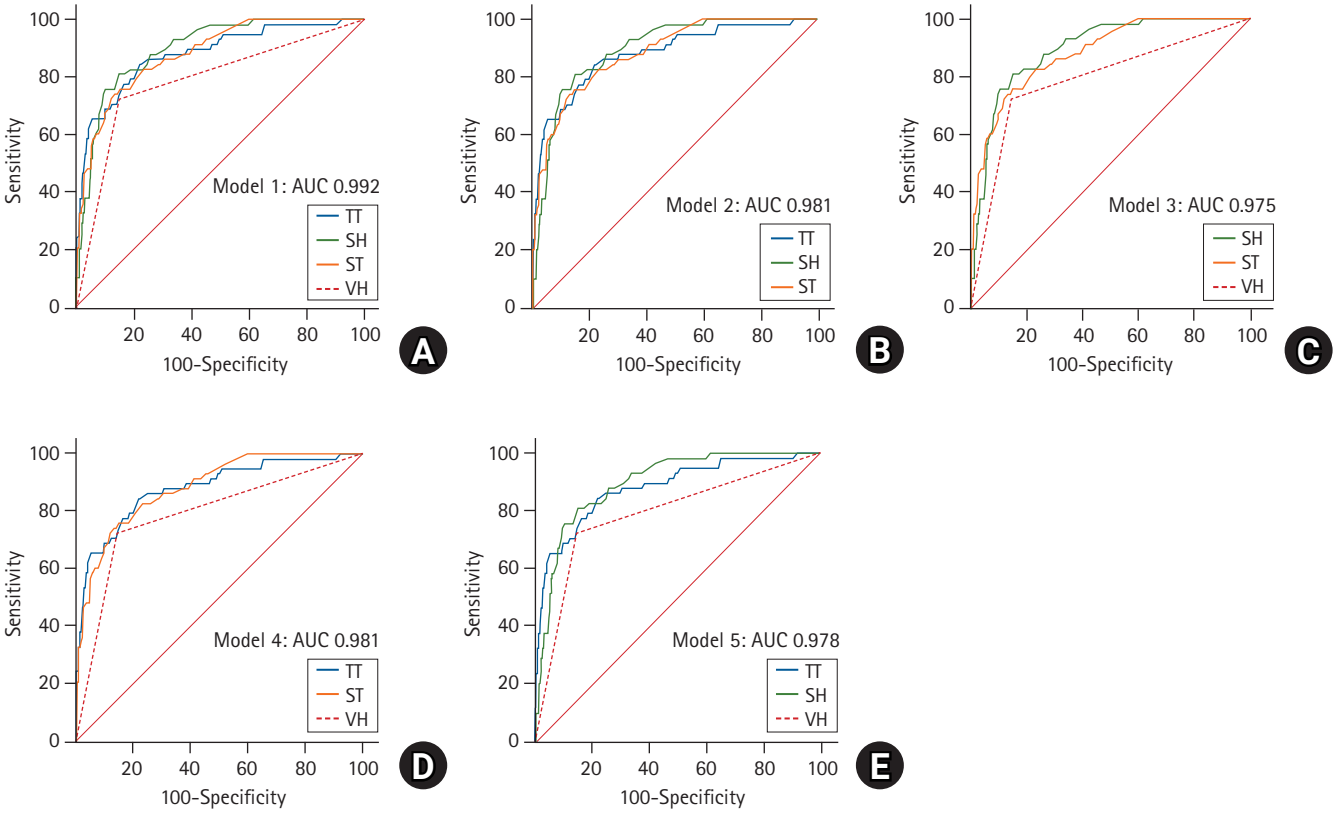

Fig. 4. Receiver operating characteristic curves (A-E) showing the usefulness of combined sonographic models (1-5) in predicting difficult intubation. AUC, area under curve; TT, tongue thickness; SH, anterior neck soft tissue thickness from skin to hyoid bone; ST, anterior neck soft tissue thickness from skin to thyrohyoid membrane; VH, invisibility of hyoid bone.

84.5% and specificity of 78.1%, with a 6% increase in the log-odds of DI per millimeter increase in TT values. Yao and Wang [6] observed that a cut-off value of TT as 6.1 cm predicted DI. The observed variation could be due to a difference in baseline demographics and ethnicities of the studied population. The increased TT also relates to the high MMP grade. Our study had a higher proportion of patients with MMP grade 2 in the DI group (mean TT of 6.1 cm) than in the EI group (mean TT of 5.8 cm). A larger TT is expected to mask the visibility of the faucal pillars, which justifies our results. Though MMP grade 1 or 2 patients are classified as EI, previous studies have shown that it as an inadequate stand-alone test for predicting difficult airway [12]. We excluded the patients with MMP grades 3 and 4 to identify the threshold for those in which difficult airway could not be anticipated by clinical examination. As no clinical predictor is sufficient to predict DI, our results serve to complement the pre-anesthetic work-up in anticipating DI. The CL grades of 1 and 2 are considered easy laryngoscopy, but 26 patients with CL grade 2 were classified as DI in our study. The factors that contributed to DI in these patients included visibility of only the posterior part of the glottis or arytenoid during direct laryngoscopy, deep-seated larynx, or reduced space within the oropharynx [13]. These patients were intubated at the third attempt by IS with MB, ILMA, or VL. Hui and Tsui [4] observed a correlation between VH and difficult laryngoscopy. We observed a similar pattern in the DI group, although VH was also observed in 14% of the EI group. The caudal displacement of the hyoid bone reduced its visibility on ultrasonography probe, possibly because of the hypopharyngeal position of the tongue or short rami of the mandible, which compromises the view of the glottis during direct laryngoscopy [4].

We also analyzed the validity of five different models with different combinations of the studied ultrasonographic parameters. The predictive ability of the combinations was significantly better than that of the individual parameters, as evidenced by an increased AUC (0.975, 0.992). 'Model 1' had the highest AUC (0.992) 'Models 2 and 4' were the next best (AUC 0.981), while the 'Model 3' had the lowest AUC (0.975). Considering the inclusion of three parameters in a single submandibular window, with no need of intraoral probe placement, and an acceptable AUC, 'Model 2' seems to be a viable option. To analyze the individual contribution of each variable in the model, we calculated the OR. Taking into account the wide CI in OR values of VH, indicating a low precision level, ST appears to have a significant impact on the validity of models. A large sample size may, however, efficiently delineate the impact of VH. Future studies can attempt to design a scoring system/formula based on combined ultrasonography-based variables, considering the weightage of each ultrasonographic parameter in predicting DI. This study can serve as the base for such trials.

Our study had several limitations. We only analyzed the anatomic parameters of the airway without taking into account the impact of functional components like head positioning, degree of neck extension, skills of performer, etc. which may alter the difficulties encountered during the intubation procedure. To avoid the associated bias, we standardized all the functional parameters in our study. Patients in the EI and DI groups were distributed unevenly, which may have affected the validity of results, but this was as expected, considering the low incidence of unanticipated DI. We could not randomize the patients, but the investigators were blinded. Thus, we expect that the above limitations did not severely distort the results.

In conclusion, the SH had better accuracy than the remaining three ultrasonographic parameters included in the study. Although the individual parameters showed limited validity, a model combining all the four parameters offered better diagnostic profile than each one of them.

Conflicts of Interest

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

Author Contributions

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https://doi.org/10.4097/kja.20114

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KJA
Korean Journal of Anesthesiology

Validity and reliability of the Korean version of the Quality of Recovery-15 questionnaire

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Clinical Research Article

Korean J Anesthesiol 2021;74(2):142-149
https://doi.org/10.4097/kja.20435
pISSN 2005-6419 • eISSN 2005-7563

Received: August 3, 2020
Revised: September 18, 2020 (1st); October 27, 2020 (2nd)
Accepted: October 27, 2020

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Background: The quality of recovery-40 questionnaire (QoR-40) has been widely used to assess quality of recovery after surgery, but it is too lengthy for clinical use. The short form of QoR-40, QoR-15, has been validated in many languages; however, an official Korean version of the QoR-15 (QoR-15K) has not yet been established. This study aimed to develop and validate QoR-15K.

Methods: Based on the previously-validated Korean QoR-40, we selected 15 items; the QoR-15K was patterned on the original QoR-15. We analyzed 210 subjects who had been scheduled for elective surgery under general anesthesia. The patients completed the questionnaire before surgery and on postoperative days one and two. The validity, reliability, and responsiveness of the QoR-15K were evaluated.

Results: We obtained excellent convergent validity on visual analog scale for recovery (ρ = 0.882, $P < 0.001$). The duration of anesthesia, post-anesthesia care unit, and overall hospital stay with the QoR-15K showed a significant negative correlation (ρ = −0.183, −0.151, and −0.185, respectively). Cronbach's α was 0.909. Cohen's effect size and standardized response mean were 0.819 and 0.721. The recruitment and completion rate were 92.9% and 100%, respectively. We based the above calculations on the results obtained on the first day following surgery.

Conclusions: The validity and reliability of the QoR-15K are comparable to those of the English version. The QoR-15K would be a good instrument to assess the quality of recovery in Korean patients after surgery.

Keywords: Cross-cultural comparison; Health care; Health status; Quality assurance; Quality of life; Surveys and questionnaires; Translation.

Introduction

Postoperative recovery is a complex process affected by various factors, such as patients, surgical methods, and anesthetic characteristics. Such factors may be accompanied by many adverse sequelae. Previous studies evaluating recovery following anesthesia have primarily assessed morbidity, mortality, incidence of anesthesia-related adverse outcomes, and changes in vital signs [1–4]. These parameters are important, but most have neglected the quality of the patients' recovery. Thus, various patient-reported outcome measurement scales and tools have been developed [1,3–8]. As anesthetic and surgical techniques have become safer, the focus has begun to shift to patients' well-being, overall quality of life, and the quality of recovery following anesthesia [9]. One of the most widely used questionnaires is the quality of recovery-40 questionnaire (QoR-40) developed by

Myles et al. [6] in 2000. The QoR-40, which is comprised of 40 items of 5 subscales, has been translated into many languages, including Japanese and Korean [10–12].

Because QoR-40 is considered to be a bit too lengthy for clinical use, a shorter form, called the QoR-15, was created by Stark et al. [4] in 2013. The QoR-15 is a self-rated 15-item questionnaire derived from the QoR-40 that is intended to evaluate the early quality of recovery and the emotional health status of patients following surgery [4,6]. This single-paged QoR-15 has been shown to be highly valid and reliable in patients who have undergone general surgery [4]. The QoR-15 has been validated and translated into many languages, including Danish, Portuguese, Chinese, Swedish, and IsiZulu [13–17]. All translated versions of QoR-15 had sufficient validity and reliability for evaluating the quality of recovery. The QoR-15 was also evaluated following a day of orthopedic surgery [18]. In a systemic review, the QoR-15 was sufficiently valid and reliable in all tested languages [19].

However, an official Korean version of the QoR-15 has not yet been developed or validated, although the Korean QoR-40 has been established. The aim of this study was to develop a Korean version of the QoR-15 (QoR-15K) and to evaluate its validity, reliability, and responsiveness for Korean patients who receive general anesthesia. The authors hypothesized that the QoR-15K would have a similar validity, reliability, and responsiveness as the original English version. This could mean that the quality of healthcare could be promoted by easily assessing the quality of recovery for Korean patients.

Materials and Methods

Patients

The Institutional Review Board of our hospital approved the clinical protocol for this study. Written informed consent was obtained from all participating patients (IRB No: 2017-05-024-003). From January 2018 to August 2018, we enrolled 226 patients who had been admitted for scheduled elective surgery under general anesthesia. All procedures involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments.

The sample size was determined from the guidance of a study validating a questionnaire. This is set at 10–20 times the number of items on the questionnaire [14]. Because the QoR-15K has 15 items, we multiplied it by 15, and we obtained 225 as the sample size.

Patients were enrolled if they were able to read and write the Korean language and had been admitted to the hospital for at least one preoperative night and three days following surgery. Those with cognitive impairment, less than 18 years or greater than 80 years of age, or American Society of Anesthesiologists (ASA) physical status IV or above were excluded from the study. Patients with a history of alcohol or any other substance abuse and those who refused to participate in this study were also excluded. Those who had major postoperative complications were also eliminated. Age, gender, educational and marital status, height, and weight were recorded on the day before surgery. The duration of anesthesia and surgery, as well as the length of the post-anesthesia care unit (PACU) and hospital stay, were collected prospectively following discharge. The demographic data are presented in Table 1.

Development of QoR-15K

This study process was preauthorized by the original author of the English QoR-15. The QoR-15 is composed of 15 items in 5 subscales: physical comfort (n = 5, question number 1–4, 13), emotional status (n = 4, question number 9, 10), psychological

Table 1. Demographic Data of the Patients (n = 210)

	Value
Age (yr)	47.4 ± 11.9
Gender	
M	88 (41.9)
F	122 (58.1)
ASA PS (I/II/III)	139/65/6
Weight (kg)	65.9 ± 13.3
Height (cm)	162.7 ± 8.4
BMI (kg/m^2)	24.8 ± 3.8
Education	
High school	23 (11.0)
College	187 (89.0)
Marital status	
Married	182 (86.7)
Single	28 (13.3)
Type or Surgery	
General	97 (46.2)
Gynecologic	46 (21.9)
Orthopedic	37 (17.6)
Otorhinolaryngologic	25 (11.9)
Others	5 (2.4)
Duration of anesthesia (min)	124.4 ± 54.1
Duration of surgery (min)	87.4 ± 50.5
PACU stay (min)	67.1 ± 22.0
Duration of admission (day)	7.0 ± 3.5

Values are presented as mean ± SD or number of patients (%). ASA PS: American Society of Anesthesiologists physical status, BMI: body mass index, PACU: post-anesthesia care unit.

support (n = 2, question number 6, 7), physical independence (n = 2, question number 5, 8), and pain (n = 2, question number 11, 12). In our previous study, we translated QoR-40 into the Korean language and developed the Korean version of QoR-40 (QoR-40K) via a translation procedure based on Beaton's and Bullinger's recommendations [11,20]. In short, two bilingual translators translated the QoR-40 into the Korean language. After reaching consensus, based on the consistency and adequacy of the meaning, backward translation into English was performed by a native English-speaking medical doctor and a linguistic specialist. An expert committee, consisting of a psychologist, a general surgeon, an anesthesiologist, and translators agreed upon the final Korean version of QoR–40. Based on translated and validated QoR-40K, the 15 items from 5 domains established by Stark et al. were selected for the development of QoR-15K [4].

The QoR-15K items are scored on an 11-point Likert scale ranging from 0 to 10. Depending on the questions, the best answers can be 10 or 0. For the positive questions, the best answers were scored 10, but they were scored 0 for the negative items. The global QoR-15K score has been derived from the summation of all items that range from 0 to 150. Higher scores indicate a better quality of recovery. The QoR-15K is presented in Appendix 1.

Investigation

Previously, the QoR-40K was evaluated in 200 selected Korean patients who had undergone surgery under general anesthesia in 2017. The results showed that all items of the QoR-40K had acceptable validity, reliability, and feasibility for assessing the quality of recovery [11]. These results were used as a pilot study, and the QoR-15K, consisting of 15 questions selected from QoR-40K, was completed.

The QoR-15K was evaluated a day before surgery and on the first and second day, following surgery by one of the authors of this study. Patients were asked to complete the QoR-15K and a 100-mm visual analog scale for recovery (VAS). VAS ranges from 0 to 100 mm, which indicates poor recovery to excellent recovery. Because there is no gold standard of measurement for postoperative recovery, the VAS was chosen for measuring criteria validity and was used as a standard control. Demographic data such as age, sex, height, weight, education level, marital status, and underlying medical condition were collected preoperatively. After the surgery, we recorded the duration of anesthesia and operation time, as well as the length of the PACU stays. We also recorded the grade classification of the procedure following surgery. All the surgeries in this study were classified as minor, intermediate, or major by the grade of surgery according to the nature of the surgical procedure, the expected duration, and the expected degree of inflammatory response using the surgical outcome risk tool (SORT) [21]. When the patient was discharged from the hospital, we noted the number of hospital days. On the first and the second postoperative days, patients were asked to complete the 100-mm VAS for recovery and the QoR-15K.

Psychometric evaluation of the QoR-15K

Validity was assessed for the accuracy of the QoR-15K. For convergent validity, we compared QoR-15K and VAS scores for recovery. Interdimensional correlations for QoR-15K were measured. We measured the associations between the QoR-15K with age, sex, duration of anesthesia, duration of stay in the PACU, and hospital stay to ascertain the construct validity of our hypothesis that they would have a negative correlation. We also measured the global QoR-15K score according to the grade to surgery. Discriminant validity showed that patients with complications and poor recovery would have a lower QoR-15K score.

Reliability indicates the consistency of QoR-15K. Reliability was assessed by internal consistency. For internal consistency, each item of QoR-15K and its own dimensions were measured by Cronbach's α.

The clinical feasibility of QoR-15K was evaluated in terms of completion and recruitment rate. The time to complete the questionnaire was measured for some randomly selected patients. Responsiveness describes the ability to detect clinically important changes. We measured responsiveness with standardized response mean (SRM) and Cohen's effect size. The SRM shows how the mean of the QoR-15K scores changed in terms of the change in the QoR-15K scores' standard deviation (SD). Cohen's effect size is the average score change divided by the SD of the pretest score. The results were calculated based on the results of the first day following surgery.

Statistical analysis

Data are presented as mean ± SD and number (%). Associations were measured using Spearman's correlation coefficient (ρ). All statistical analyses were performed using SPSS Statistics for Windows, version 25 (IBM Corp., USA). Values were considered statistically significant when $P < 0.05$.

Results

Among the 226 enrolled patients, one patient canceled operation, another patient underwent regional anesthesia, and 14 pa-

https://doi.org/10.4097/kja.20435

tients were discharged early within two days following surgery. Finally, 210 patients were included and completed the questionnaire. Surgery and anesthesia were conducted at a single medical center. Most of the surgeries were general, gynecologic, orthopedic, and otorhinolaryngologic surgeries. There was no patient who refused the questionnaire. Thus, the recruitment rate was 93%, and the completion rate among the recruited patients was 100%. The patients who fully completed the questionnaires as above were statistically analyzed for validity, reliability, and responsiveness. On the first day following surgery, we randomly selected 30 patients to measure the time it took them to complete QoR-15K questionnaire. Most patients were able to complete the questionnaire without any difficulty in less than 3 minutes.

The postoperative day-one QoR-15K score was decreased to 120.08 ± 24.74 as compared to the preoperative QoR-15K score of 136.35 ± 13.32 ($P < 0.001$). The QoR-15K score two days following surgery was increased to 121.80 ± 23.58 ($P < 0.001$). The baseline and postoperative scores showed significant differences. Thus, these results indicate excellent responsiveness. Changes in the preoperative and postoperative QoR-15K and responsiveness are presented in Table 2. Cohen's effect size and SRM between preoperative and postoperative QoR-15K was 0.82 and 0.71, where 0.2 indicated a small, 0.5 a moderate, and 0.8 or more indicated a large effect of the intervention for both the Cohen's effect size and the SRM [22]. The results described above were calculated based upon the results on the first day following surgery.

To assess convergent validity, we evaluated the correlation between the QoR-15K and the VAS for recovery. The spearman's ρ was 0.882 on the first day following surgery ($P < 0.001$), showing excellent validity. Each domain of QoR-15K also correlated well with VAS, from 0.65 to 0.75 ($P < 0.001$). The correlations of VAS and each subclass of QoR-15K are described in Table 3.

We evaluated the correlations of construct validity between the QoR-15K and clinical characteristics such as duration of anesthesia, duration in the PACU and hospital stays, etc. There were significant negative correlations between the global QoR-15K and the duration of anesthesia, duration of surgery, duration in the PACU, and hospital stays on the first and second postoperative days. For the first day, those spearman's correlation coefficients were −0.183, −0.177, −0.151 and −0.185, respectively ($P < 0.01$). The BMI and weight were also weakly correlated with the QoR-15K on the first postoperative day ($P < 0.05$).

Reliability was evaluated by Cronbach α for internal consistency. The postoperative Cronbach α was high enough to reach 0.909 on the first operative day and 0.905 on the second operative day, where the recommended reliable value for these tests is more than 0.7 [23]. The median item-to-own dimension, the Cronbach α and the Spearmann's correlation coefficient (ρ) for each dimen-

Table 2. Change in QoR-15K of Patients the Day before Surgery (Preoperative), the First and Second Day Following Surgery (Postoperative)

Score	Max score	Preoperative	Postoperative day 1	Postoperative day 2	% Change from baseline	P value	Cohen's Effect size	SRM
Global QoR-15K	150	136.4 ± 13.3	120.1 ± 24.7	121.8 ± 23.6	11.9	< 0.001	0.82	0.723
Physical comfort	50	46.3 ± 5.4	41.1 ± 8.9	41.5 ± 8.7	11.2	< 0.001	0.70	0.629
Emotional state	40	34.1 ± 6.4	32.8 ± 7.7	33.4 ± 7.2	3.8	0.012	0.19	0.170
Psychological support	20	19.0 ± 1.7	17.8 ± 3.3	17.9 ± 3.1	6.5	< 0.001	0.47	0.377
Physical independence	20	18.5 ± 2.7	14.7 ± 5.2	15.1 ± 5.1	20.3	< 0.001	0.91	0.734
Pain	20	18.5 ± 2.6	13.7 ± 4.8	14.0 ± 4.6	25.9	< 0.001	1.24	0.937

Values are presented as mean ± SD. SRM, Cohen's effect size, and percent change from baseline were calculated, based on the postoperative QoR-15K score done on the first day following surgery. QoR-15K: Korean version of quality of recovery-15 questionnaire, SRM: standardized response mean (mean change/SD).

Table 3. Correlation between the VAS and the QoR-15K

Postoperative day 1			Postoperative day 2		
Scores	ρ	P value	Scores	ρ	P value
QoR-15K	0.882	< 0.001	QoR-15K	0.824	< 0.001
Physical comfort	0.685	< 0.001	Physical Comfort	0.731	< 0.001
Emotional state	0.746	< 0.001	Emotional State	0.607	< 0.001
Psychological support	0.743	< 0.001	Psychological support	0.628	< 0.001
Physical independence	0.653	< 0.001	Physical Independence	0.593	0.001
Pain	0.659	< 0.001	Pain	0.482	0.007

Correlations are measured with Spearmann's correlation coefficient (ρ). QoR-15K: Korean version of quality of recovery-15 questionnaire, VAS: visual analog scale for recovery.

Table 4. Interdimensional Correlation for the QoR-15K

	Global QoR-15K	Physical comfort	Emotional state	Psychological support	Physical independence	Pain
Physical comfort	0.878	-				
Emotional state	0.895	0.725	-			
Psychological support	0.605	0.541	0.518	-		
Physical independence	0.824	0.673	0.668	0.525	-	
Pain	0.770	0.547	0.646	0.363	0.540	-

Interdimentional correlation was measured by Spearmann's correlation coefficient (ρ). QoR-15K: Korean version of quality of recovery-15 questionnaire. Interdimensional Cronbach α = 0.909.

Table 5. Cronbach α for Preoperative and Postoperative QoR-15K

Dimension	Preoperative	Postoperative day 1	Postoperative day 2
Global QoR-15K	0.847	0.909	0.905
Physical comfort	0.807	0.765	0.766
Emotional state	0.819	0.816	0.795
Psychological support	0.363	0.613	0.643
Physical independence	0.734	0.679	0.675
Pain	0.709	0.830	0.802

Reliability was measured by Cronbach α. QoR-15K: Korean version of quality of recovery-15 questionnaire.

sion were: physical comfort (α = 0.765, ρ = 0.878), emotional state (α = 0.816, ρ = 0.895), psychological support (α = 0.613, ρ = 0.605), physical independence (α = 0.679, ρ = 0.824) and pain (α = 0.830, ρ = 0.770). The interdimensional correlation of each dimension is presented in Tables 4 and 5.

When we measured the QoR-15 scores by sex, there was no difference between men's and women's scores (134.4 ± 13.9 vs. 136.6 ± 13.3, P = 0.457) before surgery. But a negative correlation was found that female patient scores were a bit lower than male patients' scores postoperatively (124.1 ± 18.6 vs. 117.2 ± 28.1, P = 0.033). This may come from emotional state factors (34.28 ± 6.1 vs. 31.8 ± 8.5, P = 0.013). For the comparisons of ASA physical status, the QoR-15K of ASA III was significantly lower than that of ASA I or II (ASA I: 137.4 ± 13.3 vs. ASA II: 135.1 ± 12.6 vs. ASA III: 126.3 ± 17.8, P = 0.043). No difference was found between education levels (college 120.5 ± 25.0 vs. high school 116.3 ± 22.8, P = 0.420). Patients having major surgery had significantly lower QoR-15K scores than did patients having minor or intermediate surgery (minor 121.2 ± 22.6 vs. intermediate 121.5 ± 27.6 vs. major 114.0 ± 19.8, P = 0.013). The comparisons of the QoR-15K and the grade of surgery are presented in Table 6. Floor or Ceiling effects are generally considered to be present if more than 15% of the subjects had achieved the lowest or the highest possible score, but the effects were not observed in this study [24].

Discussion

The overall result of this study indicates that QoR-15K would be a valid, reliable, and easy-to-use tool for evaluating the quality of postoperative recovery following general anesthesia in the Korean population. The QoR-15K preserves the acceptability of the original English QoR-15 and is as suitable for evaluating the quality of recovery following general anesthesia for Korean patients, as are other translations [4,13–18].

Unlike the QoR-40K, the Qor-15K is a single-page form with an 11-point Likert scale. Most patients can complete the questionnaire without any problem in fewer than 3 minutes. This indicates that QoR-15K is acceptably feasible to use, although measuring time to complete the questionnaire was not recorded for all patients. This scale can be a useful tool in busy clinical circumstances. The fact that there was no floor or ceiling effect also indicates that its feasibility for use is fairly good. A high completion rate and recruitment rate also explain its suitability because nonresponse reflects poor recovery or low score QoR-15K [19].

Although there is no gold standard for quality of recovery, we compared the QoR-15K with the VAS for recovery to evaluate its convergent validity. Convergent validity showed a correlation coefficient between the QoR-15 score and VAS exceeds the published recommendation (correlation > 0.60), which was similar to the coefficient in the original study [4,23]. Without psychometric assessment, the use of a VAS as a criterion may result in a defective scale because it is an imperfect scale that overlooks the individual components of recovery and is prone to over-rating. As there is no absolute criterion for evaluating the quality of recovery, VAS was used as an alternative for assessing recovery as it had been in the original study [4,11]. The QoR-40 cannot be used as a

https://doi.org/10.4097/kja.20435

Table 6. The Comparisons of QoR-15K and the Grade of Surgery

Grade of surgery	Numbers	Preoperative	Postoperative day 1	Postoperative day 2
Minor*	74	138.0 ± 11.1	121.2 ± 22.6	122.9 ± 21.0
Intermediate†	99	138.2 ± 13.7	121.5 ± 27.6	122.9 ± 26.7
Major‡	37	128.0 ± 13.6	114.1 ± 19.8	116.5 ± 19.0

Values are presented as mean ± SD or number of patients. QoR-15K: Korean version of quality of recovery-15 questionnaire. *Minor surgery: endoscopic sinus surgery, tonsillectomy, septorhinoplasty, parotidectomy, tympanoplasty, minor mass excision, therapeutic hysteroscopic procedure, incontinence surgery, hand surgery, thyroidectomy, hardware removal, or biopsy. †Intermediate surgery: laparoscopic abdominal surgery, laparoscopic cholecystectomy, wide mass excision, laparoscopic herniorrhaphy, pelviscopic surgery, surgery of the elbow, shoulder, or knee surgery. ‡Major surgery: open or laparoscopic gastrectomy, colorectal surgery, liver surgery, open hysterectomy, spine surgery, total hip replacement.

standard since the QoR-15 is a short form of the QoR-40, which shares all the items of the QoR-15. In our previous study, the QoR-40K scores correlated with the VAS for pain, but we utilized VAS for recovery, as did the original QoR-15 study [4,11]. The relationship between the VAS for recovery and the QoR-15K has well been correlated, indicating that QoR-15K has a good convergent validity in this study.

For construct validity, the QoR-15K was negatively correlated with duration of anesthesia, surgery time, duration in PACU, and hospital stay. Spearman correlation coefficients of surgery time, duration in PACU and hospital stay are $\rho = -0.177$ (P = 0.007), $\rho = -0.151$ (P = 0.020) and $\rho = -0.185$ (P = 0.007). Those items were as significantly correlated as were those in our previous QoR-40K study [11].

Validity was also determined by comparing patients who had minor, intermediate, and major surgery. Although there was no difference between minor and intermediate surgery, there was a significant decreased QoR-15K score in major surgery as compared to minor or intermediate surgery [19]. Those who had a more aggressive surgery would present with a lower QoR-15K score. Moreover, patients who are a higher ASA physical status had lower QoR-15K scores. Women had lower QoR-15K scores, with a weak correlation (P = 0.033). These results had their origin from their physical comfort and emotional state. It is quite understandable that women would tend to be more susceptible to situations that evoked emotional stress [11]. There was no relation between QoR-15K with age, education, or marital status. These results correlate well with previous studies involving the original English QoR-15 [13].

The QoR-15K was found to have excellent reliability, as did all versions of QoR-15. The Cronbach α was 0.90, which exceeded the recommended criterion, above 0.7 [23]. Internal consistency was measured using a median correlation between items within each dimension, and it was established by an interdimensional correlation ($\rho = 0.605$–0.895, P < 0.001). These results were enough to conclude that the QoR-15K possesses adequate reliability.

The responsiveness of the QoR-15K was assessed using Cohen's effect size and the SRM. Both of them are expressed in standardized units, assuming that 0.2 is considered to be small and 0.8 or greater is considered to be large [25]. The SRM of the overall QoR-15K was 0.72, which indicates a moderate ability to detect change. As the previous studies mentioned, East Asians may recover earlier from an emotional state than those of other cultural backgrounds, or different testing time may result in a relatively lower SRM. This result was consistent with our previous study of the QoR-40K [11]. Cohen's effect size for global QoR-15K was 0.82, which exceeds the level for a large effect, 0.8 [25]. These results demonstrate that the QoR-15K would have acceptable responsiveness. Thus, these values can be considered to be a suitable outcome for clinical trials. Responsiveness is known to be the most important psychometric index for evaluative instruments to measure changes in health outcomes [26].

This study had several limitations. First, test-retest reliability was not conducted in this study, which can be a drawback. However, the lapse between assessments for test-retest was not clearly known. In our study, the results of the first day and the second day following surgery are similar, and the result of the second day does not reach the baseline. This means that the patients had not completely recovered during the study period. The authors mainly focused on acute recovery, which is considered to be up to two days after surgery. Moreover, we had conducted the test-retest assessment in our previous QoR-40K validation [11]. To find out what the recovery period may be, investigators should consider the timing of the postoperative QoR-15K assessment should be. Second, this study was conducted in a single hospital center. Thus, the result of our study may be restricted when applying them to all populations in various settings. Despite the limitation, this study shows validation of the Korean version of QoR-15, a shorter form of QoR-40K. Further studies would facilitate the use of the QoR-15K, which is a cultural adaptation of the translated QoR-15.

In conclusion, QoR-15K has acceptable validity, reliability, feasibility, and responsiveness for assessing the quality of recovery

following general anesthesia. The QoR-15K is a single-paged, easy-to-use tool for assessing the quality of recovery, as is the original English QoR-15. The QoR-15K would be a good instrument to assess the quality of recovery in Korean patients after surgery.

Acknowledgements

We thank Dr. Paul Myles for allowing us to translate and utilize the QoR-15.

Conflicts of Interest

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

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https://doi.org/10.4097/kja.20435

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KJA
Korean Journal of Anesthesiology

Effect of preoperative dexmedetomidine nebulization on the hemodynamic response to laryngoscopy and intubation: a randomized control trial

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Clinical Research Article

Korean J Anesthesiol 2021;74(2):150-157
https://doi.org/10.4097/kja.20153
pISSN 2005-6419 • eISSN 2005-7563

Received: April 7, 2020
Revised: May 18, 2020 (1st); May 19, 2020 (2nd)
Accepted: May 20, 2020

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Background: Dexmedetomidine, an alpha-2 agonist, has been used for attenuation of hemodynamic response to laryngoscopy but not through the nebulized route. We evaluated the effects of preoperative dexmedetomidine nebulization on the hemodynamic response to laryngoscopy and intubation and examined the intraoperative anesthetic-analgesic requirements and recovery outcomes.

Methods: Overall, 120 American Society of Anesthesiologists I & II adult patients (of either gender) undergoing elective surgeries and requiring tracheal intubation, were randomized to receive nebulized dexmedetomidine (1 μg/kg in 3–4 ml of 0.9% saline) or 0.9% saline (3–4 ml), 30 min before anesthesia induction. Heart rate (HR) and non-invasive systolic blood pressure (SBP) were monitored for 10 min following laryngoscopy.

Results: After laryngoscopy, linear mixed effect modelling showed significantly lower trend of increase in HR in the dexmedetomidine group versus saline (P = 0.012); however, there was no difference in the SBP changes between the two groups (P = 0.904). Induction dose of propofol (P < 0.001), intraoperative fentanyl consumption (P = 0.007), and isoflurane requirements (P = 0.013) were significantly lower in the dexmedetomidine group. There was no difference in the 2 h incidence of postoperative nausea and vomiting (PONV) (P = 0.612) or sore-throat (P = 0.741).

Conclusions: Nebulized dexmedetomidine at 1 μg/kg attenuated the increase in HR but not SBP following laryngoscopy and reduced the intraoperative anesthetic and analgesic consumption. There was no effect on early PONV, sore-throat, or increase in incidence of adverse effects. Nebulized dexmedetomidine may represent a favorable alternative to the intravenous route in short duration surgeries.

Keywords: Dexmedetomidine; Hemodynamics; Inhalation; Intravenous anesthetics; Intubation; Laryngoscopy.

Introduction

Direct laryngoscopy and tracheal intubation following induction of anesthesia are associated with hemodynamic changes due to increased sympathoadrenal activity, which may result in hypertension and/or tachycardia [1,2]. Although transient, this exaggerated response may precipitate hypertensive crises, myocardial ischemia, arrhythmias, or increases in intracranial pressure in susceptible individuals [1]. Various drugs—including

local anesthetics, beta-blockers, calcium channel blockers, and narcotic analgesics—have been tried to blunt the laryngoscopy and intubation response, with varied success [3–9].

Dexmedetomidine is a potent and highly selective alpha-2 receptor agonist with sympatholytic, sedative, amnestic, and analgesic properties [10]. Its pleiotropic effects have led to its increasing use for reducing anesthetic and analgesic requirements in the perioperative period [10]. The efficacy of dexmedetomidine in decreasing the hemodynamic response to laryngoscopy and intubation has been studied through intravenous [11–15], intranasal [16,17], and intramuscular routes [18]. However, intravenous administration may cause bradycardia and hypotension, and intranasal administration may be associated with irritation [19].

Nebulized dexmedetomidine, administered in doses of 1 and 2 μg/kg has been found to be an effective premedication in pediatric patients [19,20]. Nebulized dexmedetomidine may offer an attractive alternative to both intravenous as well as intranasal routes of administration because drug deposition following nebulization takes place over nasal, buccal, as well as respiratory mucosa [19,20]. To the best of our knowledge, there are no studies demonstrating the effects of nebulized dexmedetomidine on the hemodynamic response to laryngoscopy and intubation.

Thus, the primary aim of this study was to evaluate the effects of preoperative dexmedetomidine nebulization (1 μg/kg) on the heart rate (HR) response to laryngoscopy and intubation in adult patients. The secondary aims were to evaluate the effects of nebulized dexmedetomidine on the systolic blood pressure (SBP) response following laryngoscopy and intubation, intraoperative anesthetic and analgesic consumption, time to extubation, and the 2-h incidence of postoperative nausea and vomiting (PONV) and sore throat.

Materials and Methods

Study design

The study was designed as a randomized, double-blinded, placebo-controlled, parallel arm clinical trial.

Study participants

The study subjects were adult patients (18–60 year) of either gender who were classified as American Society of Anesthesiologists grade I or II. All subjects were scheduled for elective short-duration, non-cardiac, non-neurosurgical operations requiring general anesthesia and tracheal intubation.

Study approval and trial registration

The Institutional Ethics Committee approved the study (T/IMNF/Anaesth/18/44), and written informed consent was obtained from each participant. The study was registered prospectively in the Clinical Trials Registry of India (CTRI) (trial registration number: CTRI/2019/01/017060, trial registration date: 14/01/2019, Principal Investigator: Dr. Satyajeet Misra). This clinical research was done following the ethical principles for medical research involving human subjects in accordance with the Helsinki Declaration 2013.

Exclusion criteria

We excluded from the study patients undergoing emergency surgeries, obese individuals (body mass index > 30 kg/m^2), patients with known or unanticipated difficult intubation and those requiring more than 15 s or two attempts at laryngoscopy, patients with heart rhythms other than sinus, patients with known allergy to dexmedetomidine, and those on anti-hypertensive medications or preoperative drugs that could be potential confounders (clonidine, gabapentin, pregabalin, steroids).

Randomization and allocation concealment

Patients were assigned to two equal groups by generating randomization codes using a simple randomization software.

Group 1 (saline) patients received 0.9% saline nebulization (3–4 ml), 30 min before induction of anesthesia.

Group 2 (dexmedetomidine) patients received 1 μg/kg dexmedetomidine nebulization diluted in 3–4 ml of 0.9% saline, 30 min before induction of anesthesia.

Allocation concealment was achieved with the use of sealed opaque envelopes that were opened once patients were received in the preoperative holding area on the day of surgery.

Nebulization procedure

The drugs for nebulization (saline or dexmedetomidine) were prepared and administered by an independent investigator in the preoperative holding area. Nebulization was carried out with an electrical compressor nebulizer (Eco Smart, Saify Healthcare and Medi Devices, India), capable of creating a fine mist, until the entire volume was dispersed–usually within 15–20 min. Nebulization was stopped when there was no further mist on tapping the volume chamber. The investigator oversaw the entire nebulization procedure and—while taking no further part in the study—was

authorized to intervene if a patient developed bradycardia or experienced increased sedation or decreases in peripheral oxygen saturation. In such an event, the nebulization was to be stopped and the patient treated accordingly.

Anesthesia protocol

After premedication with 4 mg intravenous ondansetron, 1 mg midazolam, and 2 μg/kg fentanyl. induction of anesthesia was carried out with 10 mg bolus aliquots of propofol titrated to loss of verbal response. After achieving adequate bag mask ventilation, the patient was paralyzed with an intubating dose of inj. vecuronium bromide (0.15 mg/kg). Depth of anesthesia was achieved with isoflurane in 50% air-oxygen mixture to maintain bi-spectral index (BIS; BIS Quatro, Covidien, USA) of 50–60; BIS sensors were applied before anesthesia induction. Ventilation was adjusted to maintain end-tidal carbon-dioxide at 32–35 mmHg.

Administration of additional doses of fentanyl were to be given if an increase in HR and/or SBP greater than 20% of the pre-induction baseline occurred during the surgery. Fluids were administered according to the orders of the attending physician.

The investigators who carried out the laryngoscopy and intubation each have more than 10 years of experience in anesthetic practice. Increases in blood pressure (BP) in the 10-min interval following laryngoscopy and intubation were treated with small aliquots of propofol (20–30 mg), while decreases in BP and HR were treated with inj. ephedrine (6 mg) and inj. atropine (0.6 mg), respectively.

Following surgery, neuromuscular blockade was antagonized with inj. neostigmine (0.05 mg/kg) and inj. glycopyrrolate (0.02 mg/kg). The trachea was extubated once the patient was able to follow verbal commands. Patients were kept in the postoperative care unit for an additional 3 h and discharged to the ward once they met the criteria for discharge.

Primary aim and outcome parameters

The primary aim was to study the HR changes following laryngoscopy and intubation in the two groups and, accordingly, HR was measured at various time points: before administration of nebulization, after nebulization but before induction (baseline), and at every 1-min interval until 10 min after laryngoscopy.

Secondary aims and outcome parameters

The secondary aim was to study the non-invasive SBP changes following laryngoscopy and intubation, intraoperative anesthetic and analgesic consumption, time to extubation, and the 2-h incidence of PONV and sore-throat. BP measurements were performed at the same time points as the HR. The induction dose of propofol, total dose of intraoperative fentanyl and mean minimum alveolar concentration (MAC) of isoflurane were recorded for each patient. The response to skin incision was noted and recorded as a binary 'yes/no response' (no, if < 20% changes in HR and/or SBP; yes, if > 20% changes in HR and/or SBP). If a positive response to skin incision was present, inj. fentanyl (1 μg/kg) was repeated. The time to extubation in minutes (from administration of neostigmine to removal of the tracheal tube) was noted in both the groups. The peripheral oxygen saturation and sedation scores (modified observer's assessment of alertness/sedation scale) [21] were also recorded before and after nebulization for each patient.

PONV (subjective feeling of the urge to vomit or retching and/or vomiting) was assessed at 2 h after surgery. Similarly, postoperative sore-throat (subjective feeling of irritation, discomfort or lump or pain in throat) was evaluated at 2 h after surgery, when patients would have recovered from the effects of anesthetic agents. Both of these effects were recorded as present or absent, but their severity was not assessed. All the outcome parameters were recorded by the investigator(s) in charge of the case.

Sample size calculation

Assuming that there would be a 20% difference in the maximum HR between the two groups following laryngoscopy, 50 patients in each group were required to power the study to 80% to detect the difference with an alpha error of 5% (two-tailed). The assumed pooled standard deviation was 35. Accounting for 20% drop-outs after recruitment (unanticipated difficult intubation; laryngoscopy requiring more than 15 seconds or two attempts; protocol violation), we aimed to recruit 120 patients for the study. Continuous variables were expressed as means ± SD, and categorical variables were expressed as proportions. Linear mixed effect modelling was performed to test the difference in the trend of repeated measures; i.e., HR and SBP. The difference in continuous variables were analyzed with independent t-test, and categorical variables were tested with the Chi-square test or the Fisher's exact test, as appropriate. Statistical analyses were performed with R 3.5 (R foundation, Austria).

Results

A total of 120 patients were enrolled in the study over a one-year period (study start date: January 1, 2019; end date: January 9,

https://doi.org/10.4097/kja.20153

2020; Fig. 1, consort diagram). We did not encounter any attrition (drop-out) after patient enrollment due to unanticipated difficult intubation, repeated or prolonged laryngoscopy or protocol violation. Patient demographics are presented in Table 1. Surgeries were mostly short duration, approximately 2–3 h (modified radical mastectomies, laparoscopic cholecystectomies, ileostomy closures, laparoscopic hysterectomies, etc.).

Following nebulization, there were no differences in the pre-induction hemodynamics or sedation scores between the two groups. After laryngoscopy and intubation, linear mixed effect modelling showed a significantly lower trend of increase in HR in the dexmedetomidine group versus the saline group (P = 0.012, Fig. 2). However, there was no significant difference in the SBP response between the two groups (P = 0.904, Fig. 3). The induction dose of propofol, consumption of intraoperative fentanyl, and the mean isoflurane requirements were significantly less in the dexmedetomidine group versus the saline group (Table 2). Similarly, there was a significant difference in the skin incision response, with a more positive response to skin incision seen in the saline group (Table 2). There was no difference in the time to extubation, incidence of PONV, or sore-throat between the two groups (Table 2). There were no adverse events related to dexmedetomidine nebulization, such as intra- or postoperative bradycardia and hypotension.

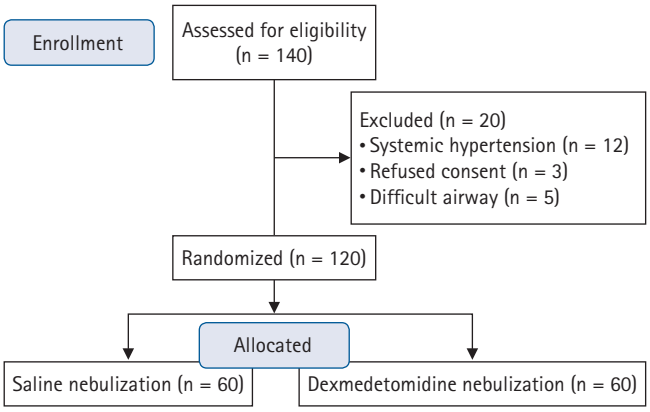

Fig. 1. CONSORT flow diagram.

Discussion

We found a significant effect of preoperative dexmedetomidine nebulization (1 μg/kg) versus saline treatment on the HR responses following laryngoscopy and intubation. Preoperative dexmedetomidine nebulization was also effective in reducing the intraop-

Table 1. Patient Demographics

Parameter	Saline group (n = 60)	Dexmedetomidine group (n = 60)
Age (yr)	40.6 ± 12.0	37.7 ± 10.5
Weight (kg)	59.1 ± 10.8	58.0 ± 9.6
ASA (I/II)	38/22	36/24
Sex (M/F)	35/25	37/23
Duration of surgery (min)	142.5 ± 67.4	123.0 ± 66.4

Values are presented as mean ± SD or number of patients. ASA: American Society of Anesthesiologists.

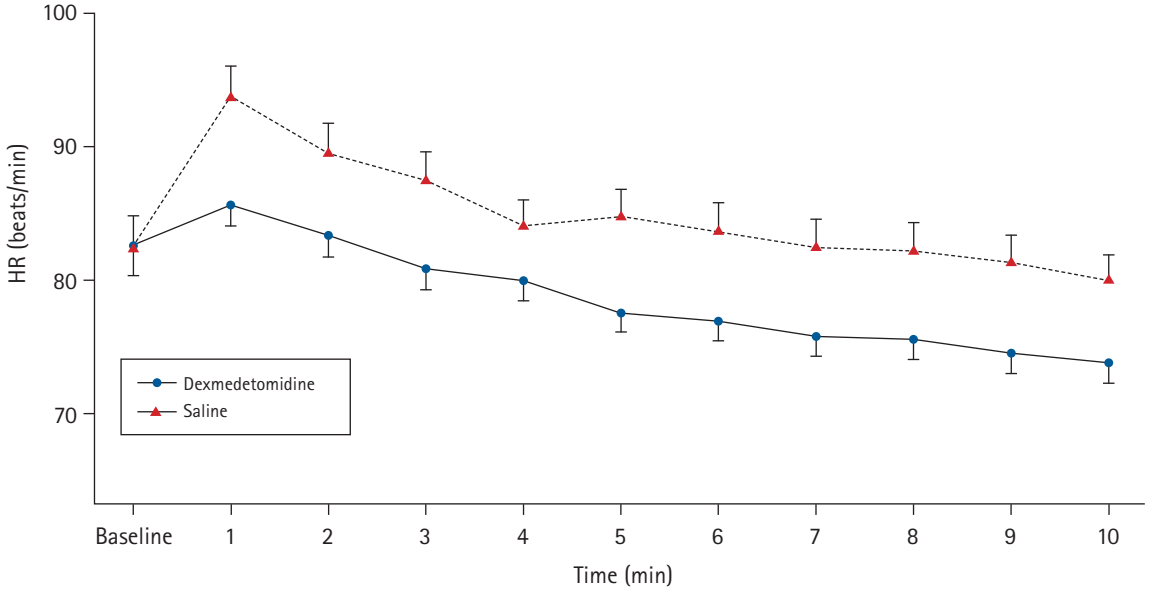

Fig. 2. Changes in heart rate (HR) in the dexmedetomidine group and the saline group. Baseline represents the post-nebulization pre-induction period. Mixed effect modelling showed a significantly lower trend of increase in HR in the dexmedetomidine group versus saline (P = 0.012). Vertical bars represent standard error of the mean.

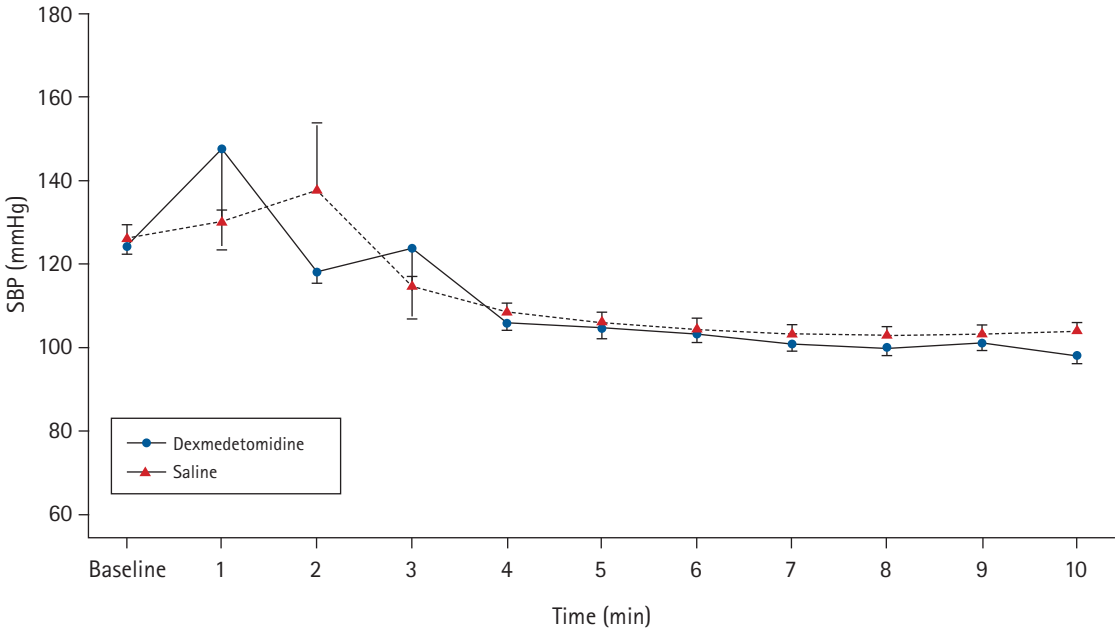

Fig. 3. Changes in systolic blood pressure (SBP) in the dexmedetomidine group and the saline group. Baseline represents the post-nebulization preinduction period. Mixed effect modelling showed no difference between the two groups in the overall trend in the SBP changes during the study period (P = 0.904). Vertical bars represent standard error of the mean.

Table 2. Secondary Outcomes

Parameter	Saline group (n = 60)	Dexmedetomidine group (n = 60)	P value	95% CI
Induction dose of propofol (mg/kg)	1.9 ± 0.6	1.5 ± 0.4	< 0.001	0.24, 0.61
Intraoperative fentanyl (μg/kg)	2.8 ± 0.9	2.4 ± 0.7	0.007	0.11, 0.67
Isoflurane (mean MAC)	0.8 ± 0.2	0.7 ± 0.2	0.013	0.01, 0.14
Response to skin incision (yes/no)	16/44	6/54	0.034	
Time to extubation following reversal of neuromuscular blockade (min)	3.7 ± 2.4	3.6 ± 2.1	0.681	0.64, 0.98
PONV (yes/no)	1/59	3/57	0.612	
Postoperative sore-throat (yes/no)	6/54	4/56	0.741	

Values are presented as mean ± SD or number of patients. MAC: minimum alveolar concentration, PONV: postoperative nausea and vomiting.

erative anesthetic and analgesic consumption. However, there was no effect of dexmedetomidine nebulization on the SBP responses following laryngoscopy or on the incidence of early PONV or postoperative sore-throat.

Common reasons for the hemodynamic changes following laryngoscopy and intubation are elevation of epiglottis, difficulty in glottic visualization, displacement of tongue, duration of laryngoscopy, and insertion of the tracheal tube [22].

Dexmedetomidine acts on various brain stem and medullary nuclei (nucleus tractus solitarus, lateral reticular nucleus) and the hypothalamus to decrease the sympathetic nervous activity and attenuate the hemodynamic response to laryngoscopy and intubation [23].

Various studies have investigated the effects of intravenous dexmedetomidine on the hemodynamic response to laryngoscopy and intubation [11–15,23–26]. While doses of 1–2 μg/kg have been found to be effective in attenuating this hemodynamic response, they are associated with significant side effects, such as bradycardia, hypotension, or respiratory depression [24,25]. Lawrence and De Lange [24], found that a single dose of 2 μg/kg dexmedetomidine caused a higher incidence of bradycardia and hypotension compared with the placebo treatment. Similarly, Mahajan et al. [25], found that with the same depth of anesthesia, there was a significant fall in HR and SBP and DBP in the dexmedetomidine group (1 μg/kg) versus the placebo group, and that this effect lasted until 30 min following drug administration.

Our results differ from those of previous studies [24,25]. Although we found that the increase in HR was significantly attenuated in the dexmedetomidine group versus saline following laryngoscopy, we did not find any incidence of bradycardia. Addition-

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ally, there was no significant difference in the SBP increases following laryngoscopy between the two groups. This can be explained by our route of administration. The bio-availability of dexmedetomidine via inhalation is 65% through nasal mucosa and 82% through buccal mucosa [19]. This may be comparable to 0.5 μg/kg of an intravenous dose [17], and as previous studies have shown, such doses only have a modest effect on hemodynamics following laryngoscopy and intubation [15,23]. Further reasons for a lack of effect of nebulized dexmedetomidine versus saline on the SBP changes following laryngoscopy could be that since the depth of anesthesia was similar in both groups, a higher MAC of isoflurane in the saline group versus a lower MAC in the dexmedetomidine group may have led to similar BP changes.

In the present study, nebulized dexmedetomidine reduced the induction dose of propofol as well as the intraoperative anesthetic and analgesic consumption. Although the duration of surgery was similar in both groups, a significantly lower consumption of fentanyl was seen in the dexmedetomidine group, despite patients undergoing a variety of surgeries. In addition, we also noted a significant difference in the response to skin incision between the groups, which may have been related to a better quality of analgesia in the dexmedetomidine group. Thus, the effects of nebulized dexmedetomidine is similar to those of intravenous dexmedetomidine on the intraoperative anesthetic and analgesic consumption [14,24,26].

Unlike Lawrence and De Lange [24], who found a significant effect of 2 μg/kg intravenous dexmedetomidine on baseline sedation, we found that the levels of sedation following nebulization and before induction of anesthesia were not different from the baseline values in either of the two groups. This may be related to the dose of dexmedetomidine used in our study and the patient population studied. While Abdel-Ghaffar et al. [20] found good sedation with 2 μg/kg nebulized dexmedetomidine in pre-school children undergoing bone marrow biopsy, Zanaty and El Metainy [19], found that in children undergoing outpatient dental surgery, doses of 1 μg/kg nebulized dexmedetomidine provided lower levels of sedation as compared to nebulized ketamine or a combination (1 μg/kg dexmedetomidine + 1 mg ketamine). Thus, a higher dose of nebulized dexmedetomidine may be required to achieve optimal sedation in adults.

While some studies have shown that supplemental dexmedetomidine administration was effective in reducing early PONV [27], other researchers have found a beneficial effect of supplemental dexmedetomidine on early nausea but not vomiting [28]. The reduction in PONV due to dexmedetomidine may be due to an opioid sparing action, a sympatholytic effect, or a direct antiemetic effect by activation of alpha-2 adrenoreceptors [28]. In our study, however, there was no significant difference in the early PONV between the two groups, despite a lower consumption of fentanyl in the dexmedetomidine group. Several reasons may have contributed to this lack of significant difference. Our anesthetic protocol included pre-induction administration of ondansetron, the effects of which is expected to last 8 h and thus may have masked any effect of dexmedetomidine on early PONV, since the surgeries were typically of short duration. Additionally, in most of the studies that have demonstrated an effect of dexmedetomidine on PONV, dexmedetomidine was either administered as a bolus dose at the end of surgery [27] or as continuous infusion [28], whereas we only administered a single dose before induction of anesthesia. Finally, the surgeries performed on the subjects in our study were mixed in nature, which may have also impacted the incidence of PONV.

The incidence of postoperative sore throat following tracheal intubation is 21–65% [29], and ranks as the eighth most adverse event in the postoperative period [30]. Previous reports have described the favorable effects of dexmedetomidine on dilatation of bronchi by relaxation of smooth muscles secondary to a direct effect on peripheral alpha-2 adrenoreceptors [31]; thus, we sought to investigate whether there is an effect of dexmedetomidine on the incidence of postoperative sore throat. However, we did not find a beneficial effect of nebulized dexmedetomidine on postoperative sore throat.

No previous studies have evaluated the effects of dexmedetomidine administered via the nebulized route on the hemodynamic response to laryngoscopy and intubation, intraoperative anesthetic and analgesic requirements, and other postoperative outcomes. Instead of using traditional statistical measures (e.g., analysis of variance) to test for the difference in hemodynamic parameters which estimates fixed effects, we utilized the mixed effect modelling for repeated measures (which tests for both fixed and random effects) since the BP or HR at any given minute may be the function of the previous reading.

We evaluated a single dose of nebulized dexmedetomidine and are thus unable to comment whether different doses will have different effects on hemodynamics. In addition, we did not use a comparator intravenous arm, which would have allowed us to compare the nebulized route of administration with the systemic route, but with the objective of finding better routes of administration, systemic administration may be avoided, especially in short duration surgeries.

In conclusion, a single dose of nebulized dexmedetomidine at 1 μg/kg, administered 30 min before induction of anesthesia, significantly attenuated the increase in HR but not SBP after laryngoscopy and decreased the intraoperative anesthetic and analgesic

consumption (compared to the saline treatment) without an increase in adverse effects. Nebulized dexmedetomidine may represent a favorable alternative to the intravenous route in adult patients undergoing short-duration surgeries.

Conflicts of Interest

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

Author Contributions

Satyajeet Misra (Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing – original draft; Writing – review & editing)
Bikram Kishore Behera (Data curation; Formal analysis; Investigation; Resources; Validation; Writing – review & editing)
Jayanta Kumar Mitra (Data curation; Investigation; Resources; Writing – review & editing)
Alok Kumar Sahoo (Data curation; Investigation; Supervision; Writing – review & editing)
Sritam Swarup Jena (Data curation; Investigation; Supervision; Writing – review & editing)
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KJA
Korean Journal of Anesthesiology

Experimental Research Article

Korean J Anesthesiol 2021;74(2):158-164
https://doi.org/10.4097/kja.20511
pISSN 2005-6419 • eISSN 2005-7563

Received: September 14, 2020
Revised: November 2, 2020
Accepted: November 4, 2020

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Intraoperative aerosol box use: does an educational visual aid reduce contamination?

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Background: The aerosol box was rapidly developed and disseminated to minimize viral exposure during aerosolizing procedures during the COVID-19 pandemic, yet users may not understand how to use and clean the device. This could potentially lead to increased viral exposure to subsequent patients and practitioners. We evaluated intraoperative contamination and aerosol box decontamination and the impact of a preoperative educational visual aid.

Methods: Using a double-blinded randomized design, forty-four anesthesiology trainees and faculty completed a simulated anesthetic case using an aerosol box contaminated with a fluorescent marker; half of the subjects received a visual aid prior to the simulation. Intraoperative contamination was evaluated at 10 standardized locations using an ultraviolet (UV) light. Next, subjects were instructed to clean the aerosol box for use on the next patient. Following cleaning, the box was evaluated for decontamination using an UV light.

Results: Median total contamination score was significantly reduced in the experimental group (5.0 vs. 10.0, $P < 0.001$). The aerosol box was completely cleaned by 36.4% of subjects in the experimental group compared to 4.5% in the control group ($P = 0.009$).

Conclusions: The use of a visual aid significantly decreased intraoperative contamination and improved box cleaning. Despite these findings, a potentially clinically significant amount of viral exposure may exist. Thorough evaluation of the risks and benefits of the aerosol box should be completed prior to use. If an aerosol box is used, a visual aid should be considered to remind practitioners how to best use and clean the box.

Keywords: Airway management; Anesthesiology; Audiovisual aids; Equipment and supplies; High fidelity simulation training; Infection control.

Introduction

The coronavirus disease (COVID-19) pandemic has led to numerous developments in personal protective equipment (PPE) as a means to protect healthcare workers from Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the virus responsible for COVID-19 [1,2]. Respiratory failure associated with COVID-19 often necessitates tracheal intubation, a high risk procedure exposing healthcare workers to droplet and aerosol particles carrying a significant viral load [3–5].

One potential exposure mitigation strategy is the use of a barrier device, such as a clear plastic aerosol box, over the patient's head to contain any aerosols or droplets [6,7]. Early

in the pandemic, news outlets and social media rapidly disseminated the construction and use of these aerosol boxes [8] and numerous variations on this basic design exist [9–11].

Simulation studies have demonstrated the effectiveness of aerosol boxes in preventing droplet spread [12–14], but concerns exist regarding clinical effectiveness in aerosol prevention and possible unintended complications with their use [8,15–18]. Due to the rapid development and dissemination of this medical device, no formal instructions or guidelines for use exist. Users may not know how to appropriately use and decontaminate the aerosol box that may lead to the box itself becoming a vector for viral transmission between patients or practitioners. Furthermore, the simple design may lead users to believe they know how to use the device even though they may not. Because medical devices should include instructions for proper use and this device lacks any such instructions, the authors postulate that an educational visual aid for proper aerosol box use may lead to safer utilization of the aerosol box.

In this study, we aim to evaluate the potential for viral particle spread using a fluorescent marker during a simulated anesthetic utilizing an aerosol box. Specifically, we have included an educational visual aid, containing a targeted list of recommendations describing best practices for the use and cleaning of this novel medical device [19–21]. Our primary endpoint was decreased intraoperative contamination of the anesthesia work area, while our secondary endpoint was improved decontamination of the aerosol box following use.

Materials and Methods

This study received an exemption from written consent by our Institutional Review Board. Anesthesiology trainees and faculty were voluntarily recruited to participate in this prospective, double-blinded, randomized-controlled study. Randomization was completed using a computer-generated randomization program (Research Randomizer, Urbaniak GC Plous S, www.randomizer.org). The study was completed in the Mount Sinai Department of Anesthesiology HELPS Simulation Center.

Each subject was randomized to an experimental group and received a visual aid describing how to use an aerosol box (Fig. 1), or to a control group without a visual aid. The visual aid content was developed using World Health Organization recommendations [19] as well as anesthesiology-specific guidelines [20,21] for infection control and intubation during the COVID-19 pandemic.

One study team member not involved in data collection provided the subject with a simulation prompt describing a patient under investigation for COVID-19 requiring a laparoscopic appendectomy. The study team member also provided the educational visual aid for subjects in the experimental group. The subject then had the opportunity to practice intubating a mannequin with an aerosol box in place, using a video laryngoscope (GlideScope™, Verathon Inc., USA); each subject was provided with sufficient time until they felt comfortable. The subjects were then brought into another room for the simulation. The visual aid was left in the previous room in order to keep the remaining study team members blinded to their group allocation.

The aerosol box was created using the initial widely publicized design specifications [6] and constructed using clear acrylic plastic and rubber cement. The aerosol box was then placed over an airway management trainer (Laerdal, Norway). An ultraviolet (UV) fluorescent marker (Glo-germ™, Glo-Germ Company, USA) was used in a lotion and powder form. One ml of the lotion was placed on the high-fidelity simulator's lips and inside the mouth to simulate oral secretions, while ⅛ teaspoon of the powder was distributed uniformly within the inside of the aerosol box using a powder brush, to simulate droplet contamination (Fig. 2). The fluorescent marker is not fluorescent under normal lighting conditions and was minimally visible during the simulation.

A standardized simulation sequence was utilized (Supplementary Table 1). Vital signs were generated using a high-fidelity patient simulator (CAE human patient simulator, Canada). Subjects were instructed to wear standard PPE for patients under investigation for COVID-19, including a gown, gloves, and surgical mask according to our hospital protocols. In order to conserve PPE, N95 respirators, masks, eye protection, and head coverings were not used in the study. Each subject then induced anesthesia and intubated the high-fidelity patient simulator with a video laryngoscope with the aerosol box in place. Subjects were required to administer drugs using saline filled syringes through a stop-

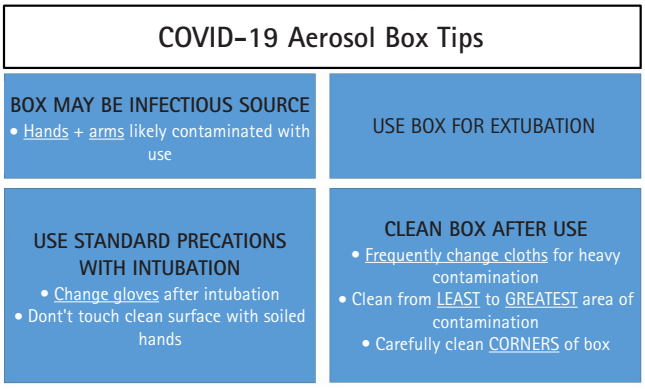

Fig. 1. Educational visual aid for aerosol box use provided to the experimental group.

cock on the intravenous line. Additional relaxation was requested by the simulated surgeon prior to incision, in order to prompt additional medications to be administered through the intravenous line. Upon completion of the simulated surgery, the subject then prepared for and performed extubation of the high-fidelity simulator.

Upon completion of the simulation, 10 standardized sites (Table 1) were evaluated for viral contamination using an UV light by two study team members who were blinded to subject randomization. These sites were selected based on previous intraoperative contamination studies [22–24]. Sites were deemed clean if no fluorescence was observed (0) or contaminated if any amount of fluorescence was visualized (1). The primary outcome was determined to be a total contamination score with a maximum score of 10. Subjects waited in the adjacent room while contamination scoring took place. Additionally, a secondary outcome was individual sites of contamination.

Finally, subjects were then instructed to clean the aerosol box in order for it to be used for their next patient. Cleaning wipes capable of cleaning the fluorescent marker (PDI Sani-Cloth, USA) were provided and subjects were able to clean the box until they were satisfied with its cleanliness. Two study team members blinded to subject randomization then examined the box under a UV light for areas not cleaned by the cleaning wipe. A scoring system was developed using a numbering system as follows: 1 = completely clean, 2 = 1–2 areas missed, 3 = 3–4 areas missed and 4 = 5 or more areas missed. Box cleaning scores were evaluated as a secondary endpoint.

Between simulations, all surfaces in the simulation lab were fully cleaned, as confirmed by two members of the study team using a UV light. Any materials that could not be fully cleaned were discarded and replaced.

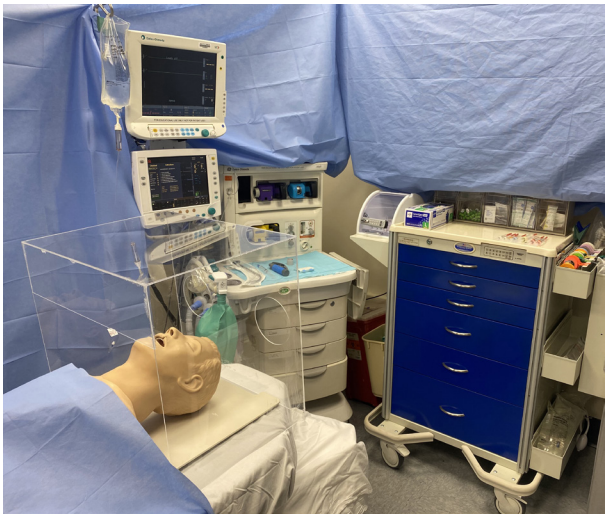

Fig. 2. Image of simulated operating room with aerosol box in position.

Table 1. Individual Sites Evaluated for Fluorescent Marker Contamination Following Simulated Anesthetic

1. Outside of the aerosol box
2. Reservoir bag
3. Adjustable Pressure Limiting (APL) valve
4. Anesthesia machine workstation
5. Vital signs monitor or ventilator screen
6. Intravenous stopcock
7. Medication syringes
8. Anesthesia supply cart
9. Subject gown
10. Subject gloves

Statistical analysis

Prior to the beginning of the study, pilot simulations without the educational visual aid had a median contamination score of 8.0 (Q1, Q3; 7.0, 9.0). We predicted the educational visual aid would decrease the contamination score that would be decreased by 50% to a median contamination score of 4.0. Using an α of 0.05 and a of 0.2 and the predicted 50% decrease in contamination score, it was determined that a sample size of 22 subjects in each group would be needed for sufficient power. In order to allow for potential dropout, we aimed to recruit 24 subjects per group in order to reach our targeted sample size, though no subjects dropped out and we were able to achieve a full sample of 22 subjects per group. All continuous variables were first assessed for normality via Shaprio-Wilk or Kolmogorov–Smirnov tests, where applicable as well as visual inspections of histograms. All continuous variables were found to be non-normal and are reported as median (Q1, Q3). Proportions are reported as n (%). For categorical variables, chi-square tests were utilized, unless one value in the 2 x 2 matrix was under 5, in which case Fischer's exact test was utilized. For binary tests, odds ratios with 95% CIs are reported. For continuous non-normally distributed variables, Mann-Whitney *U* test was used, with differences between groups and 95% CIs estimated via Hodges-Lehman estimation. All calculations were performed via SPSS Statistics Version 24 (IBM Corp., USA).

Results

Forty-four subjects were enrolled in the study with 22 subjects in each group (Fig. 3). The control group consisted of 16 trainees and six faculty members, while the experimental group consisted of 14 trainees and eight faculty members. All subjects completed

https://doi.org/10.4097/kja.20511

the study.

Our primary endpoint, median total contamination score, was 10.0 (8.0, 10.0) for the control group and 5.0 (4.0, 8.25) for the experimental group (Supplementary Fig. 1). Total contamination score was found to be significantly reduced in the experimental group (P < 0.001). When evaluating only trainees, the median total contamination scores were 10.0 (8.25, 10.0) and 6.0 (4.75, 9.0) for the experimental group (P = 0.002). For faculty members, the median total contamination scores were 8.5 (7.5, 10.0) for the control group and 5.0 (4.0, 5.0) for the experimental group (P = 0.001).

Individual site rates of contamination, a secondary exploratory endpoint, are in Table 2. Sites with statistically significant reductions in contamination for the experimental group include the reservoir bag (P = 0.002), adjustable pressure limiting (APL) valve (P = 0.003), vital signs monitor or ventilator screen (P < 0.001), I.V. stopcock (P = 0.026), medication syringes (P < 0.001), and anesthesia supply cart (P = 0.012). No statistically significant difference in contamination was noted for outside of the aerosol box, anesthesia machine workstation, gown, or gloves.

The distribution of aerosol box cleaning scores, a secondary endpoint, is shown in Fig. 4. A statistically significant difference in distribution between the control and experimental group was found (P = 0.009). In the experimental group, 36.4% of subjects completely cleaned the aerosol box compared to only 4.5% in the control group (P = 0.009, OR = 1.5 [1.08, 2.08]).

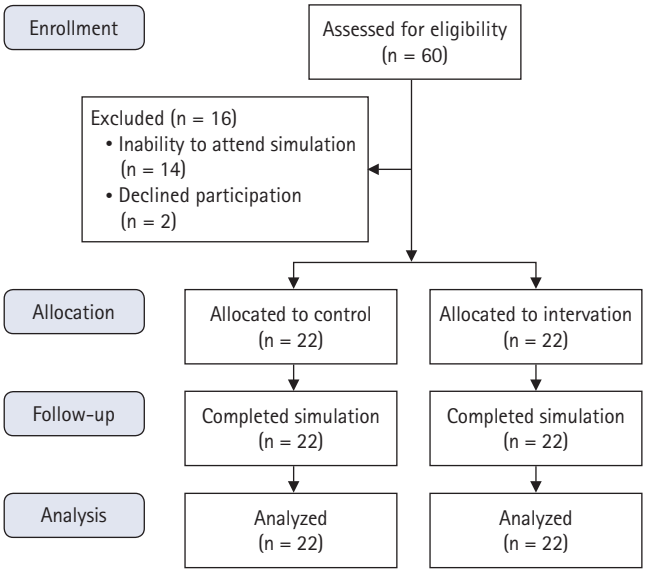

Fig. 3. CONSORT diagram.

Discussion

The aerosol box has been promoted throughout scientific journals, news, and social media as an effective method for limiting viral exposure during aerosolizing procedures, yet no high-quality evidence for its effectiveness exists. Despite its use, concerns exist regarding practitioner understanding of proper aerosol box use and potential unintended viral contamination associated with improper box use.

Our study is significant for several findings. First, we demonstrated that intraoperative contamination can be decreased with the use of a visual aid as measured as a decrease in the total contamination score. Individual sites with consistent contamination for all subjects included the outside of the aerosol box, the anesthesia workstation, and the subjects' gown and gloves; therefore care must be taken to consistently avoid contamination of these sites. This contamination, particularly of the gown and gloves, could lead to increased intraoperative contamination and potential viral exposure to healthcare workers or subsequent patients. Furthermore, contamination of the anesthesia workstation may

Table 2. Presence of Fluorescent Marker Contamination Following Simulated Anesthetic at Individual Locations with Total Contamination Score

Location	Control group (n = 22)	Experimental group (n = 22)	P value
Outside of the aerosol box	22 (100)	19 (86.3)	0.073
Reservoir bag	17 (77.3)	7 (31.8)	0.002
Adjustable Pressure Limiting (APL) valve	20 (90.9)	11 (50.0)	0.003
Anesthesia machine	20 (90.9)	17 (77.3)	0.216
Vital signs monitor or ventilator screen	18 (81.8)	6 (27.3)	< 0.001
Intravenous stopcock	18 (81.8)	11 (50.0)	0.026
Medication syringes	18 (81.8)	6 (27.3)	< 0.001
Anesthesia supply cart	18 (81.8)	10 (45.5)	0.012
Subject gown	22 (100.0)	22 (100.0)	N/A
Subject gloves	21 (95.5)	21 (95.5)	1.000
Total score*	10	5	< 0.001

Values are presented as number (%). *Reported as total score number, not as a number or percent contaminated.

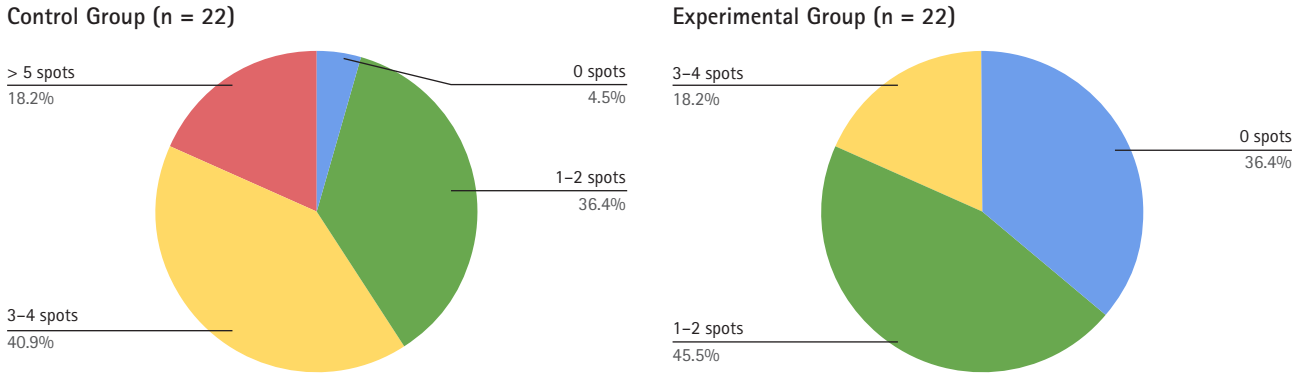

Fig. 4. Aerosol box cleaning ratings. Data represents number of spots on the aerosol box that were not cleaned. Data with significant difference between control and experimental groups (P = 0.009).

provide a reservoir for further contamination throughout an anesthetic or procedure despite proper hand hygiene [25].

Secondly, this study showed that cleaning of an aerosol box can be increased with the use of a visual aid. The effectiveness of this visual aid is likely associated with the lack of any pre-existing instructions accompanying this rapidly developed device as well as the visual aid serving as a reminder of the infectious potential associated with aerosol box use. In spite of the visual aid, nearly two thirds of aerosol boxes remained contaminated in the experimental group. Of particular note was the remaining contamination at the corners and edges of the box that suggests that these may be areas to focus on to fully decontaminate the box. The potential for incomplete terminal cleaning of operating rooms exists [26,27] and any amount of contamination may become clinically relevant if viral transfer to a 'clean' environment occurs. SARS-CoV-2 has been shown to be stable on plastic and steel surfaces for up to 72 hours [28] and could easily be transmitted between patients or practitioners if intraoperative surfaces or the aerosol box were improperly cleaned.

Finally, and most strikingly, we demonstrated potentially clinically significant contamination of the operating room and aerosol box independent of visual aid use. Several explanations for high rates of intraoperative contamination and contaminated aerosol boxes exist. The aerosol box could potentially be seen as a false sense of security to the subjects that could lead to less vigilance for infection control when compared to intubation without an aerosol box. Studies prior to the COVID-19 pandemic have found intraoperative contamination to be high [25] despite recommendations such as improved intraoperative hand hygiene [29], double gloving for intubation [23], protective devices during intubation [24], and more. Additionally, the aerosol box is an unfamiliar device to most practitioners and the novelty of it may cause changes in practice leading to increased intraoperative contamination or lack of thorough decontamination. The box's geometry may also lend to a lack of thorough cleaning as the corners and edges were most often missed by subjects.

Our study adds to the growing number of criticisms associated with aerosol box use. Concerns associated with increased difficulty with airway management, restricted access to the patient for assistants, difficulties with portability in emergencies, the requirement for specialized supplies, potential to damage PPE, and potential redirection of aerosols towards the intubator have all been raised [8,15–18]. As a result of the current study, we would add potential for viral contamination to the list of concerns with aerosol boxes. Further investigation into intubation barrier devices' effectiveness and safety are required.

The greatest limitation of this study is related to the simulation environment. Subjects were told they were in an operating room taking care of a person under investigation for COVID-19, but in reality, were in a simulation lab and may not have been as careful as a real-life situation. Similarly, the subjects knew they were being observed for the study and the Hawthorne effect must be considered. Although the fluorescent powder used in this study has commonly been used as a marker for viral and bacterial contamination, its use as a simulated SARS-CoV-2 virus has not been proven. One modification to this study could have been to evaluate if the fluorescent marker contamination was spread to the next simulated patient following cleaning, but this was not done due to time constraints. Subjects had no prior experience using the aerosol box during a simulation or in-patient care, but all were aware of the concept through scientific journals, news, and social media. Despite this lack of prior experience, we believe this data is generalizable because prior to COVID-19 the aerosol box was not used by any practitioners. However, these findings may be different in a practitioner with more experience using the aerosol box. Finally, numerous barrier devices exist and several modifications to the original design used in this study have been made; it is unclear how the current study's findings would translate to other aerosol

https://doi.org/10.4097/kja.20511

box designs.

We recommend a thorough evaluation of needs for those considering aerosol box use as it may have numerous unintended consequences. If an aerosol box is used, all users should receive at minimum a visual aid describing how to best use and clean the aerosol box. Given the uncertain benefits, our recommendation is to forgo aerosol box use and utilize appropriate PPE with all necessary precautions such as a rapid sequence induction and intubation with a video laryngoscope [1,30]. It is vital that all practitioners, regardless of aerosol box use, stay vigilant during use and cleaning of the operating room.

Funding

This research was supported internally by the Department of Anesthesiology, Perioperative & Pain Medicine at the Icahn School of Medicine at Mount Sinai. No external funding was received for this research.

Conflicts of Interest

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

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Supplementary Materials

Supplementary Table 1. Standardized simulation sequence
Supplementary Fig. 1. Total contamination score for control and experimental groups.

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https://doi.org/10.4097/kja.20511

KJA
Korean Journal of Anesthesiology

Tube-in-tube airway management in a patient with Montgomery T-tube in situ -a case report-

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Case Report

Korean J Anesthesiol 2021;74(2):165-168
https://doi.org/10.4097/kja.20171
pISSN 2005-6419 • eISSN 2005-7563

Received: April 16, 2020
Revised: May 20, 2020 (1st); June 18, 2020 (2nd)
Accepted: June 26, 2020

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Background: Montgomery T-tube (MTT) is a useful airway device but is seldom used. Owing to its specific shape and structure, it is challenging for anesthesiologists to manage airway in patients with MTT in situ who require general anesthesia and continuous positive-pressure ventilation (CPPV).
Case: A 48-year-old man (weight 74 kg) with an MTT in situ was scheduled for local pancreatic resection under general anesthesia. We transorally inserted a cuffed endotracheal tube into the intratracheal limb of the MTT to achieve CPPV and to deliver the inhalation anesthetic. The endotracheal tube was removed successfully after the patient fully recovered from anesthesia. No tracheal injury or hemorrhage occurred after intubation or extubation, and the location of the MTT remained unchanged.
Conclusions: Transoral insertion of a cuffed endotracheal tube into the intratracheal limb of the MTT could therefore be considered as a safe and feasible approach for airway management.

Keywords: Airway management; Anesthesia; Anesthetic management; Endotracheal T-tube; Montgomery T-tube; T-shaped airway stent.

The use of a Montgomery T-tube (MTT) was first described in 1965 [1]. The MTT is employed as both a stent and a tracheal tube in patients with airway collapse, subglottic stenosis, and those undergoing laryngotracheal reconstruction [2]. It is a silicone T-tube that consists of an intratracheal limb placed into the trachea and an extratracheal limb passing through the tracheotomy stoma. The intratracheal limb is uncuffed, while the extratracheal limb has no standard connector for anesthetic circuit [1]. MTT is available in different sizes, with outer diameter (OD) ranging from 4.5 mm to 16 mm, which can be selected to fit the trachea in both adults and children [3]. Owing to its distinctive design and infrequent use, anesthesiologists have less experience managing the airways of patients with MTT in situ who require general anesthesia and continuous positive-pressure ventilation (CPPV). Herein, we describe a case of tube-in-tube airway management in a patient with MTT in situ to administer CPPV.

Case Report

A 48-year-old man (weight 74 kg) who was diagnosed with necrotizing pancreatitis was scheduled for local pancreatic resection under general anesthesia. One year earlier, the patient developed acute pancreatitis and underwent mechanical ventilation by endotracheal intubation. After his discharge from the hospital for one month, a severe dyspnea happened, caused by subglottic stenosis. His tracheal stenosis was mostly attributed to

the previous instance of prolonged intubation, mechanical ventilation, and cuff injury. Unfortunately, repeated balloon dilatation under bronchofibroscopy failed to cure his tracheal stenosis. Finally, a 12-mm sized MTT (Boston Medical Products, USA) was used to support his trachea. The West China Hospital Review Board approved the study (no. 2020-75) and informed consent was obtained.

Preoperatively, we intended to replace the MTT with a cuffed tracheostomy tube before anesthesia induction. However, the otorhinolaryngologist and respiratory physician who performed the tracheostomy and MTT insertion, respectively, forewarned of a high risk of tracheal hemorrhage or collapse after MTT removal, and that re-insertion of the MTT would be extremely difficult. Therefore, we decided to retain the MTT in situ in the trachea and prevent its displacement.

Based on the information provided by the manufacturer, the OD of the intratracheal and extratracheal limbs were 12 mm and 11 mm, respectively, and the lengths of the intratracheal and extratracheal limbs were 65 mm and 50 mm, respectively. Preoperative chest computed tomography (CT) scan and bronchofibroscopy examination showed that the lumens of the MTT were unobstructed. According to preoperative CT images, the internal diameters (ID) of the intratracheal and extratracheal limbs were estimated to be 10 mm and 8 mm, respectively (Fig. 1). We evaluated that either a size 6.5 (ID: 6.5 mm, OD: 8.9 mm) or size 6.0 (ID: 6.0 mm, OD: 8.2 mm) cuffed endotracheal tube (Covidien LLC, USA) could pass through the intratracheal limb, while simultaneously ensuring sufficient tidal volume. Finally, we planned for transoral insertion of an endotracheal tube through the MTT's intratracheal limb to administer CPPV (Fig. 2).

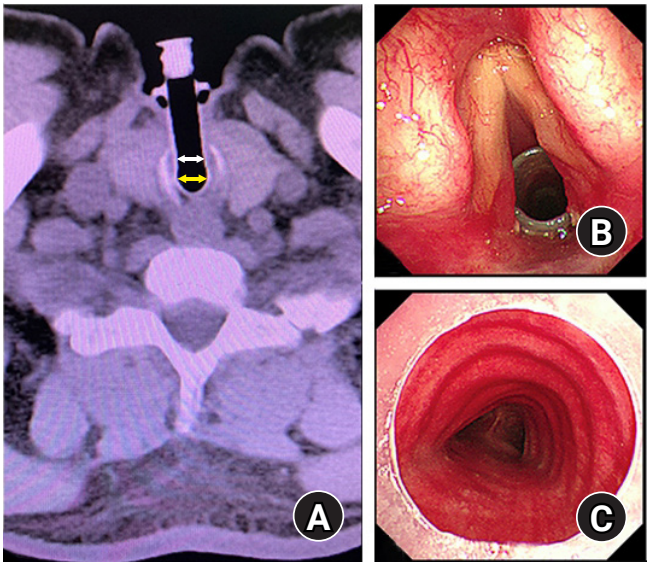

Fig. 1. (A) Based on preoperative chest computed tomographic image, the internal diameters of the intratracheal limb (yellow arrow) and extratracheal limb (white arrow) were approximately 10 mm and 8 mm, respectively. Preoperative bronchofibroscopy examination showed (B) the superior end and (C) inferior end of the intratracheal limb were unobstructed without granulation tissue or sticky secretion.

The patient's blood pressure, heart rate, pulse oxygen saturation, and bispectral index were monitored routinely. A well-lubricated video laryngoscope (E.An-II Plus, Tianjin Medan Medical Corp., China), cuffed endotracheal tubes (size 6.5 and 6.0), and a fiberoptic scope were prepared. First, the respiratory tract was cleaned by suction through the extratracheal limb of the MTT before anesthesia induction. Then, the patient inhaled 100% oxygen through a facemask that covered both his nose and mouth. Simultaneously, the extratracheal lumen was occluded. After 6 minutes of preoxygenation, 1% sevoflurane was inhaled through the facemask, and the sevoflurane concentration was gradually increased to 4%. When the patient was unconscious, but still breathing spontaneously, positive-pressure facemask ventilation was initiated, with no obvious gas leakage observed at the tracheostomy stoma. Thereafter, succinylcholine (100 mg) and propofol (100 mg) were intravenously administrated, and a video laryngoscope was immediately inserted into the mouth after the fasciculation disappeared. The glottis and the upper end of the intratracheal limb in the subglottis, without granulation tissue, were clearly visualized by the video laryngoscope. A size 6.5 cuffed endotracheal tube was inserted into the intratracheal lumen smoothly. To prevent MTT displacement, an assistant held the extratracheal limb lightly during intubation. Then, bronchofibroscopy was used to guide the distal end, and the cuff of the endotracheal tube passed entirely through the intratracheal limb and located above carina. The

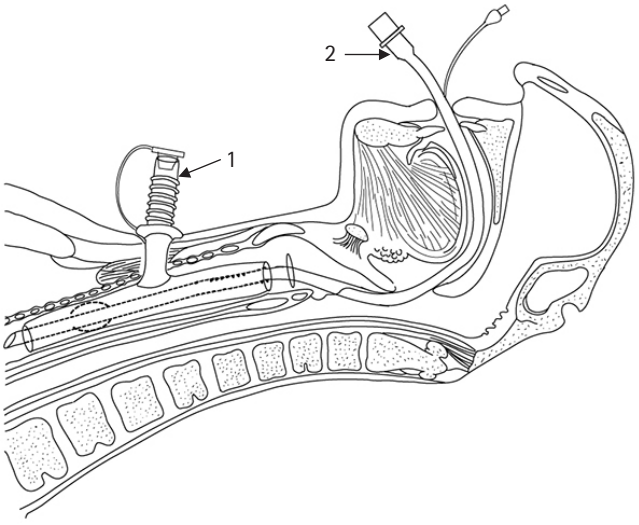

Fig. 2. Diagram of a tube-in-tube approach for airway management with Montgomery T-tube in situ. 1: Montgomery T-tube, 2: Cuffed endotracheal tube.

https://doi.org/10.4097/kja.20171

depth of the endotracheal tube was 23 cm. While the cuff was inflated, the endotracheal tube was connected to the anesthetic circuit for CPPV. An inspiratory pressure of 15 cmH_2O achieved a 6–8 ml/kg of tidal volume. Clear and symmetrical breath sounds were confirmed without MTT displacement or tracheal hemorrhage. Then, sufentanil (20 μg) and cisatracurium (10 mg) were infused. Anesthesia was maintained using sevoflurane inhalation (1–2%), with continuous remifentanil infusion and intermittent administration of cisatracurium.

The operation lasted approximately 4 hours, and the respiratory tract was regularly cleaned through the endotracheal tube till the end of the surgery. After the patient fully recovered from anesthesia, extubation was performed under bronchofibroscopy, while holding the extratracheal limb. No tracheal injury or hemorrhage was detected, and the location of MTT remained unchanged.

Discussion

MTT is usually used as a stent to maintain airway patency in patients with airway collapse, subglottic stenosis, or post-laryngotracheal reconstruction [2]. There were few cases of airway management in patients with MTT in situ who required general anesthesia and CPPV. Most anesthesiologists are unfamiliar with this irregular tracheal device.

Comprehensive preoperative assessment is very important for anesthesiologists to determine whether the pre-existing MTT could be kept while inducing general anesthesia. The common complications of MTT in situ are tracheal obstruction and re-stenosis, which are mostly induced by sticky secretions or granulation tissue at either ends of the MTT [2]. Because MTT itself is relatively soft, distortion occasionally occurs to limbs if it is compressed by local tracheal stenosis or cicatricial contracture. In these circumstances, the MTT may not be retained when patients are undergoing CPPV or induced with general anesthesia. If the shape and function of the MTT are normal, it could be considered to be reserved.

For patients with a normal MTT in situ, a laryngeal mask has been proposed for CPPV, with the occlusion of the extratracheal limb [3–5]. However, for patients with a high risk of aspiration, CPPV with laryngeal masks may not be a safe method for airway protection [3]. Connectors of endotracheal tubes have also been used to connect the extratracheal limb of the MTT with anesthetic circuit for mechanical ventilation, and with the upper lumen of intratracheal limb occluded simultaneously by a balloon catheter [3,4]. Because the connector is non-standard, it may not fit well with the MTT well, and the tightness and reliability of the connection cannot be ensured. An ill-matched connector may damage the wall of extratracheal limb. Additionally, no specialized balloon catheter is available for MTT.

It was also suggested that an endotracheal tube could be inserted from the extratracheal limb into the inferior lumen of the intratracheal limb before anesthesia induction [4]. The advantage of this method is that the airway may be protected before anesthesia induction because the procedure can be performed when the patient is conscious. However, for most MTTs, the ID of the extratracheal limb is smaller than that of the intratracheal limb, which will necessitate a much smaller endotracheal tube that can pass through it. In contrast, the intratracheal limb was almost perpendicular to the extratracheal limb, which made it difficult to insert an endotracheal tube through an angle with approximately 90 degree.

Placing a cuffed endotracheal tube transorally into the intratracheal limb may be regarded as a feasible and safe method. Because only the data of OD and length of each limb are provided by the manufacturer, it is very important for anesthesiologists to measure the ID of each limb. Occasionally, some irregular types of MTT are also used that have an intratracheal limb with tapered ends [4]. Thus, to select a suitable size of endotracheal tube that can pass entirely through the intratracheal limb of the MTT, the minimal ID of the intratracheal limb should be evaluated. Otherwise, a small endotracheal tube will induce high airway pressure or insufficient tidal volume, and a large endotracheal tube may cause repeated intubation or displacement of the MTT. CT examination is a useful method to obtain the minimal ID of each limb by measuring at different cross sections.

To improve success rate of first intubation or minimize tracheal injury, preparation of visual equipment and well-lubricated endotracheal tubes are prerequisite. In our case, muscle relaxation with succinylcholine might have aided the successful intubation with a relatively large endotracheal tube. Holding the extratracheal limb can decrease the risk of unexpected removal or displacement of the MTT both during intubation and extubation [3]. To occlude the trachea completely and to prevent gas leakage or damage to the MTT wall, the cuff of the endotracheal tube should entirely pass through the intratracheal limb under bronchofibroscopy guidance. Bronchofibroscopy examination should be performed both after intubation and extubation to detect any abnormalities of the trachea or MTT. Moreover, a skilled otorhinolaryngologist or respiratory physician should be present during intubation and extubation for emergency tracheostomy tube insertion or MTT re-insertion. The administration of anticholinergic agents in patients under these conditions may be controversial because, though it can reduce secretion, it may induce stickier secretions. Full suction is needed for cleaning the respiratory tract.

If MTT cannot be kept in situ due to severe tracheal obstruction or re-stenosis, it needs to be removed or replaced with a new one or a cuffed tracheostomy tube by respiratory physician or otorhinolaryngologist before anesthesia. Another solution is replacing the abnormal MTT with an endotracheal tube before anesthesia induction and then re-inserting a new MTT immediately after extubation by multi-discipline cooperation. However, the feasibility of this assumption needs further validation. A comprehensive preoperative assessment, multi-discipline cooperation, and adequate preparation are crucial for anesthetic planning in patients with MTT in situ. Transoral insertion of a suitable-sized cuffed endotracheal tube into the intratracheal limb could be considered a safe and feasible approach for the airway management in those patients who require CPPV.

Acknowledgements

We are grateful to Chaozhi Luo and Chunling Jiang, who provided help in anesthetic management of this patient.

Conflicts of Interest

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

Funding

This study was supported by National Natural Science Foundation of China (81971772).

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https://doi.org/10.4097/kja.20171

KJA
Korean Journal of Anesthesiology

Infection control of operating room and anesthesia for cesarean section during the COVID-19 outbreak in Daegu, the Republic of Korea -a case series-

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Case Report

Korean J Anesthesiol 2021;74(2):169-174
https://doi.org/10.4097/kja.20204
pISSN 2005-6419 • eISSN 2005-7563

Received: April 29, 2020
Revised: May 28, 2020
Accepted: June 1, 2020

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Background: The coronavirus disease-19 (COVID-19) was first reported in Wuhan, China, with Korea being subsequently exposed. In Korea, COVID-19 screening guidelines have been established in every hospital as an attempt to prevent its spread. There has been a previous report of a successful cesarean section of a confirmed mother; however, there remain no guidelines for suspected mothers. Cesarean section is often urgently operated without sufficient infection evaluations. We would like to suggest anesthetic management guidelines for cesarean section patients suspected of COVID-19.
Case: Our hospital, which is located in Daegu, Korea, was designated as a quarantine and delivery facility for suspected mothers. We performed the cesarean section on seven suspected mothers and one confirmed mother.
Conclusions: This case report presents guidelines for infection control during surgery and anesthesia for cesarean section of mothers with suspected COVID-19 involving operating room preparation and protection strategy.

Keywords: Cesarean section; COVID-19; Guidelines; Pandemics; Personal protective equipment; Pregnancy; SARS-COV-2.

In 2019, the novel coronavirus disease-19 (COVID-19) was reported in Wuhan, which has since spread in China and worldwide, including Korea [1,2]. Our hospital's medical staff have established and followed guidelines to prevent the virus spread in the operating room, as well as exposure of medical staff to the virus. Specifically, uninfected fetuses at risk of viral infection have been delivered from COVID-19 confirmed mothers through cesarean section (C-sec), which indicates the possibility of safe delivery from COVID-19 confirmed mothers [3]. However, since C-sec is often performed urgently since the life of the mother or fetus could be at risk, surgeons proceed with the surgery before receiving the results of COVID-19 reverse transcription-polymerase chain reaction (RT-PCR). Here, we aim to present reports regarding the management of confirmed and suspected patients with COVID-19, as well as the guidelines of perioperative management for surgery and anesthesia preparation.

Case Reports

Our hospital is located in Daegu, which has the largest number of infected patients among the cities in Korea. A total of twelve mothers with suspected COVID-19 were ad-

mitted for delivery between February 26 and April 3, 2020. Four mothers with fever symptoms gave birth through normal vaginal delivery. After consulting an obstetrician, eight COVID-19 related mothers (including one confirmed and seven suspected) undergoing C-sec were treated (Table 1). Case #4 had been previously diagnosed with COVID-19 infection and had self-isolated at home. Among these patients, three had preeclampsia, two had premature rupture of membranes (PROM) with dystocia, one had PROM with fetal distress, one had dystocia caused by cephalopelvic disproportion, and one had preterm labor with fetal distress. Five of the seven suspected patients had fever, one had dyspnea, and one had both fever and dyspnea. Given the patients' symptoms, COVID-19 could not be excluded; therefore, they were transferred through an exclusive passage and elevator from the hospital entrance triage without passing the gynecology outpatient clinic in our hospital. They were admitted to the negative pressure- quarantine room in the delivery center for a minimum of 15 minutes and a maximum of 60 minutes until just before surgery. The preoperative evaluation involved laboratory tests, chest X-ray, electrocardiogram, and COVID-19 RT-PCR. However, if C-sec was to perform urgently, the surgery was performed without waiting for the results of routine laboratory tests. Case #4 (COVID-19 confirmed patient) was admitted for emergency C-sec due to obstructed labor caused by cephalopelvic disproportion. After admission, she had a COVID-19 RT-PCR test again. An urgent C-sec was required immediately before the reception of the RT-PCR results for the seven suspected mothers. All seven suspected patients were prepared for surgery and anesthesia as per the hospital's guidelines for patients with COVID-19 (Fig. 1).

C-sec preparations were performed in the operating room, which is a negative-pressure room in the delivery center temporarily designed as part of the hospital policy for COVID-19 related C-sec. Unnecessary instruments for the surgery were removed and built-in instruments in the operating room were covered using plastic paper. Fluids, drugs, and other equipment required for surgery and anesthesia were prepared in sufficient quantities. Equipment and unused drugs and fluids were wiped using sodium dichloroisocyanurate solution immediately after surgery and before storage. Initially, spinal anesthesia was considered; however, equipment for general anesthesia was prepared in case of failed spinal anesthesia. These included a ventilator, breathing circuit, video laryngoscope (McGRATH MAC, Aircraft Medical Ltd., UK), high-efficiency particulate air (HEPA) filter, and drugs. All the health care workers (HCWs) wore enhanced personal protective equipment (PPE), including an N95 mask, full-body impermeable suit, double gloves, shoe covers, hood with a surgical cap, and powered air-purifying respirator (PAPR) before the patient

Table 1. COVID-19 Related Patient for Cesarean Section

Patient	Age	Operation date	Gestational age	Obstetric underlying disease	SARS-COV-2 related symptoms	SARS-COV-2 PCR	Newborn state (APGAR score 1 min→5 min)	Type of anesthesia	Chest X-ray image	Chest CT image
1	39	February 26	37^{+3}	Preeclampsia	Dyspnea, SpO_2: 94%	Negative	Good (9→10)	Spinal	U-R	-
2	30	February 27	25^{+3}	Preeclampsia	Fever: 37.6°C	Negative	Still birth (0)	General	U-R	-
3	29	February 28	40^{+0}	Preeclampsia	Fever: 38.1°C	Negative	Still birth (0)	Spinal	Increased vascular marking	-
4	28	March 6	37^{+6}	Cephalopelvic disproportion	None	Converted to negative before surgery	Good, PCR (-) (9→10)	Spinal	Consolidation in LLL	r/o pneumonia
5	25	March 8	38^{+4}	PROM	Fever: 38.8°C	Negative	Cyanosis, good (6→8)	Spinal	Increased vascular marking	-
6	33	March 9	33^{+5}	Preterm labor	Fever: 37.8°C	Negative	RDS, good (6→8)	Spinal	r/o pneumonia	r/o pneumonia (DDx: viral infection, less likely)
7	30	March 29	38^{+1}	PROM	Fever: 37.6°C	Negative	Good (9→10)	Spinal	No active lesion	-
8	34	April 3	22^{+4}	PROM	Fever: 37.8°C	Negative	RDS, expired (5→7)	Spinal	No active lesion	-

COVID-19: coronavirus disease-19, SARS-COV-2: severe acute respiratory syndrome coronavirus 2, Chest CT: chest computed tomography, PCR: polymerase chain reaction, PROM: premature rupture of membranes, RDS: respiratory distress syndrome, LLL: left lower lobe, r/o: rule out.

https://doi.org/10.4097/kja.20204

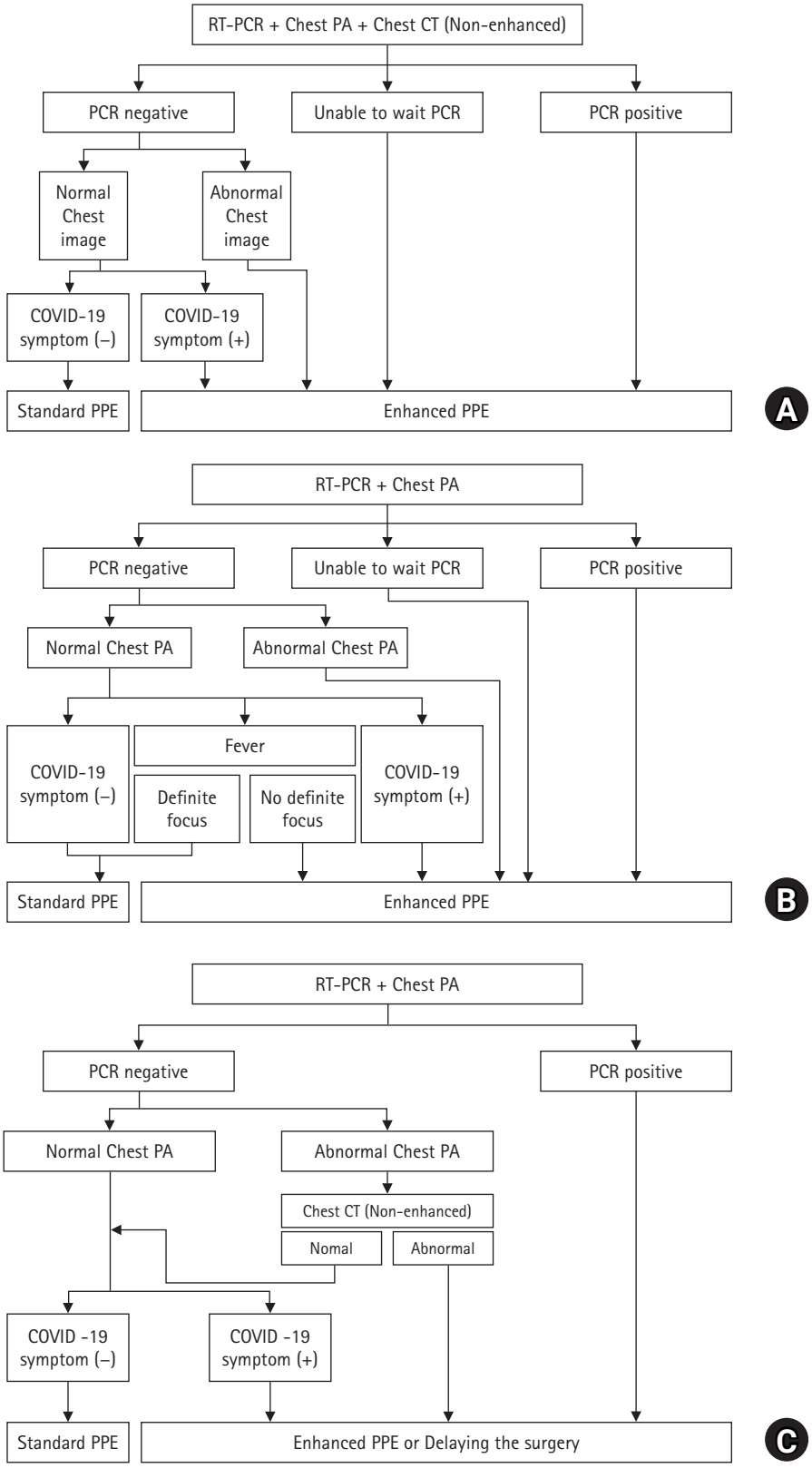

Fig. 1. Guidelines for operation during the Coronavirus disease-19 (COVID-19) outbreak. Enhanced personal protective equipment (PPE) includes N95 mask, full body impermeable suit, double gloves, shoe covers, and hood with surgical cap. Standard PPE includes goggle, N95 mask, plastic gown, and disposable surgical gloves. (A) Guideline for emergent surgery. (B) Modified guidelines for cesarean section. (C) Guideline for elective surgery. COVID-19 symptoms include fever, cough, dyspnea, myalgia or fatigue, sputum production, headache, and diarrhea. RT-PCR: reverse transcription-polymerase chain reaction, Chest PA: chest posteroanterior, Chest CT: chest computed tomography.

arrived at the operating room (Fig. 2A). Standard PPE (Fig. 2B) was applied to HCWs who cared for asymptomatic COVID-19 exposed patients. Standard PPE includes surgical gloves, surgical gowns, eye shields and N95 mask. All 8 cases had COVID-19 suspected symptoms, HCWs all wore enhanced PPE.

After the anesthesiologist, surgeon, and nurses were ready and the operating room was set-up, the patients were transferred from the quarantine room to the operating room. Upon patient entry to the operating room, the door was not allowed to open. Patient intraoperative monitoring included electrocardiogram, non-invasive blood pressure, and SpO_2. Seven patients underwent spinal anesthesia while one (case #2) underwent general anesthesia. For this procedure, a well-experienced anesthesiologist and one nurse were present in the operating room while another anesthesiologist was on call for unexpected situations. For spinal anesthesia, a 25-gauge Pencan spinal needle was inserted into the lumbar 3rd–4th intervertebral space; subsequently, 0.5% heavy bupivacaine 9 mg/1.8 cc with fentanyl 20 μg/0.4 cc was intrathecally injected. After 5 min, the neuraxial blockade was confirmed to reach the T4 level. The patient wore an N95 mask during anesthesia, surgery, and recovery. Case #2 underwent general anesthesia due to the failure of regional anesthesia caused by severe edema. A HEPA filter was applied between the breathing circuit and face mask where the patient was preoxygenated for 5 min. Subsequently, rapid sequence intubation without manual ventilation was performed to prevent the aerosolized virus from spreading in the room. Next, a video laryngoscope was used to increase the successful intubation rate. After the operation was completed, extubation was performed after confirmation of established regular breathing, adequate spontaneous ventilation, eye opening, and obeying commands. Further, 100% O_2 2 L was supplied via a nasal cannula, which was covered with an N95 mask.

Fig. 2. Personal protective equipment (PPE). (A) Enhanced PPE and (B) Standard PPE.

After surgery completion, the patients recovered in the operating room without being admitted to the post-anesthesia care unit. The anesthesiologist and nurse involved in the C-sec were similarly involved in the patient's postoperative recovery. The patients who received spinal anesthesia recovered until the blockage level decreased to T8–T10. The patient who underwent general anesthesia was considered to have recovered when her post anesthetic recovery score was ≥ 9. In case of pain complaints, previously prepared analgesic agents, including opioids and non-steroidal anti-inflammatory drugs, were intravenously administered. We followed the post-anesthesia care unit discharge criteria as appropriate; however, given the fatigue of the HCWs, the recovery time was limited to 1 h. After recovery, the confirmed patient was transferred to the COVID-19 ward while the suspected patients were transferred to the COVID-19 suspect ward through an exclusive passage and elevator for patients with COVID-19. On the first post-operative day, all eight patients were confirmed to be negative by RT-PCR and were transferred to the general ward for postoperative treatment.

Discussion

COVID-19 is a quick-spreading virus; therefore, it is important to prevent its transmission from the operating room to vulnerable surgical patients and HCWs. Consequently, both confirmed and suspected patients should be isolated in the management of the operating room. For patients with any suspected symptoms, strict guidelines for isolation and operation room management are necessary [4]. Jiang et al. [5] reported that COVID-19 is clinically manifested as fever (> 90%), cough (around 70%), dyspnea (up to 50%), myalgia or fatigue (31–44%), sputum production (20–28%), headache (6.5–16%), and diarrhea (2–14%). Further, 81%, 14%, and 5% of patients present with mild, severe, and critical symptoms, respectively. The fatality rate is about 2.3% and it increases with age [6]. Therefore, early diagnosis and treatment are necessary even for mild symptoms [7]. In case of emergency C-sec patients with suspected symptoms, further evaluation and follow-up for COVID-19 diagnosis are required even after a successful operation.

According to our hospital's emergency surgery guidelines for COVID-19, radiologic findings, RT-PCR findings, and clinical symptoms are the main diagnostic tools for COVID-19. Among the radiologic imaging tools, chest computed tomography (CT) is a highly helpful tool for early infection detection and access to the disease course of COVID-19 pneumonia [8]. Even with suspected

https://doi.org/10.4097/kja.20204

COVID-19 symptoms without significant abnormal findings in chest imaging, guidelines for confirmed patients should be followed. All eight mothers were not outpatients of our hospital; however, they were transferred from other hospitals as per the hospital policy. Therefore, the mothers required urgent C-sec before the COVID-19 RT-PCR results were received. HCWs should wear enhanced PPE and the surgery should be performed in a negative pressure operating room as per emergency surgery guidelines for COVID-19 (Fig. 1A). However, there are difficulties in following these guidelines for urgent C-sec cases. First, obtaining the RT-PCR results requires more than 6 h and it is necessary to urgently perform emergency C-sec cases before receiving the results. Second, although chest CT requires a short duration of 5 min, it was not applied to all mothers given the need to avoid the radiation exposure of the fetus. All eight patients were managed according to the guidelines shown in Fig. 1A; therefore, we were required to wear enhanced PPE in all cases. Based on the aforementioned difficulties, we removed the chest CT from the guidelines and we now apply revised emergency C-sec guidelines (Fig. 1B).

After the COVID-19 outbreak in Daegu, our institution was designated for the delivery of suspected or confirmed mothers with COVID-19 with several delivery cases being expected. Therefore, the entire delivery center was converted to a negative pressure environment. To avoid interfering with other elective surgeries, C-sec cases were performed in a separate delivery center from the main operating room. Fortunately, since our hospital was designated for C-sec of COVID-19 confirmed and suspected mother, those without COVID-19 symptoms were not admitted during this period. Given that the delivery center was not originally designed as an operating room, the exact negative pressure could not be measured. Therefore, the smoke test was used to confirm the negative pressure in the C-sec operating room [9].

There are two anesthesia options: general and regional anesthesia. For general anesthesia, intubation should be performed with endotracheal intubation and extubation considered as high-risk aerosol-generating procedures [10]. Therefore, all HCWs, especially anesthesiologists, should wear enhanced PPE with PAPR. In the aerosol state, COVID-19 is viable for > 3 h in case of aerosol transmission [11]. Therefore, operations on suspected patients should be performed in a negative pressure room with the assumption that the aerosolized virus can spread. Moreover, there is a need for sufficient post-intubation or post-extubation time to remove airborne contaminants. According to the Center for Disease Control and Prevention, when the air changes/hour (ACH) is 12 times, 99% airborne-contaminant removal efficiency takes 23 min while 99.9% takes 35 min [12]. The ACH of our hospital is 12–16 times. Consequently, the door is not allowed to open for at least 30 min after extubation, which is informed to all the HCWs participating in the surgery. Given the aforementioned reasons, we preferred regional anesthesia over general anesthesia. For regional anesthesia, the mother wears an N95 mask to minimize the possibility of virus transmission.

Among the seven mothers suspected of COVID-19 infection, six presented with fever; among them, two delivered stillborn babies, two had preterm labor, and two had PROM. Two of the seven suspected patients presented with dyspnea, which improved after child-birth. Dyspnea is common during pregnancy and could occur during severe labor pain [13]. All suspected patients lacked additional post-delivery symptoms and the COVID-19 was negative after several post-surgery hours. Despite the aforementioned results, it is currently difficult to differentially diagnose the presence or absence of COVID-19 even with mild symptoms. Therefore, in cases where COVID-19 results cannot be waited for, strict guidelines for managing the operating room are required. In addition, there have been reports of presymptomatic (silent) patients [14] who were reported by Song et al. [15] to reach about 10% (3 of 28 patients). Moreover, there are guidelines for elective surgery patients in pandemic situations regarding operation room management to distinguish presymptomatic patients from uninfected patients (Fig. 1C).

In conclusion, it is essential to isolate the confirmed patients as per the institutional perioperative COVID-19 infection prevention protocol. These case reports emphasize on the perioperative management guidelines for suspected COVID-19 cases to prevent virus transmission. Therefore, suspected patients with symptoms should be managed using strict guidelines similar to those of confirmed patients.

Funding Statement

This study was supported by the Research Program of Medicity Daegu Council funded by Daegu Metropolitan City (fund code: COVID19_DM23).

Conflicts of Interest

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

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https://doi.org/10.4097/kja.20204

KJA
Korean Journal of Anesthesiology

Continued catastrophic cardiovascular collapse following intraoperative hydrogen peroxide irrigation: time to reconsider its use!

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Letter to the Editor

Korean J Anesthesiol 2021;74(2):175-177
https://doi.org/10.4097/kja.20375
pISSN 2005-6419 • eISSN 2005-7563

Received: July 9, 2020
Accepted: July 12, 2020

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Hydrogen peroxide (H_2O_2) is commonly used for cleansing infected wounds in orthopedic and other surgeries. While often thought to be innocuous, the use of H_2O_2 has led to severe and fatal consequences [1]. Published literature is unclear about the volume of H_2O_2 that is safe for use. We present a case in which excessive volume of H_2O_2 was used for deep bilateral leg wound debridement leading to sudden cardiovascular collapse and cardiac arrest. We explored the recommended volume of H_2O_2 safe for use and lay down recommendations to avoid future mishaps. Written consent has been obtained from the patient for publication of this report.

We describe the management of a 37-year-old man who was allergic to naproxen and admitted for left knee septic arthritis and right calf cellulitis. He suffered from hypertension, uncontrolled type II diabetes mellitus, bilateral peroneal vein thrombosis (on treatment with enoxaparin) and acute kidney injury. He underwent left knee open arthrotomy, followed by second-look washout 4 days later, both under general anesthesia, uneventfully. Bilateral lower leg magnetic resonance imaging showed multiple septic emboli with deep pockets of pus in his right posterior calf and left gastrocnemius muscles.

He was scheduled for his 3rd surgery for exploration and drainage of abscesses in both lower limbs. A single-shot left femoral nerve block (15 ml of 0.5% ropivacaine) and a right popliteal block (20 ml of 0.5% ropivacaine) were performed before induction of general anesthesia. He received fentanyl (50 μg), lignocaine (10 mg), propofol (150 mg), and atracurium (30 mg), and airway was secured with an endotracheal tube. He had also received these drugs in the previous two surgeries. He was placed in the right lateral decubitus position for surgery. Anesthesia was maintained with sevoflurane and intermittent atracurium and morphine. End-tidal carbon dioxide ($EtCO_2$) was maintained at 36–42 mmHg. He remained hemodynamically stable throughout surgery. Towards the final stages of surgery, wounds on both lower limbs were irrigated with mixed H_2O_2 (3% w/w, PharmaKoe, ICM Pharma, Singapore) and normal saline. A total of 800 ml of 3% H_2O_2 was used considering extensive bilateral deep wounds. While wounds were irrigated, the patient showed signs of breathing, and atracurium (10 mg) was administered. A few minutes later, a sudden drop in $EtCO_2$ (7 mmHg) was noted. Breathing circuits and carbon dioxide sampling line were checked. The patient was hand ventilated with 100% oxygen.

Saturation remained > 97%; however, blood pressure dropped to 81/22 mmHg, and bradycardia developed (37 beats/min). Two separate doses of atropine 0.6 mg were administered without improvement. The carotid pulse was absent. Pulseless electrical activity was declared, and the patient was turned supine for external chest compressions. He received three boluses of 1 mg adrenaline before the return of spontaneous circulation.

The total resuscitation time was 5 min. Post-resuscitation blood pressure was 128/108 mmHg, with a heart rate of 154 beats/min. The left radial artery was cannulated, and a blood sample for arterial blood gas revealed respiratory acidosis (pH: 7.189, pCO_2: 65.9 mmHg). A central venous line was inserted, and an infusion of noradrenaline (0.2 μg/kg/min) was started. The patient was transferred to the intensive care unit. There was no evidence of pulmonary embolism on computed tomography pulmonary angiography. Postoperative troponin (33.9 pg/ml), and electrocardiogram (ECG) were unremarkable. Two-dimensional echocardiography revealed no abnormalities. Wound cultures from both calves grew methicillin-susceptible Staphylococcus aureus; however, blood cultures were negative. The patient was extubated the next day and transferred to the general ward. Subsequently, the patient underwent wound debridement thrice without H_2O_2 under general anesthesia uneventfully.

The cause of cardiovascular collapse in this patient may include anaphylaxis due to atracurium, myocardial infarction, septic shock, and pulmonary embolism. However, anaphylaxis due to atracurium was unlikely in the absence of bronchospasm and skin rashes. Sepsis was ruled out because there was no rise in temperature and the blood culture was negative. Myocardial infarction was ruled out because troponin was within the expected range and ECG remained unremarkable. Cardiovascular collapse in the true sense coincided with washing of wounds with H_2O_2.

The exact mechanism of cardiovascular collapse is unknown, but embolic phenomenon is widely accepted. Urban et al. [2] recommended 3% H_2O_2 solution as a safe and effective irrigation solution but did not specify the volume. In published literature, the concentration and volume of H_2O_2 are 1–3% and up to 300 ml, respectively [3]. At standard temperature and pressure, 1 ml of 3% H_2O_2 elaborates approximately 10 ml of oxygen [3]. H_2O_2 in closed cavities under pressure is considered to pose a higher risk of oxygen embolus [4]. In our case, 800 ml of 3% H_2O_2, certainly excessive, was used to clean bilateral large deep wounds, which probably released 8 L of oxygen. Some oxygen entered into the closed spaces, which had no egress, thus entering the blood vessels through the perforation of a plexus vein. The injection of bubbles into the plexus vein led to gas emboli entering the right heart, causing a decrease in the cardiac output, resulting in catastrophic cardiovascular collapse [3].

Lu and Hansen [5] suggested that the use of H_2O_2 in orthopedic surgery requires more large-scale clinical studies to determine its effectiveness and safety as an adjunct antiseptic. The UK Medicines and Healthcare Regulatory Agency [4] published a safety alert advising not to use H_2O_2 in closed body cavities and deep wounds. We performed internet searches on the maximum recommended doses of H_2O_2, but no conclusive results emerged. We contacted the local supplier PharmaKoe (Singapore) and Health Sciences Authority (Singapore's regulatory body for healthcare products); however, they had no firm information about recommended doses (email communications).

In conclusion, H_2O_2 is considered a safe agent for wound debridement, however, cases of catastrophic cardiovascular collapse have been reported, and its utility has been questioned [1]. Currently there is no clear recommendation for either H_2O_2 concentration or volume, and a consensus guidance is required. Until the availability of clear recommendations, greater vigilance is necessary when H_2O_2 irrigation is used.

Conflicts of Interest

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

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https://doi.org/10.4097/kja.20375

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KJA
Korean Journal of Anesthesiology

Letter to the Editor

Korean J Anesthesiol 2021;74(2):178-180
https://doi.org/10.4097/kja.20398
pISSN 2005-6419 • eISSN 2005-7563

Received: July 18, 2020
Revised: August 5, 2020
Accepted: August 6, 2020

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Continuous erector spinae plane blocks with automated boluses for analgesia following percutaneous nephrolithotomy

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Percutaneous nephrolithotomy (PCNL) is a minimally invasive surgical procedure providing an alternative to open surgery for removal of large stones from the kidney [1]. Despite its minimally invasive nature, the procedure can still be associated with significant postoperative pain and opioid requirements, either of which may prohibit same-day discharge. This is especially true in cases of multiple access tracts, larger tract size, or the use of a postoperative nephrostomy tube. The erector spinae plane (ESP) block was first described by Forero et al. [2] as an analgesic modality for thoracic neuropathic pain. This block has since been described for analgesia following PCNL and other retroperitoneal urologic surgeries [3]. However, these reports have focused on single injection nerve blocks, and the duration of pain following PCNL with nephrostomy tube placement is likely to exceed that of a single injection nerve block. Continuous peripheral nerve blocks offer a much longer duration of analgesia; however, it remains unknown whether a continuous technique may be applied to the ESP block, especially in the context of analgesia following PCNL. We report on five patients who had a continuous ESP block following PCNL. This series represents the first evidence that a continuous ESP block may provide postoperative analgesia and facilitate discharge in patients undergoing PCNL and suggests that automated boluses and an infusion delay timer may increase the spread and duration of the infusion.

The University of California San Diego Institutional Review Board waives review requirements for short case series. Written informed consent for the ESP block and publication of relevant, non-identifiable history and imaging in the form of a case report was obtained from all patients. Five patients, ranging in age from 34 to 75 years, underwent PCNL with nephrostomy tube placement and had a continuous ESP block for postoperative analgesia. In the preoperative area, patients were positioned prone with standard American Society of Anesthesiologists monitors and oxygen delivered via facemask. Using either a 5- to 2-MHz curvilinear probe (C60xi, Edge II®, SonoSite, USA) or a 13- to 6-MHz high frequency linear probe (HFL38xi, Edge II®, SonoSite, USA), the transverse process of the 10th thoracic vertebra was identified by counting up from the 12th rib. After sterilely prepping and draping the insertion site, the skin was anesthetized with 2 ml lidocaine 1%. A 17-gauge (G) Tuohy needle (FlexTip Plus®, Teleflex Medical, USA) was then advanced under ultrasound guidance with an in-plane technique to a point just to the depth of the erector spinae muscle and superficial to the 10th transverse process ipsilateral to the surgical side (Fig. 1). The plane to the depth of the muscle was opened by injecting 30 ml ropivacaine 0.5% with 2.5 μg/ml epinephrine. The local anesthetic was visualized spreading in both cephalad and caudad directions to the depth of the erector

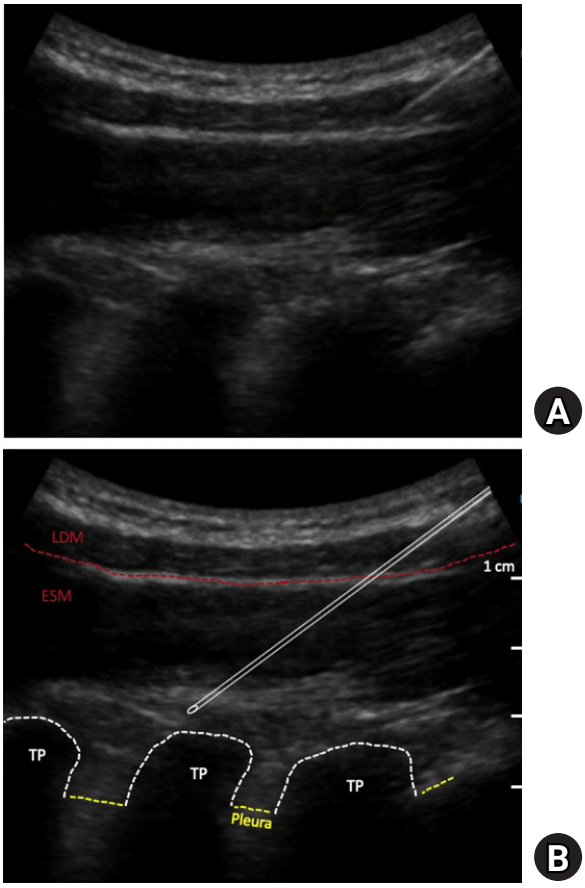

Fig. 1. (A) The 10th thoracic vertebral transverse process is identified to the depth of the erector spinae and latissimus dorsi muscles. A 17-gauge Tuohy needle is advanced toward this transverse process. (B) Schematic demonstrating the latissimus dorsi (LDM) and erector spinae (ESM) muscles, as well as the transverse processes (TP), pleura, and needle trajectory (white outline).

spinae muscle. A 19 G flexible, single-orifice perineural catheter (FlexTip Plus®, Teleflex Medical, USA) was inserted under ultrasound guidance. Correct location of the catheter was confirmed by injection of an additional 1–2 ml ropivacaine 0.5% with visualization of spread on the plane to the depth of the erector spinae muscle. The catheter was then secured at the skin with clear, occlusive dressings and 2-octyl cyanoacrylate adhesive to prevent dislodgement of the catheter, leakage, and infection.

Patients received intermittent boluses of ropivacaine 0.2% (15 mL automatic bolus every 2 hours with 5 ml patient-controlled bolus available every 30 minutes) using an ambulatory electronic pump (Nimbus™ II PainPRO®, InfuTronix, USA) with a 500 ml reservoir of ropivacaine 0.2%. As the block was initially administered with a long-acting local anesthetic (typically 8–12 h duration), a 6-hour delay was set for the automated bolus doses to increase the total duration of the initial block combined with the postoperative local anesthetic administration. Prior to discharge, detailed instructions on catheter care and removal were provided to the patients and a caregiver. They were instructed to assess the catheter site daily for evidence of infection or dislodgement and educated on the removal of the catheter. All patients were discharged on either the day of surgery or the first postoperative day and received daily telephone follow-up during which they reported excellent analgesia with minimal or no supplementation by oral opioid analgesics for the duration of the continuous ESP block. All catheters were successfully removed by the patients with the help of a caregiver on either the second or third postoperative day.

Historically, continuous peripheral nerve blocks have been administered primarily as a continuous infusion supplemented by patient-controlled boluses. However, there is evidence that larger, repeated bolus doses provide superior analgesia, possibly as a result of improved spread of the local anesthetic [4]. Evidence for the improved spread may be found in one study demonstrating automated boluses increasing the number of affected dermatomal levels compared to continuous infusions for continuous paravertebral blocks [5]. Since plane blocks, such as ESP, rely on the spread of local anesthetic on an interfacial plane, automated boluses may be particularly useful for this group of blocks. However, until recently, ambulatory pumps capable of providing automated boluses in addition to patient-controlled boluses were unavailable [4].

In the presented series, ESP perineural local anesthetic administered in automated boluses with patient-controlled dose supplementation provided outstanding analgesia with minimal opioid requirements in five outpatients following PCNL. Further investigation involving randomized, controlled trials is indicated to determine the clinical benefit of continuous ESP blocks for PCNL and other urologic surgeries, as well as the optimal dosing strategies for the block.

Funding Statement

InfuTronix (Natick, MA, USA) provided the ambulatory infusion pumps used for these cases.

Conflicts of Interest

John J. Finneran IV: Dr. Finneran's institution has received funding and/or product for his research from Myoscience, Epimed, InfuTronix, Ferrosan Medical Devices, and SPR Therapeutics.

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

Seth K. Bechis: Dr. Bechis is a paid consultant for Boston Scien-

tific and Karl Storz.

Roger L. Sur: Dr. Sur is a paid consultant for Boston Scientific, Karl Storz, Cook Medical, Lumenis, and serves as Chief Medical Officer for CalyxoTM

Brian Ilfeld: Dr. Ilfeld's institution has received funding and/or product for his research from Myoscience, Epimed, InfuTronix, Ferrosan Medical, Heron Therapeutics, and SPR Therapeutics.

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https://doi.org/10.4097/kja.20398

KJA
Korean Journal of Anesthesiology

The indirect benefits of a quadratus lumborum block in urgent laparotomy, hepatic resection, and open aortic surgery

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Letter to the Editor

Korean J Anesthesiol 2021;74(2):181-182
https://doi.org/10.4097/kja.20417
pISSN 2005-6419 • eISSN 2005-7563

Received: July 25, 2020
Accepted: August 9, 2020

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The analgesic indications of quadratus lumborum block (QLB) using various approaches have been described in different surgical procedures such as proctosigmoidectomy, above-knee amputation, abdominal hernia repair, breast reconstruction, colostomy closure, radical nephrectomy, lower extremity vascular surgery, laparotomy, colectomy, cholecystectomy, hysterectomy, caesarian section, pelvic bone fracture surgery, and hip surgery.

The excellent work of Aoyama et al. [1] comparing the analgesic benefits of QLB versus a posterior transverse abdominis plane block in laparoscopic gynecologic surgery must be recognized. However, lower pain scores at rest and at 48 h were observed in the QLB group; these results should have been highlighted, and not ignored, in the conclusions.

A recent systematic review by Jin et al. [2], focused on postoperative analgesic outcomes, showing the contribution of QLB in improving postoperative pain in renal surgery, cesarean section, and also in other abdominal, pelvic and hip surgeries despite the quality of evidence is low in these latter cases.

Nevertheless, there are still some topics and particular scenarios related to the use of QLB in some abdominal surgeries that need to be explored. QLB is important in special situations, depending on the type of patient, surgery, or clinical scenario. These advantages are not limited to strict perioperative analgesia.

Despite systemic infection not being a contraindication for neuraxial techniques, the American Society of Regional Anesthesia and Pain Medicine recommend that we should consider alternatives to neuraxial techniques for patients with a high-risk of infection to minimize the occurrence of serious complications [3].

In urgent laparotomy (in patients suffering from peritonitis), a single-shot QLB is certainly an option, as it provides significant somatic and visceral analgesia up to 24 h postoperatively [2], which may diminish the need of a continuous technique and subsequent risk of catheter colonization. In the current literature, single-shot QLB has been associated to a reduction in pain and opioid consumption up to 48 h after gynecologic/obstetric surgery [1]. Moreover, an eventual interfascial infection would be more manageable or treatable than a neuraxial infection/abscess which would be signifciantly different in terms of possible permanent complications.

Patients undergoing surgeries such as open aortic surgery or liver resection, in which significant blood loss is expected, also carry an increased risk of hematoma associated with the neuraxial catheter placement or withdrawal as consequence of acquired perioperative coagulopathy [4]. Despite deep peripheral blocks and neuraxial anesthesia having similar recommendations for patients taking drugs that affect hemostasis, the occurrence of hematoma associated with different degrees of perioperative coagulopathy due to blood loss and transfusion is not directly addressed in the "Regional Anesthesia in the

Patient Receiving Antithrombotic or Thrombolytic Therapy" guidelines [3]. Obviously, a neuraxial hematoma would have the potential to be much more damaging (leading to permanent neurological symptoms) than an interfascial hematoma, which has more insidious symptoms and less need for an emergent decompressive intervention. In this case, the longer analgesic action of a single-shot technique is once again very important, as bilateral continuous QLB techniques are laborious techniques.

Hepatic resection performed under low central venous pressure to reduce blood loss and to improve surgical conditions will limit the safety of a combined anesthetic technique (general anesthesia plus thoracic epidural technique), because an epidural technique is hard to titrate and can produce hypotension. Hence, an epidural block is used mostly for postoperative analgesia, because if hypotension occurs, unwanted fluid administration in the resection phase may be needed, which may increase blood loss and complicate surgical conditions. In this type of surgery, a right-sided QLB block can contribute to hemodynamic management during general anesthesia by reducing the amounts of hypnotic drugs and opioids given, which diminishes the need for fluid and vasopressor administrations associated with greater anesthetic depth [5].

In the postoperative period of hepatic resection surgery, QLB analgesia will provide better thoracic expansion, which reduces the need for mechanical ventilation support, particularly in upper abdominal surgeries, and improves venous return and subsequent hemodynamic stability.

Complications related to a deep interfascial block should always be taken into consideration. We should not forget that QLB poses a risk of local systemic toxicity and carries a minimal risk of hypotension (described occasionally in bilateral techniques) due to the spread of local anesthetic to the paravertebral space [5].

To my knowledge, these aspects related to the QLB use in each particular scenario have not yet been comprehensively addressed. The longer duration of action of QLB has the potential to minimize the need for epidural catheterization and its related complications. Hepatic resection surgery is an interesting model to study the intraoperative benefits of QLB that can surpass the advantages of epidural use.

Conflict of Interest

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

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https://doi.org/10.4097/kja.20417

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Delayed recurrent spontaneous pneumothorax in a patient recovering from COVID-19 pneumonia

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Letter to the Editor

Korean J Anesthesiol 2021;74(2):183-185
https://doi.org/10.4097/kja.20400
pISSN 2005-6419 • eISSN 2005-7563

Received: July 19, 2020
Revised: August 5, 2020
Accepted: August 26, 2020

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While spontaneous pneumothorax in coronavirus disease (COVID-19) pneumonia is currently a well-known complication, recurrent delayed pneumothorax has not been reported. We report on a patient with recurrent delayed pneumothorax 9 weeks after presenting with COVID-19 pneumonia, when she was deemed to have recovered. This report is published with the written consent of the patient's legal guardian.

A 66-year-old woman presented to the emergency department with fever and non-productive cough in the last 12 days and dyspnea in the last 3 days. She was healthy, a non-smoker, and had a history of well-controlled asthma, thyroidectomy, and parathyroidectomy. Twelve hours later, she required intubation and mechanical ventilation for worsening respiratory failure. A diagnosis of COVID-19 was confirmed after testing the tracheal sample. Subsequently, she became critical and developed neuropathy leading to significant quadriparesis; she was slowly weaned from the ventilator. Percutaneous tracheostomy was performed; ventilator support was adjusted to pressure support 8 cm H_2O, positive end-expiratory pressure 5 cmH_2O, and FiO_2 0.35. Chest computed tomography (CT) on Day 19 of hospitalization showed extensive bilateral patchy ground glass opacification, significant bronchial distortion, and traction bronchiectasis; no pneumatoceles were observed. She received pulsed intravenous methylprednisolone for 3 days. Chest radiography on Day 27 showed two pneumatoceles approximately 3–4 cm in diameter in the right lung. The following day, she spontaneously developed a large pneumothorax and broncho-pleural fistula on the contralateral side requiring a chest drain. CT on Day 31 showed new onset pneumomediastinum, persistence of pneumothorax on the left side, and appearance of additional pneumatoceles in the right upper zone. There was no evidence of pulmonary embolism. Application of low-pressure suction led to complete re-expansion of the left lung, and the broncho-pleural fistula resolved over the next week. Repeat bronchial samples tested negative for COVID-19.

On Days 37 and 41, *Serratia marcescens* was isolated from the sputum culture and *Klebsiella aerogenes* was isolated from the blood culture, respectively; both were susceptible to a week's course of meropenem. She was completely weaned off ventilatory support by Day 54. Repeat CT showed resolution of the pneumomediastinum, reduction in size of the right lung pneumatoceles, and appearance of new pneumatoceles in the left lung. Trachea was decannulated on Day 59, and she was transferred to the medical ward 3 days later. On Day 68, she spontaneously developed tension pneumothorax on the left side requiring emergency decompression and chest drain (Fig. 1). She did not require any additional ventilatory support except supplemental oxygen, and the chest drain was removed a week later. She required another 3 weeks to recover and be discharged. The total duration of hospitalization was 3 months. SpO_2 of approximately 90% on room air was deemed acceptable and arrangements were put in place for follow-up and home oxygen

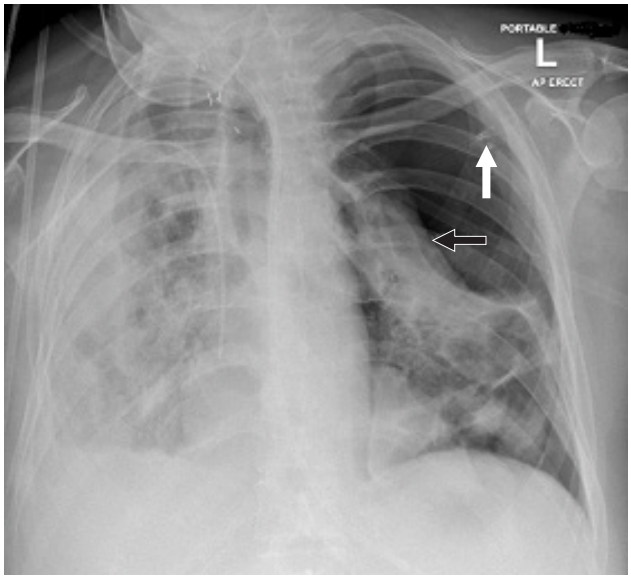

Fig. 1. Chest radiograph on Day 68 showing the pneumothorax on the left side with compression of the lung (black arrow). The hub of the cannula used to decompress the tension pneumothorax is still in situ (white arrow). The trachea has been decannulated.

supplementation if required.

Pneumothorax in COVID-19 pneumonia can be a presenting feature or develop in the acute phase [1]. Hollingshead and Hanrahan [2] reported on a patient who presented with loculated pneumothorax in the fourth week of illness. There have been no reports of recurrent delayed spontaneous pneumothorax occurring several weeks later. Our report suggests that pneumatoceles could be the precursor for the development of pneumothorax in COVID-19. In an autopsy series of 38 patients, Carsana et al. [3] found that loss of pneumocytes was present in 100% of the cases, with a multifocal distribution comprising the majority. The mean duration of hospitalization in this series was only 7 days, with a maximum of 23 days. It is possible that the process of lung destruction continues with a longer duration of illness.

Although the first pneumothorax was expected on the same side as that of the pneumatoceles, it developed on the contralateral side in this patient. The speed at which the pneumatoceles developed is notable. In previous case reports, the pneumomediastinum and pneumothorax resolved with time [4]. While the pneumomediastinum did resolve in our patient, the pneumatoceles not only persisted but new ones continued to appear much later in the clinical course, despite the repeat sample testing negative for COVID-19. Klebsiella pneumonia has been associated with the formation of pneumothorax and empyema [5]. In all such cases, the bacterium is cultured from the sputum or pus specimen. In our patient, Klebsiella was cultured from blood and not from any of the sputum specimens. The pleural drain fluid was not purulent. Thus, it is unlikely that the pneumothorax was caused by the Klebsiella infection.

This report highlights the need for a high index of suspicion for pneumothorax in patients with severe COVID-19 pneumonia, when they deteriorate acutely after appearing to stabilize. Considering that this can happen in very late stages of the disease when there is no sign of an active infection, close monitoring is required in the presence of radiological evidence of pneumatoceles.

Acknowledgements

The authors gratefully acknowledge the support of Dr. SR Haynes and Dr. WPM Chan.

Conflicts of Interest

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

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Pulmonary vasculature in COVID-19: mechanism to monitoring!

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Letter to the Editor

Korean J Anesthesiol 2021;74(2):186-187
https://doi.org/10.4097/kja.20536
pISSN 2005-6419 • eISSN 2005-7563

Received: September 25, 2020
Accepted: September 29, 2020

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Although the different mechanisms affecting the extent of hypoxemia in severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) pneumonia, the relevance of the proposed phenotypic classification of COVID-19 related acute respiratory distress syndrome (ARDS), and the ideal ventilation strategies according to the existing ARDSnet protocol continue to be debated, the recognition of COVID-19 as an endothelial disease with vascular endothelium breakdown at the root of organ dysfunction is beyond debate [1]. The pulmonary vasculature in particular is prone to insult given that the protective endothelial glycocalyx (EG) is peculiarly thin in the pulmonary capillaries. The disruption of the EG due to systemic inflammation and the resultant cytokine storm, along with dynamic alteration in the endothelial angiotensin-converting enzyme 2 and angiotensin peptide levels, disturb the pulmonary vascular homeostasis, culminating in vascular hyperpermeability and pulmonary edema, leading to substantial oxygenation impairment [2].

While a rigid division of the distinct COVID-19 phenotypes into Type-L (low ventilation/perfusion ratio, lung weight, and recruitability with preserved compliance) and Type-H (high right-to-left shunt, lung weight, and recruitability with reduced compliance) has been referred to as anecdotal by a few, the proponents of the classification themselves suggest a possible transition from Type-L to Type-H as the disease evolves [1]. The latter research group cites negative intrathoracic pressure (patient self-induced lung injury) and inflammation-associated enhanced permeability as the major causative factors for interstitial lung edema in such circumstances [1]. It is noteworthy that autopsies performed on those who succumb early during the COVID-19 disease process showed remarkable pulmonary vascular congestion [2]. Vascular disease can also explain the massive elevations seen in the D-dimer levels, which heralds multisystem involvement with vasculopathy at the heart of the matter [2].

As an extension of the aforementioned realization of the mechanistic role of vascular dysfunction in SARS-CoV-2ARDS, monitoring of the pulmonary vasculature by lung ultrasound and/or transpulmonary thermodilution (TPTD) based assessment of extravascular lung water (EVLW) can be of considerable assistance in characterizing lung edema. Serial EVLW assessment can also help to monitor lung protective ventilation and recruitment maneuvers, guide fluid-diuretic therapy, and evaluate overall response to treatment [3]. Moreover, the pulmonary vascular permeability index (PVPI, preload-indexed EVLW) may also be computed (in the presence of other TPTD-derived preload variables), which when elevated pinpoints enhanced capillary permeability as the primary cause of pulmonary edema [3].

Groeneveld and Verheij [4] outlined that a link between pulmonary vascular injury and an increase in PVPI extends from the cohort of mechanically ventilated patients with pneumonia to those with extrapulmonary sepsis-induced forms of ARDS, which supports the role of monitoring for the same during the various progressive stages of

COVID-related ARDS. A prospective multicenter large-scale study by Kushimoto et al. [5] discovered that PVPI values ranging from 2.6 to 2.85, rendered a definitive ARDS diagnosis with a specificity of 0.90 to 0.95, while a PVPI value < 1.7 effectively ruled out a diagnosis of ARDS with a specificity of 0.95. In addition, by following the quantitative diagnosis of pulmonary edema (EVLW > 10 ml/kg), monitoring of PVPI can also assist in the management of patients with COVID-19 with associated cardiac morbidities by an augmented delineation of the cardiogenic causes (elevated EVLW with normal PVPI) from the non-cardiogenic causes (elevated EVLW and PVPI, signifying 'leaky' pulmonary capillaries).

While the results of the prospective cohort study 'Extra vascular lung water and pulmonary permeability in critically ill patients with SARS-CoV-2 (COVID-19) (PiCCOVID)' (NCT04376905) are ardently awaited, the aforementioned discussion adequately highlights that a more objective form of disease progression and therapeutic response monitoring can develop as our comprehension of the COVID-19 related pathophysiology improves.

Conflicts of Interest

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

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Fluid responsiveness in the pediatric population

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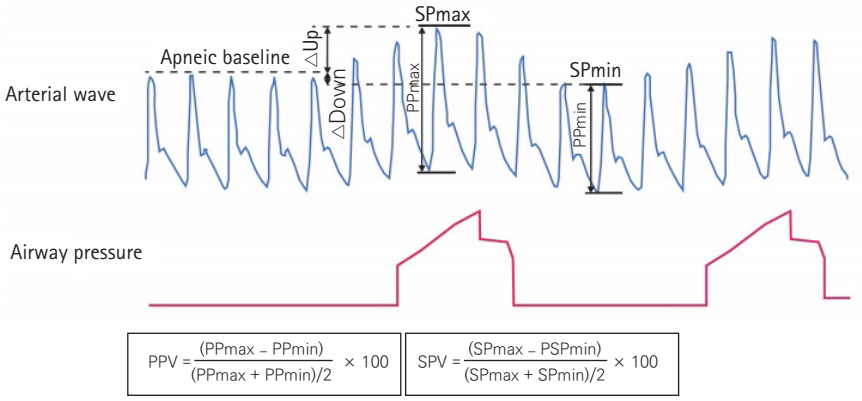
Corrigendum

Korean J Anesthesiol 2021;74(2):188
https://doi.org/10.4097/kja.19305.e1
pISSN 2005-6419 • eISSN 2005-7563

Korean J Anesthesiol 2019 October 72(5): 429-440
https://doi.org/10.4097/kja.19305

The article by Lee et al. entitled, "Fluid responsiveness in the pediatric population" (Korean J Anesthesiol 2019 Oct; 72(5): 429-440) should add the following explanation in Fig. 2.



The unit of the suggested equations for PPV and SPV is %.

Although SPV (mmHg) is traditionally calculated as SPmax-SPmin or ΔUp + ΔDown, SPV(%) has been used for pediatric patients.

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Notice

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Enacted March 24, 1995
Recently revised (26th) Jan 28, 2021

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The Editor assumes that all authors listed in a manuscript have agreed with the following policy of the KJA on submission of manuscript. Except for the negotiated secondary publication, manuscript submitted to the KJA must be previously unpublished and not be under consideration for publication elsewhere. Under any circumstances, the identities of the referees will not be revealed. If a new author should be added or an author should be deleted after the submission, it is the responsibility of the corresponding author to ensure that the author concerned are aware of and agree to the change in authorship. The KJA has no responsibility for such changes. Minimum publication charges and additional fee for reprints will due on every manuscript. Color illustrations are charged to the authors. All published manuscripts become the permanent property of the KSA and may not be published elsewhere without written permission.

General information

1. Publication types

The KJA focuses on Original articles (Clinical trial/Experimental research, Meta-analysis), Case reports, Reviews, Letters to the editor, Statistical round, and Editorials.

2. Language

Manuscripts submitted to the KJA should be compiled in English. Spellings should abide by American spellings. Medical terminology should be written based on the most recent edition of Dorland's Illustrated Medical Dictionary. Accepted manuscripts are requested to be proofread by professional English editors.

3. Submission of manuscript

In addition to members of the KSA, any researcher throughout the world can submit a manuscript if the scope of the manuscript is appropriate. Authors are requested to submit their papers electronically by using the online manuscript submission system, available at: https://www.editorialmanager.com/kja/default.aspx. Authors, reviewers, and editors send and receive all correspondences through this system.

4. Peer review process

Under any circumstances, the identities of the reviewers will not be revealed and the reviewers will be blinded to the names of the authors and the institutions from which the manuscripts have been sent. Submitted manuscripts will be reviewed by 2 or more experts in the corresponding field. The Editorial Board may request authors to revise the manuscripts according to the reviewer's opinion. After revising the manuscript, the author should upload the revised files with a reply to each item of the reviewer's opinion. The author's revisions should be completed within 30 days after the request. If it is not received by the due date, the Editorial Board will not consider it for publication again. To extend the revision period to more than 30 days, the author should negotiate with the Editorial Board. The manuscript review process should be finished the second review. If the authors wish further review, the Editorial Board may consider it. The Editorial Board will make a final decision on the approval for publication of the submitted manuscripts and can request any further corrections, revisions, and deletions of the article text if necessary. Statistical editing is also performed if the data need professional statistical review by a statistician. The review and publication processes that are not described in the Instructions for Authors will be incorporated into the Editorial Policy Statements approved by the Council of Science Ed-

itors Board of Directors, available at: www.councilscienceeditors.org/.

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For the policies on research and publication ethics that are not stated in these instructions, the Good Publication Practice Guidelines for Medical Journals, available at: https://www.kamje.or.kr/board/view?b_name=bo_publication&bo_id=13, or the Guidelines on Good Publication, available at: publicationethics.org/, can be applied.

1. Conflict-of-interest statement

Conflict of interest exists when an author or the author's institution, reviewer, or editor has financial or personal relationships that inappropriately influence or bias his or her actions. Such relationships are also known as dual commitments, competing interests, or competing loyalties. These relationships vary from being negligible to having a great potential for influencing judgment. Not all relationships represent true conflict of interest. On the other hand, the potential for conflict of interest can exist regardless of whether an individual believes that the relationship affects his or her scientific judgment. Financial relationships such as employment, consultancies, stock ownership, honoraria, and paid expert testimony are the most easily identifiable conflicts of interest and the most likely to undermine the credibility of the journal, the authors, or of the science itself. Conflicts can occur for other reasons as well, such as personal relationships, academic competition, and intellectual passion (http://www.icmje.org/conflicts-of-interest/). If there are any conflicts of interest, authors should disclose them in the manuscript. The conflicts of interest may occur during the research process as well; however, it is important to provide disclosure. If there is a disclosure, editors, reviewers, and reader can approach the manuscript after understanding the situation and the background of the completed research.

2. Statement of informed consent and Institutional Review Board approval

If the study in the article is on human subjects or human-originated material, informed consent for the study and the Institutional Review Board (IRB) approval number needs to be provided. Copies of written informed consents and IRB approval for clinical research should be kept. If necessary, the editor or reviewers may request copies of these documents to make potential ethical issues clear.

3. Statement of human and animal right

Clinical research should be done in accordance of the Ethical Principles for Medical Research Involving Human Subjects, outlined in the Helsinki Declaration of 1975 (revised 2013) (available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). Authors should indicate whether the procedures were conducted in accordance with the Helsinki Declaration-2013 in the Text. Clinical studies that do not meet

the Helsinki Declaration will not be considered for publication. Human subjects should not be identifiable, such that patients' names, initials, hospital numbers, dates of birth, or other protected healthcare information should not be disclosed. For animal subjects, research should be performed based on the National or Institutional Guide for the Care and Use of Laboratory Animals, and the ethical treatment of all experimental animals should be maintained.

4. Registration of the clinical trial research

Any researches that deals with clinical trial should be registered with the primary national clinical trial registration site such as Korea Clinical Research Information Service (cris.nih.go.kr/) or other sites accredited by WHO or International Committee of Medical Journal Editor such as ClinicalTrials.gov (clinicaltrials.gov/).

5. Reporting guidelines

The KJA recommends a submitted manuscript to follow reporting guidelines appropriate for various study types. Good sources for reporting guidelines are the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Network (www.equator-network.org/) and the U.S. National Library of Medicine's (NLM's) Research Reporting Guidelines and Initiatives (www.nlm.nih.gov/services/research_report_guide.html). The appropriate checklist (and flow diagram, if applicable) must be included with each submission.

6. Authorship

Authorship credit should be based on: 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; AND 2) drafting the article or revising it critically for important intellectual content; AND 3) final approval of the version to be published; AND 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet these 4 conditions. If the number of authors is equal to or greater than 2, there should be a list of each author's role in the submitted paper. Authors are obliged to participate in peer review process. All others who contributed to the work who are not authors should be named in the Acknowledgements section. KJA has a strict policy on changes to authorship after acceptance of the article and will only consider changes in the most extraordinary situations once the article is accepted.

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8. Secondary publication

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9. Feedback after publication

If the authors or readers find any errors, or contents that should be revised, it can be requested from the Editorial Board. The Editorial Board may consider erratum, corrigendum or a retraction. If there are any revisions to the article, there will be a CrossMark description to announce the final draft. If there is a reader's opinion on the published article with the form of Letter to the editor, it will be forwarded to the authors. The authors can reply to the reader's letter. Letter to the editor and the author's reply may be also published.

9-1. Process to manage the research and publication misconduct

When the Journal faces suspected cases of research and publication misconduct such as a redundant (duplicate) publication, plagiarism, fabricated data, changes in authorship, undisclosed conflicts of interest, an ethical problem discovered with the submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and other issues, the resolving process will follow the flowchart provided by the Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts). The Editorial Board of KJA will discuss the suspected cases and reach a decision. KJA will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

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1) Article withdrawal

Articles in Press (articles that have been accepted for publication but which have not been formally published and will not yet have the complete volume/issue/page information) that include errors, or are discovered to be accidental duplicates of

other published article(s), or are determined to violate our journal publishing ethics guidelines in the view of the editors (such as multiple submission, bogus claims of authorship, plagiarism, fraudulent use of data or the like), may be "Withdrawn".

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Errors serious enough to invalidate a paper's results and conclusions (Infringements of professional ethical codes, such as multiple submission, bogus claims of authorship, plagiarism, fraudulent use of data or the like) may require retraction.

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Replacement (retraction with republication) can be considered in cases where honest error (e.g., a misclassification or miscalculation) leads to a major change in the direction or significance of the results, interpretations, and conclusions. If the error is judged to be unintentional, the underlying science appears valid, and the changed version of the paper survives further review and editorial scrutiny, then replacement of the changed paper, with an explanation, allows full correction of the scientific literature.

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KJA accepts the ICMJE Recommendations for data sharing statement policy (http://icmje.org/icmje-recommendations.pdf). All manuscripts reporting clinical trial results should submit a data sharing statement following the ICMJE guidelines from 1 July 2018. Authors may refer to the editorial, "Data Sharing statements for Clinical Trials: A Requirement of the International Committee of Medical Journal Editors," in Annals on 6 June 2017 (http://www.icmje.org/news-and-editorials/data_sharing_june_2017.pdf).

Manuscript preparation

1. Word processors and format of manuscript

A manuscript must be written in proper and clear English. The manuscript, including tables and their footnotes, and figure legends, must be typed in one double space. Materials should be prepared with a standard 12-point typeface or greater (Times New Roman typeface is preferred). The manuscript should be in the following sequence: cover letter (optional), title page file, manuscript (title and running title, abstract and keywords, introduction, materials and methods, results, discussion, references, tables, and figure legends), figures, other submission elements. All pages should be numbered consecutively starting from the title page. All numbers should be written in Arabic numerals throughout the manuscripts. Our preferred file format is DOCX or DOC. A single PDF file containing all materials in a file including figures and figure legends. In that case, authors should add line numbers throughout the document. Manuscript containing anything in headers and footers, except of page numbers, will be returned to authors. If your PDF submission is accepted, you will be asked to upload your final document file in DOCX or DOC format as well. Make sure to update your PDF file with the most recent version of your manuscript.

2. Abbreviation of terminology

Abbreviations should be avoided as much as possible. When they are used, full expression of the abbreviations following the abbreviated word in parentheses should be given at the first use. Common abbreviations, however, may be used, such as DNA. Abbreviation can be used if it is listed as a MeSH subject heading (http://www.ncbi.nlm.nih.gov/mesh).

3. Word-spacing

1) Leave 1 space for each side, using arithmetic marks as +, −, ×, etc.

Leave no space for hyphen between words.

2) Leave 1 space after " , " and " ; ". Leave 2 spaces after " . " and " : ".

3) Using parentheses, leave 1 space each side.

4) Brackets in parentheses, apply square brackets.

4. Citations

1) If a citation has 2 authors, write as "Hirota and Lambert." If there are more than 3 authors, apply 'et al.' at the end of the first author's surname. Ex) Kim et al. [1].

2) Citation should be applied after the last word or author's surname.

3) Apply citation before a comma or period.

4) Identify reference by several or coupled Arabic numbers, enclosed in square brackets on the line as [1,3,5].

5. Arrangement of manuscript

ALL articles should be arranged in the following order.

Cover letter (optional)

Title Page file, uploaded separately

Manuscript, as a single file in word processing format (eg, .doc), consisting of Title and running title, Abstract (if required for the article type; see relevant section), Body Text, References, Tables, Figure Legends, if any (in numerical order, on the same page); be sure to number all pages of the manuscript file

Figures (each Figure should be a separate file in figure file format)

Other submission elements (Supplemental Digital Content, etc.)

Each new section's title should begin on a new page. The conclusion should be included in the discussion section. Number pages consecutively, beginning with the first page. Page numbers should be placed at the middle of the bottom of page. For survey-based clinical studies, the original survey document does not need to be included in the body of the manuscript but may be supplemented in an appendix.

6. Statistical Analysis

1) Describe the statistical tests employed in the study with enough detail so that readers can reproduce the same results if the original data are available. The name and version of the statistical package should be provided.
2) Authors should describe the objective of the study and hypothesis appropriately. The primary/secondary endpoints are predetermined sensibly according to the objective of the study.[1]
3) The characteristics of measured variables should determine the use of a parametric or nonparametric statistical method. When a parametric method is used, the authors should describe whether the basic statistical assumptions are met.[2,3]
4) For an analysis of a continuous variable, the normality of data should be examined. Describe the name and result of the particular method to test normality.
5) When analyzing a categorical variable, if the number of events and sample is small, exact test or asymptotic method with appropriate adjustments should be used. The standard chi-squared test or difference-in-proportions test may be performed only when the sample size and number of events are sufficiently large.
6) The Korean Journal of Anesthesiology (KJA) strongly encourages authors to show confidence intervals. It is not recommended to present the P value without showing the confidence interval. In addition, the uncertainty of estimated values, such as the confidence interval, should be described consistently in figures and tables.[4]
7) Except for study designs that require a one-tailed test, for example, non-inferiority trials, the P values should be two-tailed. A P value should be expressed up to three decimal places (not as "$P < 0.05$"). If the value is less than 0.001, it should be described as "$P < 0.001$" but never as "$P = 0.000$." For large P value greater than 0.1, the values can be rounded off to one decimal place, for example, $P = 0.1$, $P = 0.9$.
8) A priori sample size calculation should be described in detail[5]. Sample size calculation must aim at preventing false negative results pertaining to the primary, instead of secondary, endpoint. Usually, the mean difference and standard deviation (SD) are typical parameters in estimating the effect size. The power must be equal to or greater than 80 percent. In the case of multiple comparisons, an adjusted level of significance is acceptable.[6]
9) It is recommended using mean ± SD or median (Q1, Q3) format to present representative values of continuous variables. Results must be written in significant figures. The measured and derived numbers should be rounded off to reflect the original degree of precision. Calculated or estimated numbers (such as mean and SD) should be expressed in no more than one significant digit beyond the measured accuracy. Therefore, the mean ± SD of body weight in patients measured on a scale that is accurate to 0.1 kg should be expressed as 65.45 ± 2.52 kg.
10) Except when otherwise stated herein, authors should conform to the most recent edition of the American Medical Association Manual of Style.[7]

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[1]Lee S, Kang H. Statistical and methodological considerations for reporting RCTs in medical literature. Korean J Anesthesiol 2015; 68: 106-15.

[2]Kim TK. T test as a parametric statistic. Korean J Anesthesiol 2015; 68: 540-6.

[3]Nahm FS. Nonparametric statistical tests for the continuous data: the basic concept and the practical use. Korean J Anesthesiol 2016; 69: 8-14.

[4]Park S. Significant results: statistical or clinical? Korean J Anesthesiol 2016; 69: 121-5.

[5]In J. Considerations when calculating the sample size for an inequality test. Korean J Anesthesiol 2016; 69: 327-31.

[6]Lee S and Lee DK. What is the proper way to apply the multiple comparison test? Korean J Anesthesiol 2018; 71: 353-60.

[7]http://www.amamanualofstyle.com/

7. Organization of manuscript

1) Clinical or Experimental research

(1) Title page

① Title

Title should be concise and precise.

For the title, only the first letter of the first word should be capitalized.

② Author information

First name, middle initial, and last name of each author, with their highest academic degree(s) (M.D., Ph.D., etc.), and institutional affiliations; make sure the names of and the order of authors as they appear on the Title Page and entered in the system match exactly.

③ Running title

A running title of no more than 40 characters, including letters and spaces, should be described. If inappropriate, the editorial board may revise it.

④ Corresponding Author

Name, mailing address, phone number, and e-mail address of the corresponding author

⑤ Previous presentation in conferences

Title of the conference, date of presentation, and the location of the conference may be described.

⑥ Conflict of interest

It should be disclosed here according to the statement in the Research and publication ethics regardless of existence of conflict of interest. If the authors have nothing to disclose, please state: "No potential conflict of interest relevant to this article was reported."

⑦ Funding

Funding to the research should be provided here. Providing a FundRef ID is recommended including the name of the funding agency, country and if available, the number of the grant provided by the funding agency. If the funding agency does not have a FundRef ID, please ask that agency to contact the FundRef registry (e-mail: fundref.registry@crossref.org). Additional detailed policy of FundRef description is available from http://www.crossref.org/fundref/.

⑧ Acknowledgments

Any persons that contributed to the study or the manuscript, but not meeting the requirements of an authorship could be placed here. For mentioning any persons or any organizations in this section, there should be a written permission from them.

⑨ IRB number

⑩ Clinical trial registration number

If any of these elements are not applicable to your submission, write "not applicable" after the number and topic; for example, "Prior Presentations: Not applicable."

(2) Manuscript

① Title and Running title

② Abstract

All manuscripts should contain a structured abstract that is written only in English. Provide an abstract of no more than 250 words. It should contain 4 subsections: Background, Methods, Results, and Conclusions. Quotation of references is not available in the abstract. A list of keywords, with a minimum of 6 and maximum of 10 items, should be included at the end of the abstract. The selection of keywords should be from MeSH (http://www.ncbi.nlm.nih.gov/mesh) and should be written in small alphabetic letters with the first letter in capital letter. Separate each word by a semicomma (;), and mark a period (.) at the end of the last word.

③ Introduction

The introduction should address the purpose of the article concisely and include background reports that are relevant to the purpose of the paper.

④ Materials and Methods

- The materials and methods section should include sufficient details of the design, subjects, and methods of the article in order, as well as the data analysis methods and control of bias in the study. Sufficient details need to be addressed in the methodology section of an experimental study so that it can be further replicated by others.
- When reporting experiments with human or animal subjects, the authors should indicate whether they received approval from the IRB for the study and the IRB approval number needs to be provided. When reporting experiments with animal subjects, the authors should indicate whether the handling of the animals was supervised by Institutional Board for the Care and Use of Laboratory Animals. "American Society of Anesthesiologists physical status classification" should not be abbreviated. As a rule, subsection titles are not recommended.
- Clearly describe the selection of observational or experimental participants. Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors

should justify why, except in obvious cases (e.g., prostate cancer). For additional information, please visit http://www.icmje.org/about-icmje/faqs/icmje-recommendations/.

· Reports of randomized trials must conform to the revised CONSORT guidelines and should be submitted with the CONSORT flow diagram. The CONSORT checklist should be submitted as a separate file along with the manuscript. The CONSORT statement, checklist, and flow diagram can be found at http://www.consort-statement.org or EQUATOR Network (https://www.equator-network.org/home/)

· Units

Laboratory information should be reported in International System of Units [SI]. Please refer to A Guide for Biological and Medical Editors and Authors, 6th Edn. Baron DN and Clarke HM, ed. (2008), CRC Press. or visit http://www.icmje.org/about-icmje/faqs/icmje-recommendations/

· Exceptions

A. The unit for volume is "L", others in "dl, ml, μl".

B. The units for pressure are mmHg or cmH_2O.

C. Use Celsius for temperature

D. Units for concentration are M, mM, μM.

E. When more than 2 items are presented, diagonal slashes are acceptable for simple units. Negative exponents should not be used.

F. Leave 1 space between number and units.

Exception) 5%, 36°C

· Drug Names and Equipment

Use generic names. If a brand name must be used, insert it in parentheses after the generic name. Provide ® or ™ as a superscript and manufacturer's name, and country.

· Ions

Ex) Na^+ [O], Mg^{2+} [O], Mg^{++} [X], Mg^{+2} [X]

· Statistics

Statistical methods must be described with enough detail so that readers can reproduce the same results if the original data available. The KJA strongly encourages authors to show confidence intervals. It is not recommended to present the P value without showing the confidence interval. A sample size calculation should be described in detail. Sample size calculation must aim at preventing false negative results pertaining to the primary, instead of secondary, endpoint.

⑤ Results

Results should be presented in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat all of the data in the tables or illustrations in the text; emphasize or summarize only the most important observations. Results can be sectioned by subsection titles but should not be numbered. Citation of tables and figures should be provided as Table 1 and Fig. 1.

⑥ Discussion

The discussion should be described to emphasize the new and important aspects of the study, including the conclusions. Do not repeat the results in detail or other information that is given in the Introduction or the Results section. Describe the conclusions according to the purpose of the study but avoid unqualified statements that are not adequately supported by the data. Conclusions may be stated briefly in the last paragraph of the Discussion section.

⑦ References

The description of the journal reference follows the descriptions below. Otherwise, it follows the NLM Style Guide for Authors, Editors, and Publishers (Patrias, K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling, DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007 [updated 2009 Jan 14; cited 2009 May 1]. Available at: www.nlm.nih.gov/citingmedicine).

· References should be obviously related to documents and should not be exceed 50. For exceeding the number of references, it should be negotiated with the Editorial Board. References should be numbered consecutively in the order in which they are first mentioned in the text. Provide footnotes in the body text section. All of the references should be stated in English, including author, title, name of journal, etc.

· If necessary, the editorial board may request original documents of the references.

· The journal title should be listed according to the List of Journals Indexed for MEDLINE, available at: www.nlm.nih.gov/archive/20130415/tsd/serials/lji.html or the List of KoreaMed Journals, available at: koreamed.org.

· Six authors can be listed. If more than 6 authors are listed, only list 6 names with 'et al.'.

· Provide the start and final page numbers of the cited reference.

· Abstracts of conferences are not allowed to be included in the references. The American Society of Anesthesiologists (ASA) refresher course lecture is not acceptable as a reference.

· Description format

A. Regular journal

Author name. Title of journal Name of journal published

year; volume: start page-final page.

Ex) Rosenfeld BA, Faraday N, Campbell D, Dorman T, Clarkson K, Siedler A, et al. Perioperative platelet activity of the effects of clonidine. Anesthesiology 1992; 79: 256-61.

Ex) Hirota K, Lambert DG. Ketamine: its mechanism(s) of action and unusual clinical uses. Br J Anaesth 1996; 77: 441-4.

Ex) Kang JG, Lee SM, Lim SW, Chung IS, Hahm TS, Kim JK, et al. Correlation of AEP, BIS, and OAA/S scores under stepwise sedation using propofol TCI in orthopedic patients undergoing total knee replacement arthroplasty under spinal anesthesia. Korean J Anesthesiol 2004; 46: 284-92.

Ex) '2006; 7(Suppl 1): 64-96' '2007; 76: H232-8'

B. Monographs

· Author. Book name. Edition. Place, press. Published year, pp (start page)-(End page).
· If reference page is only 1 page, mark 'p'.
· Mark if it is beyond the 2nd edition.

Ex) Nuwer MR. Evoked Potential monitoring in the operating room. 2nd ed. New York, Raven Press. 1986, pp 136-71.

C. Chapter

Ex) Blitt C. Monitoring the anesthesized patient. In: Clinical Anesthesia. 3rd ed. Edited by Barash PG, Cullen BF, Stoelting RK: Philadelphia, Lippincott-Raven Publishers. 1997, pp 563-85.

D. Electronic documents

Ex) Grainge MJ, Seth R, Guo L, Neal KR, Coupland C, Vryenhoef P, et al. Cervical human papillomavirus screening among older women. Emerg Infect Dis [serial on the Internet]. 2005 Nov [2005 Nov 25]. Available from wwwnc.cdc.gov/eid/article/11/11/05-0575_article

E. Online journal article

Ex) Sampson AL, Singer RF, Walters GD. Uric acid lowering therapies for preventing or delaying the progression of chronic kidney disease. Cochrane Database Syst Rev 2017; 10: CD009460.

F. Papers that have been submitted and accepted for publication should be included in the list, with the phrase 'in press' replacing volume and page number. Authors should be prepared to give the volume and page number at the time of proof correction.

Ex) Baumbach P, Gotz T, Gunther A, Weiss T, Meissner W. Chronic intensive care-related pain: Exploratory analysis on predictors and influence on health-related quality of life. Eur J Pain 2017. Advance Access published on Nov 5, 2017. doi:10.1002/ejp. 1129.

⑧ Table

· Type or print each table on a separate sheet of paper.
· Number tables consecutively in the order of their first citation in the text.
· Supply a brief title
  Tables should be more than 4 rows and should not be over 1 page.
· Except for titles and first letters, all of the text in the tables should be written in small alphabetic letters.
· In demographic data, sex would be provided as M/F, and age in yr. Data of year, weight, height, and any other units would be provided with 1 decimal place.
· "±" sign in the upper column of table should be lined up with the lower column.
· Footnotes should be provided consecutively in order of the cited tables or statistics.
· Marks for footnote should be given in order of *, †, ‡, §, 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.

⑨ Legends for figures and photographs

· All of the figures and photographs should be described in the text separately.
· The description order is the same as in the footnotes in tables and should be in recognizable sentences.
· Define all abbreviations every time they are repeated.

(3) Figures and illustrations

① The KJA publishes in full color, and encourages authors to use color to increase the clarity of figures. Please note that color figures are used without charge for online reading. However, since it will be charged upon the publication, authors may choose to use colors only for online reading.

② Standard colors should be used (black, red, green, blue, cyan, magenta, orange, and gray). Avoid colors that are difficult to see on the printed page (e.g., yellow) or are visually distracting (e.g., pink). Figure backgrounds and plot areas should be white, not gray. Axis lines and ticks should be black and thick enough to clearly frame the image. Axis labels should be large enough to be easily readable, and printed in black.

③ Figures should be uploaded as separate tif, jpg, pdf, gif, ppt files. Width of figure should be 84 mm (one column). Contrast of photos or graphs should be at least 600 dpi. Contrast

of line drawings should be at least 1,200 dpi. Number figures as "Fig. (Arabic numeral)" in the order of their citation. (ex. Fig. 1).

④ Photographs should be submitted individually. If Figure 1 is divided into A, B, C and D, do not combine it into 1, but submit each of them separately. Authors should submit line drawings in black and white.

⑤ In horizontal and vertical legends, the letter of the first English word should be capitalized.

⑥ Connections between numbers should be denoted by "-", not "~". Do not space the numbers (ex. 2–4).

⑦ Figures (line drawings) should be clearly printed in black and white.

⑧ Figures should be explained briefly in the footnotes. The format is the same as the table format.

⑨ An individual should not be recognizable in the photographs or X-ray films unless written consent of the subject has been obtained and is provided at the time of submission.

⑩ Pathological samples should be pictured with a measuring stick.

(4) Other submission elements (Video submission)

The KJA publishes supplemental video (movie) clip(s) that will be available online. Not only recording of the abstract, text, audio or video files, but also data files should be added here.

Each video clip should clearly illustrate the primary findings within an adequate amount of viewing time and be discussed in the text. Authors should provide appropriate labeling (e.g., arrows, abbreviations of anatomic structures, etc.) in the video clips. However, all identifying information, including patient name and/or ID number, hospital name, and date of the procedure, should be removed.

Video clips should contain succinct teaching points that must be supported by the current literature or standard reference texts, preferably those most accessible to the general reader. The adequacy of the teaching points will be evaluated during the review process and finally confirmed by the editorial board at the end of the review process.

Video clips are uploaded as the last file(s) at the time of manuscript submission and should be marked as supplementary video files.

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

② The maximum number of video clips is 20.

③ The video clip(s) should be playable on both Windows and MAC computers. The video clip(s) should be tested for playback before submission, preferably on computers not used for their creation, to check for any compatibility issues.

④ Individual video files should be a minimum of 480 x 320 pixels (smaller clips will not be accepted) and a maximum of 2 GB. Files of < 15 MB will be rejected outright unless special arrangements have been made with the editorial board prior to submission. Approval of files of > 2 GB will be made at the end of the review process.

⑤ Supplemental still images that correspond to the respective video clip(s) should be, but are not always required to be, accompanied by legends. The video clip file name(s) should refer to the corresponding figure number(s).

2) Systematic review and meta-analysis

Systematic reviews are systematic, critical assessments of literature and data sources in order to answer a specific question, and/or includes a statistical technique leading to a quantitative summary of results and examining sources of differences in results among studies, if any. The subtitle should include the phrase "A systematic review" and/or "A Meta-analysis."

Organization of systematic review and meta-analysis: Same as clinical and experimental studies, except,

- All systematic reviews and meta-analyses should be registered at an appropriate online public registry (eg, PROSPERO; http://www.crd.york.ac.uk/PROSPERO/), and registration information should be included with the submission.
- Authors of reports of meta-analyses of clinical trials should submit the PRISMA flow diagram. The PRISMA checklist should be submitted as a separate file along with the manuscript. For information regarding PRISMA guidelines, please visit http://www.prisma-statement.org or EQUATOR Network (https://www.equator-network.org/home/). Systematic reviews and meta-analyses of observational studies in epidemiology should be reported according to MOOSE guidelines. For more information regarding MOOSE guidelines, please visit http://www.equator-network.org/reporting-guidelines/meta-analysis-of-observational-studies-in-epidemiology-a-proposal-for-reporting-meta-analysis-of-observational-studies-in-epidemiology-moose-group/.
- No limitation the number of the references.

3) Case Reports

A case report is almost never a suitable means to describe the efficacy of a treatment or a drug; instead, an adequately powered and well-controlled clinical trial should be performed to demonstrate such efficacy. The only context in which a case report can be used to describe efficacy is in a clinical scenario, or

population, that is so unusual that a clinical trial is not feasible.

Case reports of humans must state in the text that informed consent to publication was obtained from the patient or guardian. Authors should submit copies of written informed consents by using the online manuscript submission system. If it is unavailable, the IRB approval should be needed. Copy of IRB approval should be kept. If necessary, the editor or reviewers may request copies of these documents. Rarity of a disease condition is itself not an acceptable justification for a case report.

(1) Title page: Same as clinical and experimental studies.

(2) Manuscript

① Title and Running title.

② Abstract: All case reports should contain a structured abstract that is written only in English. Provide an abstract of no more than 150 words. It should contain 3 subsections: Background, Case, and Conclusions. A list of keywords, with a minimum of 6 and maximum of 10 items, should be included at the end of the abstract. The selection of keywords should be from MeSH (http://www.ncbi.nlm.nih.gov/mesh) and should be written in small alphabetic letters with the first letter in capital letter. Separate each word by a semicomma (;), and mark a period (.) at the end of the last word.

③ Introduction: Should not be separately divided. Briefly describe the case and background without a title.

④ Case report: Describe only the clinical statement that is directly related to diagnosis and anesthetic management.

⑤ Discussion: Briefly discuss the case, and state conclusions at the end of the case. Do not structure the conclusion section separately.

⑥ References: Do not exceed 15 references. For exceeding the number of references, it should be negotiated with the Editorial Board.

⑦ Tables and figures: Proportional to clinical and experimental studies.

4) Reviews

Review articles synthesize previously published material into an integrated presentation of our current understanding of a topic. Review articles should describe aspects of a topic in which scientific consensus exists, as well as aspects that remain controversial and are the subject of ongoing scientific disagreement and research. Review articles should include unstructured abstracts equal to or less than 250 words in English. Figures and tables should be provided in English. References should be obviously related to documents and should not be exceed 100. For exceeding the number of references, it should be negotiated with the Editorial Board. Body text should not exceed 30 A4 pages, and the number of figures and tables should be equal to or less than 6.

5) Letters to the Editor

Letters to the Editor also should include brief constructive comments on the articles published in KJA and interesting cases. Book reviews as well as news of scientific societies and scientific meeting dates in Korea or abroad can be included. Letters to the editor of humans must state in the text that informed consent to publication was obtained from the patient or guardian. Authors should submit copies of written informed consents by using the online manuscript submission system. If it is unavailable, the IRB approval should be needed. Copy of IRB approval should be kept. If necessary, the editor or reviewers may request copies of these documents. Letters to the Editor cover individual articles not described by any of the above categories. The short manuscripts with a constructive note on the Journal or the anesthesiology at large are welcome.

Cover pages should be formatted as those of clinical research papers. The body text should not exceed 1,000 words and should have no more than 5 references. For exceeding the number of references, it should be negotiated with the Editorial Board. A figure or a table may be used. A maximum of five 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.

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 February 2021 submissions.