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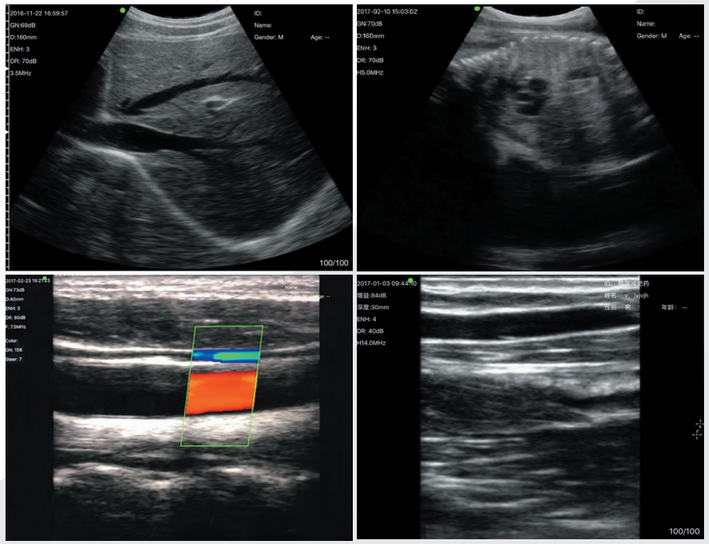

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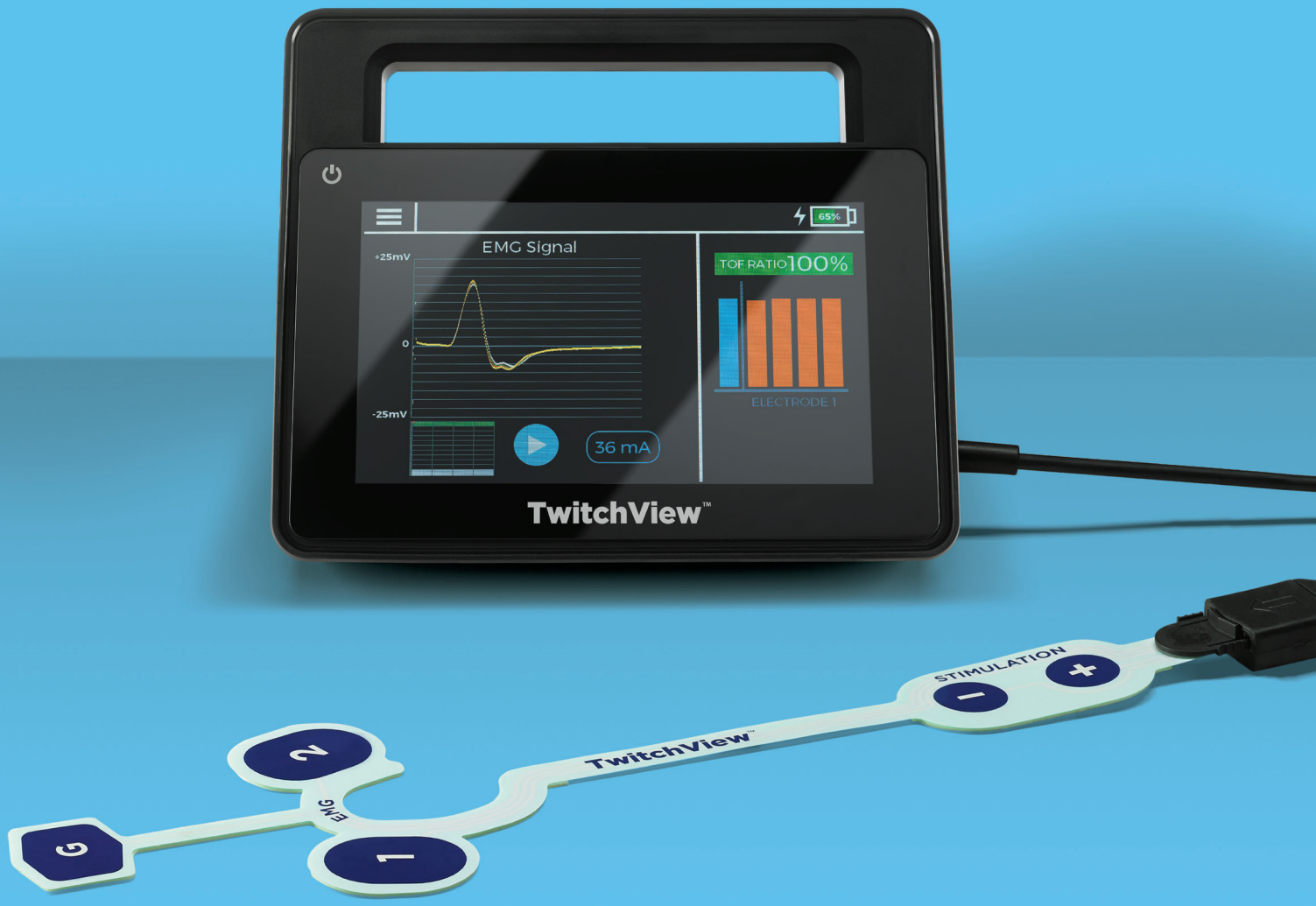

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Aims and Scope

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

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

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

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Experimental Research Article

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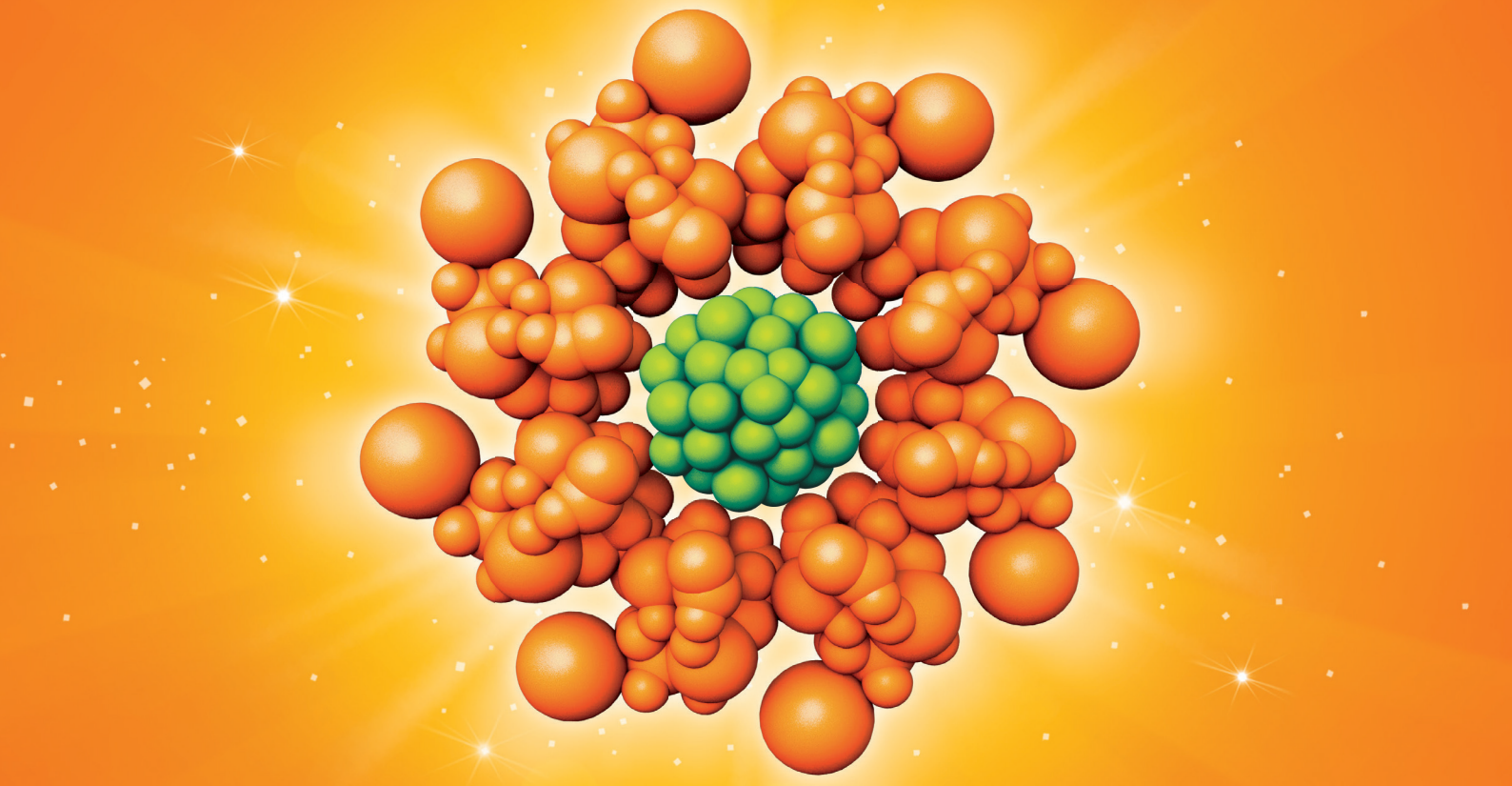
Letters to the Editor

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_4/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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Review Article

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Raw and processed electroencephalography in modern anesthesia practice: a brief primer on select clinical applications

현대 마취 영역에서 뇌파의 임상 적용에 대한 간략한 입문서

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Department of Anesthesiology [1]and Pain Medicine, Haeundae Paik Hospital, Inje University College of Medicine, Busan, Korea, [2]University of Utah, Salt Lake City, UT, USA

마취제 사용을 조절하기 위해 수술 중 뇌파(processed EEG)를 사용하는 것에 대한 논의는 오래전부터 시작되었다. 이 논문에서는 뇌파의 주요 특징 및 선택된 환자군과 마취 방법에서 뇌파의 임상적 사용에 대해 알아보고자 한다. 첫 번째 주제는 취약한 뇌에 관한 것인데, 이 용어는 마취제에 민감도가 증가하거나 마취 후 신경인지 기능 저하가 발생한 환자에 대한 설명에서 대두되기 시작하였다. 취약한 뇌를 갖고 있다고 알려져 있거나 의심되는 환자에서 suppression ratio, alpha band power, processed EEG 지수 등에 초점을 맞춘 모니터링은 유용할 수 있다. 둘째, 근이완제를 사용하는 정맥마취에서 processed EEG 감시하에 마취제 용량을 조절하는 것은 수술 중 각성의 위험을 최소화 할 수 있다. 셋째, 혈압에 유해한 변화가 발생했을 때 processed EEG 감시를 하는 것은 마취 및 소생 관리에 있어 중요한 역할을 할 수 있음을 이 논문에서는 제시하고자 한다. 네 번째 주제는 processed EEG 감시하 전신마취는 약물 중독이거나 의심되는 환자에서 필요한 마취 요구량을 더 잘 식별할 수 있고, 적절한 마취 용량 조절을 하는 데 사용될 수 있다는 것이다.

Keywords: Alpha rhythm; Anesthesia; Brain waves; Electroencephalography; Hemodynamics; Intraoperative awareness; Substance-related disorders; Vulnerable populations.

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Obesity and anesthetic pharmacology: simulation of target-controlled infusion models of propofol and remifentanil

비만과 마취약리학: 프로포폴 및 레미펜타닐의 목표 농도 조절 주입 모델의 시뮬레이션

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Review Article

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비만의 유병률이 증가함에 따라 비만 자체와 비만으로 인한 질병을 치료하기 위한 수술 건수가 증가하고 있다. 비만 환자에서 발생하는 약동학 및 약력학적 변화뿐만 아니라 관련 동반 질환으로 인해 적절한 마취제의 용량을 조절하기가 어렵다. 약동학적인 변화에 영향을 미치는 요인으로는 지방조직, 제지방 체중, 세포외액 및 비만으로 인한 심박출량 증가 등이 포함된다. 이러한 생리학적 및 신체 구성 변화는 약동학 및 약력학 매개변수의 변화를 야기한다. 증가된 중심 분포 부피와 약물 제거의 변화는 비만 인구에서 프로포폴(propofol)과 레미펜타닐(remifentanil)의 혈장 농도에 영향을 미친다. 또한, 비만은 EC50 (50% 최대 효과 농도) 또는 Ke0 (효과처 평형속도상수)와 같은 약력학 특성에 영향을 미칠 수 있다. 비만 환자를 포함하는 약동학 및 약력학 모델을 기반으로 한 목표 농도 조절 주입 시뮬레이션은 임상의가 이 모집단과 관련된 마취제의 약동학 및 약력학 변화를 더 잘 이해하는 데 도움이 될 수 있다.

Keywords: Cardiac output; Computer simulation; Ideal body weight; Metabolic clearance rate; Obesity; Pharmacokinetics.

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Transparency considerations for describing statistical analyses in research

통계 분석 기술 시 고려할 점

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가설을 설정하고 해당 데이터를 수집하고 검정하여 결론을 도출하는 연구에서는 통계 분석과정에 대한 내용을 연구 방법 단락에 기술한다. 통계 분석 내용을 구체적이고 명확하게 기술하는 것은 연구에 사용된 약물의 용량이나 중재방법을 명확하게 기술하는 것처럼 매우 중요하며, 도달한 결과의 과학성과 투명성을 확보하는 데 필수적이다. 이 글에서는 2020년 2월부터 2021년 2월까지 Korean Journal of Anesthesiology에 출판된 31개 임상연구 논문의 통계 분석 과정기술 내용을 6개의 항목으로 나누어 Likert 척도로 점수화를 하여 분석하였다(3점: 구체적인 기술, 2점: 부분적인 기술, 1점: 기술의 부재). 이 항목들은 크게 통계 분석 방법과 관련된 내용(통계 분석 방법, 통계 분석 방법의 목적 및 구체적 설명, 통계 분석 후 제시하는 지표)과 통계 분석 방법 이외의 내용(통계 분석 소프트웨어 및 버전, 유의수준 값, 검정의 종류[단측검정 vs. 양측검정])으로 분류하였다. 통계 분석 방법에 대해서는 분석에 포함된 모든 논문이 3점에 해당되었다. 반면, 검정의 종류에 대한 기술은 31개 중 4개의 논문(12.9%)에서만 3점이었고, 나머지 논문들은 기술이 전혀 없었다(1점). 임상연구의 통계 분석과정을 서술할 때 구체적인 검정의 종류(단측검정 vs. 양측검정) 기술이 다른 항목들에 비하여 부족하므로, 연구자들은 통계 분석과정을 작성할 때 검정의 종류에 대한 기술을 항상 유념하여야 한다.

Keywords: Data analysis; Probability; Research; Software; Statistical data interpretation; Statistics.

Statistical Round

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The analgesic efficacy of anterior femoral cutaneous nerve block in combination with femoral triangle block in total knee arthroplasty: a randomized controlled trial

슬관절전치환술에서 대퇴삼각차단과 전방 대퇴피부신경차단을 병행한 경우의 진통 효과: 무작위 대조군 시험

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배경: 초음파 유도 대퇴삼각차단(femoral triangle block, FTB)은 운동을 보존하는 전방 무릎 진통을 제공할 수 있다. 그러나 이것은 전방 대퇴피부신경(anterior femoral cutaneous nerve, AFCN)이 완전히 마취되지 않을 수 있다. 본 연구에서는 AFCN 차단(AFCNB)을 FTB와 함께 사용하면 FTB 단독에 비해 수술 직후 12시간 동안 운동 중 통증을 감소시킬 것이라는 가설을 세웠다.

방법: 이 연구는 슬관절전치환술을 받을 예정인 환자 80명을 대상으로 하였고, 복합적 진통제 요법(multimodal analgesia)의 일부로서 FTB 단독(FTB 그룹) 또는 FTB와 AFCNB (AFCNB + FTB 그룹)를 함께 시행하는 두 군으로 무작위 배정하였다. 일차 결과변수는 수술 후 12시간에 움직임시 측정한 통증이었다. 이차 결과변수는 통증점수(NRS), 수술 절개 부위의 통증 발생률, 모르핀 소모량, 즉각적인 기능 수행, 환자 만족도 및 입원 기간이 포함되었다.

결과: 수술 후 12시간의 운동에 대한 NRS 통증 점수는 AFCNB + FTB 그룹에서 FTB 그룹 환자에 비해 유의하게 낮았다(평균 차이: −2.02, 95% CI: −3.14, −0.89, $P < 0.001$). 수술 24시간 후 수술 절개 부위의 통증 발생률과 수술 후 48시간 이내 모르핀 소모량은 유의하게 낮았으며 ($P < 0.001$), 수술 직후 0°에서 대퇴사두근 근력은 AFCNB + FTB 그룹에서 유의하게 높았다 ($P = 0.04$).

결론: FTB에 초음파 유도 AFCNB를 추가하면 슬관절전치환술후 FTB 단독에 비해 더 효과적으로 진통을 통제할 수 있으며, 아편유사제 요구량이 감소했고, 수술 당일 즉각적인 기능 수행능력을 향상시킬 수 있었다.

Keywords: Arthroplasty; Knee; Nerve block; Peripheral nerves; Postoperative pain; Ultrasonography.

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Analysis of endotracheal intubation-related judicial precedents in South Korea

한국에서의 기관내 삽관법 관련 판례 분석

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배경: 기관내 삽관과 관련된 의료과실은 치명적인 합병증을 초래할 수 있다. 그러나 아직까지 국내에서는 이에 초점을 맞춘 연구는 보고된 바가 없었다. 본 연구에서는 국내 법원 판결문을 활용하여 기관내 삽관과 관련하여 발생한 심각한 합병증과 관련된 의료과실을 알아보고자 하였다.

방법: 대법원 데이터베이스 활용하여 1994년 1월부터 2020년 6월까지 기관내 삽관과 관련된 종결된 판결문을 검색하였다. 판결문에서 임상적 및 법적 특성을 분류하였고, 이를 통해 의료과실을 분석하였다.

결과: 검색된 판결문 중 기관내 삽관과 관련된 의료과실이 포함된 사건은 총 63건이었다. 가장 흔한 사건 발생장소는 수술실(20건, 31.7%)이었다. 세 건을 제외한 모든 사건에서 심각한 영구적 손상이 발생하였으며, 사망은 총 31명이었다. 기관내 삽관 중 발생한 가장 흔한 문제는 기관내 삽관 실패 또는 지연이었다(56건, 88.9%). 기관내 삽관 삽입이 지연되거나 실패한 경우 5.2%(3건)에서 성문 위 기도유지 기구를 사용하였고, 법원에서 인정한 가장 흔한 의료과실은 대체 기도유지 방법 미시도(32건, 50.8%)가 가장 많았다. 그다음으로 설명의무 위반(10건, 15.9%)이 뒤를 이었다. 손해배상 청구 소송에서 원고 승소 판결을 받은 사건은 51건(81%)으로, 원고 승소시 판결액은 원화 중간값으로 133,897,845원이었다(사분위수 범위: 38,000,000, 308,538,274).

결론: 본 연구는 의사들에게 심각한 합병증으로 이어질 수 있는 기관내 삽관과 관련된 의료과실의 중요성을 상기시킬 수 있으며, 이는 환자의 안전을 보장하는 데 도움이 될 것이다.

Keywords: Airway management; Complications; Emergency treatment; Intratracheal intubation; Medical legislation; Medical liability.

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A comparison of adductor canal block before and after thigh tourniquet during knee arthroscopy: a randomized, blinded study

무릎 관절경 수술에서 대퇴 지혈대 적용 전후에 시행된 내전근관 차단술의 효과: 무작위 눈가림 연구

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배경: 내전근관 차단술(adductor canal block, ACB)은 관절경 무릎 수술 후 효과적인 통증 조절 방법으로 주목받고 있다. 그러나 대퇴 지혈대(thigh tourniquet) 적용이 ACB에 어떤 영향을 미치는지에 대한 데이터는 충분하지 않다. 우리는 대퇴 지혈대를 적용하기 전과 후에 수행된 ACB의 진통 효능을 조사하고 이와 관련된 대퇴사두근(quadriceps femoris) 근력 약화를 평가하고자 하였다.

방법: PreT 군에서는 지혈대를 가압하기 전에 ACB가 시행되었고, PostT 군에서는 가압한 후에 시행되었다. PO 군에서는 지혈대 감압 후 수술 종료시에 ACB가 시행되었다.

결과: 인구학적 데이터 측면에서 군 간에 통계적으로 유의한 차이는 없었다. 수술 후 아편유사제 복용량 역시 세 군 간에 통계적으로 유의한 차이는 없었다(P = 0.513). 환자 만족도와 구제 진통제 투여량도 군 간에 유의한 차이가 없었다. 군 간의 정적 및 동적 시각통증등급 점수도 유의한 차이가 없었다(24시간 동안: 각각 P = 0.306 및 P = 0.271). 대퇴사두근의 운동 차단 발생률은 PreT 군(8명)에서 PostT 군(0명) 및 PO 군(1명)에서 보다 더 높았다(P = 0.005).

결론: ACB 전후에 대퇴 지혈대를 적용함에 따라 ACB의 진통효과는 차이가 나지 않았다. 그러나 ACB 직후에 지혈대를 가압하는 것은 대퇴사두근의 근력 약화를 초래할 수도 있다.

Keywords: Conduction anesthesia; Knee joint; Nerve block; Postoperative pain; Tourniquets; Ultrasonography.

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Comparison of the ulnar nerve blockade between intertruncal and corner pocket approaches for supraclavicular block: a randomized controlled trial

쇄골상 차단법에 대한 Intertruncal 및 Corner Pocket 접근 간의 자신경 차단 비교: 무작위 대조군 시험

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배경: 쇄골상차단(supraclavicular block, SCB)을 위한 corner pocket (CP) 접근 방식은 하부 체간에 바늘을 가까이 접근하여 자신경이 불완전하게 차단되는 것을 방지한다. 초음파 해상도가 개선되면서 intertruncal (IT) 접근법이 적절한 대안이 될 수 있다고 제안하였다. 본 연구에서는 자신경(ulnar nerve, UN) 차단에 대한 이 두 가지 접근법의 효율성을 비교하였다.

방법: 60명의 환자가 초음파 유도 CP 또는 IT 접근법을 사용하여 SCB를 받도록 무작위 배정되었다. 하부체간 차단을 위해 10 ml의 국소 마취제(0.75% 로피바카인[ropivacaine]과 1% 리도카인[lidocaine]의 1 : 1 혼합약물)를 CP 부위(CP 접근법) 또는 체간하부와 체간중부 사이(IT 접근법)에 주사하였다. 추가로 15 ml을 동일하게 주입하여 두 그룹 간 체간중부 및 체간상부를 함께 차단하였다. 중재 후 UN의 감각 및 운동 차단을 평가하였다.

결과: SCB 이후 15분 만에 UN의 완전한 감각 차단(75.9% [22/29] vs. 43.3% [13/30], P = 0.023)과 완전한 운동차단(82.8% [24/29] vs. 50.0% [15/30], P = 0.017)은 CP 그룹보다 IT 그룹에서 훨씬 더 자주 발생하였다. UN의 감각 차단 시작 시간은 CP 그룹에 비해 IT그룹에서 유의하게 짧았다(15.0 [10.0, 15.0]분 vs. 20.0 [15.0, 20.0]분, P = 0.012).

결론: IT 접근 방식은 CP 접근 방식보다 UN 차단 시작 시간이 빨랐다. 이러한 결과는 IT접근이 CP접근에 대한 적절한 대안이 될 수 있으며, 보다 빠른 수술 준비를 제공할 수 있음을 시사한다.

Keywords: Brachial plexus block; Nerve block; Orthopedics; Subclavian artery; Ulnar nerve; Ultrasonography.

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Previous presentation in conferences:
These findings were briefly presented at the ANESTHESIOLOGY 2012 Annual Meeting of The American Society of Anesthesiologists (ASA), October 2012, Walter E. Washington Convention Center, Washington, DC, USA.

Edaravone attenuates sustained pial arteriolar vasoconstriction independently of endothelial function after unclamping of the abdominal aorta in rabbits

에다라본은 토끼에서 복부 대동맥의 클램핑 해제 후 지속되는 대뇌 연질막 세동맥의 혈관 수축을 약화시킨다

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배경: 대뇌 혈류(cerebral blood flow)는 신경 기능 및 신경 인지 장애에 직접적인 영향을 미친다. 복부 대동맥 수술로 인한 산화 스트레스는 대뇌 혈류 장애의 병태생리에 주요한 영향을 미친다. 에다라본(edaravone)은 정맥 내 활성 산소 제거제(free radical scavenger)이다. 본 연구에서는 복부 대동맥 수술로 유발된 연질막 세동맥 직경 변화에 대한 에다라본의 효과와 그 변화에 대한 내피의 관여도를 조사하였다.

방법: 첫 번째 실험에서는 토끼를 세 군으로 나눈 후(대조군, n = 6; 에다라본 10 μg/kg/min 정주군, n = 6; 에다라본 100 μg/kg/min 정주군, n = 6), 에다라본 지속정주 15분 후 복부 동맥을 20분간 클램핑을 하였다가 해제한다. 두개골 윈도 기술을 이용하여 연질막 세동맥 직경 변화를 측정한다. 두 번째 실험에서는 아세틸콜린(acetylcholine)을 두개골 윈도에 국소적으로 도포한 후 복부 대동맥 교차 클램핑 전과 해제 후 에다라본을 정맥 투여했을 때 혈관 확장 반응을 조사하였다(대조군, n = 6; 에다라본 100 μg/kg/min 정주군, n = 6).

결과: 복부동맥 클램핑 해제로 인한 혈관 수축은 에다라본을 100 μg/kg/min으로 지속적으로 주입 시 유의하게 약화되었다. 클램핑 제거 후 Ach의 국소 적용은 대조군과 에다라본군에서 클램핑 전과 비교하여 연질막의 세동맥 반응에 어떠한 변화도 일으키지 않았다. 클램프 제거 후 국소 Ach에 대한 반응의 변화에 군 간 차이는 없었다.

결론: 복부 대동맥 수술 중 활성 산소(free radical)는 토끼의 내피 기능과 독립적으로 대뇌 혈관을 수축시킬 수 있다. 활성 산소의 억제는 대동맥 클램핑 후 연질막 세동맥 혈관 수축을 약화시켰다. 활성 산소 제거제는 내피 기능과 독립적으로 대뇌 혈류를 유지하는 뇌 보호 효과를 가질 수 있다.

Keywords: Cerebrovascular circulation; Edaravone; Endothelium; Free radical scavengers; Reperfusion injury; Vascular surgical procedures.

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Difficult intubation: lessons learned from the courts of South Korea

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Editorial

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Endotracheal intubation is one of the most common practices during general anesthesia and a daily procedure for most anesthesiologists working in the operating room. Furthermore, the introduction of advanced equipment, such as video-laryngoscopy, into our routine has made intubation easier to perform, increasing the success rate at the first attempt [1]. Therefore, our caution for difficult intubation seems to be diminishing. However, difficult intubation has been a major contributor to adverse patient outcomes worldwide [2–5]. Moreover, previous analyses of anesthesia-related medical disputes using the Korean Society of Anesthesiologists database also showed that difficulties in airway management were related to more than half of the disputes [6,7]. Therefore, attention must be paid to difficult airway management. To improve difficult airway management, it is essential to analyze the complications following airway management. However, the incidence of difficult airways or its complications is very low [8]. Therefore, analyses of past closed claims related to difficult airway management have been used for management [2–5].

In the current issue of the *Korean Journal of Anesthesiology*, Cho et al. [9] published an article analyzing the closed judicial precedents of intubation-related complications registered between 1994 and 2020, using the Korean Supreme Court database. It reveals medical malpractices and severe complications related to endotracheal intubation in South Korea. Among the 63 cases analyzed, the most common problem was failed or delayed intubation (88.9%). Most cases (95.2%) were associated with severe injury, more than half of which resulted in deaths. These findings suggest that the occurrence of intubation-related complications causing major permanent injury can lead to legal conflict. The article also describes common types of malpractices recognized by the courts. The most common type of malpractice is not attempting the alternative airway technique. It is particularly surprising that the supraglottic airway device was used in only 5.2% of delayed or failed intubation cases. The guidelines for difficult intubation management emphasize on attempting the use of supraglottic airway devices if intubation fails, to provide a route for oxygenation, limit the number of airway interventions to minimize trauma from repetitive airway interventions, and get time to review how to proceed [10,11]. Therefore, not attempting alternative airway techniques seems to have been recognized as a malpractice, which is a reminder of the importance of training to become experts in difficult airway management guidelines.

This article deals with extreme cases of difficult intubation that ended up in courts. Evidently, the findings in this article do not comprehensively reflect the difficult intubation management in South Korea. However, such cases of rare and severe complications have attracted attention. It can be hoped that this would serve as an opportunity to check our level of difficult airway management and infrastructure for difficult airway situations.

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Conflicts of Interest

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

References

1. Berkow LC, Morey TE, Urdaneta F. The Technology of Video Laryngoscopy. Anesth Analg 2018; 126: 1527-34.
2. Joffe AM, Aziz MF, Posner KL, Duggan LV, Mincer SL, Domino KB. Management of difficult tracheal intubation: a closed claims analysis. Anesthesiology 2019; 131: 818-29.
3. Hove LD, Steinmetz J, Christoffersen JK, Møller A, Nielsen J, Schmidt H. Analysis of deaths related to anesthesia in the period 1996-2004 from closed claims registered by the Danish Patient Insurance Association. Anesthesiology 2007; 106: 675-80.
4. Cook TM, Scott S, Mihai R. Litigation related to airway and respiratory complications of anaesthesia: an analysis of claims against the NHS in England 1995-2007. Anaesthesia 2010; 65: 556-63.
5. Fornebo I, Simonsen KA, Bukholm IRK, Kongsgaard UE. Claims for compensation after injuries related to airway management: a nationwide study covering 15 years. Acta Anaesthesiol Scand 2017; 61: 781-9.
6. Roh WS, Kim DK, Jeon YH, Kim SH, Lee SC, Ko YK, et al. Analysis of anesthesia-related medical disputes in the 2009-2014 period using the Korean Society of Anesthesiologists database. J Korean Med Sci 2015; 30: 207-13.
7. Choi JW, Kim DK, Cho CK, Park SJ, Son YH. Trends in medical disputes involving anesthesia during July 2009-June 2018: an analysis of the Korean Society of Anesthesiologists database. Korean J Anesthesiol 2019; 72: 156-63.
8. Cook TM, Woodall N, Frerk C; Fourth National Audit Project. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 1: anaesthesia. Br J Anaesth 2011; 106: 617-31.
9. Cho HY, Shin S, Lee S, Yoon S, Lee HJ. Analysis of endotracheal intubation-related judicial precedents in South Korea. Korean J Anesthesiol 2021; 74: 506-13.
10. Frerk C, Mitchell VS, McNarry AF, Mendonca C, Bhagrath R, Patel A, et al. Difficult Airway Society 2015 guidelines for management of unanticipated difficult intubation in adults. Br J Anaesth 2015; 115: 827-48.
11. Black AE, Flynn PE, Smith HL, Thomas ML, Wilkinson KA; Association of Pediatric Anaesthetists of Great Britain and Ireland. Development of a guideline for the management of the unanticipated difficult airway in pediatric practice. Paediatr Anaesth 2015; 25: 346-62.

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Raw and processed electroencephalography in modern anesthesia practice: a brief primer on select clinical applications

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Review Article

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The evidence supporting the intraoperative use of processed electroencephalography (pEEG) monitoring to guide anesthetic delivery is growing rapidly. This article reviews the key features of electroencephalography (EEG) waveforms and their clinical implications in select patient populations and anesthetic techniques. The first patient topic reviewed is the vulnerable brain. This term has emerged as a description of patients who may exhibit increased sensitivity to anesthetics and/or may develop adverse neurocognitive effects following anesthesia. pEEG monitoring of patients who are known to have or are suspected of having vulnerable brains, with focused attention on the suppression ratio, alpha band power, and pEEG indices, may prove useful. Second, pEEG monitoring along with vigilant attention to anesthetic delivery may minimize the risk of intraoperative awareness when administering a total intravenous anesthesia in combination with a neuromuscular blockade. Third, we suggest that processed EEG monitoring may play a role in anesthetic and resuscitative management when adverse changes in blood pressure occur. Fourth, pEEG monitoring can be used to better identify anesthesia requirements and guide anesthetic titration in patients with known or suspected substance use.

Keywords: Alpha rhythm; Anesthesia; Brain waves; Electroencephalography; Hemodynamics; Intraoperative awareness; Substance-related disorders; Vulnerable populations.

Introduction

Since the brain is the target organ of many anesthetic drugs, clinical investigators have been interested in developing brain function monitors that reliably measure anesthetic drug effects. Several electroencephalography (EEG) monitoring devices have been introduced to measure frontal electrical cortical activity and process the EEG signal to generate indices of brain electrical activity that closely correlate with the hypnotic effects of anesthetics [1–3]. These brain function monitors are designed to measure the adequacy of anesthesia, including expired anesthetic gas concentrations, hemodynamic and respiratory variables, and clinical assessments such as patient movement as a complement to other techniques.

Although processed EEG (pEEG) monitors have been available for decades, they have not been widely used in clinical practice. Without adequate training, the clinical utility of raw EEG waveforms, indices of hypnosis, burst suppression ratios, spectral edge frequency, and various graphical displays on EEG are not obvious. Furthermore, in contrast to standard deterministic monitors, such as electrocardiograms, the pEEG is a stochastic

measure that must typically be interpreted probabilistically; therefore, it is inherently less robust than routine clinical monitoring systems. In addition, as a clinical state monitor that requires 15–30 s of raw EEG waveform data, the pEEG indices reflect brain activity from the very recent past; however, real-time data cannot be retrieved as they can with standard deterministic monitors [4].

Despite these limitations, the application of pEEG monitoring in anesthesia patient care has increased. With advances in the understanding and interpretation of raw EEG waveforms, pEEG parameters, and graphical EEG displays (such as spectrograms), the technology has emerged as an important tool for optimizing anesthesia delivery. This review briefly outlines the clinical rationale underlying the application of pEEG monitoring in modern anesthesia practice.

Raw and processed EEG: key features

First, a brief review of basic features of the EEG waveform and how the raw waveform can be processed into various parameters and graphical displays is provided as a framework for EEG interpretation in the clinical setting. Additionally, data supporting the application of pEEG to improve anesthesia care is provided. Key elements include raw EEG waveform morphology, spectral analysis, burst suppression, and alpha power.

EEG waveform morphology

The raw EEG waveform, plotted in microvolts versus time, is characterized in terms of frequency and amplitude and continually cycles around electrical zero. Frequencies are arbitrarily described using five bands measured in cycles per second or Hertz (Hz): delta (< 4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (14–32 Hz), and gamma (> 32 Hz). Amplitudes are described using power, defined as the amplitude squared (so that the amplitude is always a positive number), and reported in decibels (dB) using a logarithmic scale that provides a convention to visualize a wide range of amplitudes. The changes in amplitude are referred to as oscillations. Given that available commercial pEEG monitors require sensors that are placed over the forehead, waveform frequency and amplitude signals reflect electrical activity largely from the frontal cortex.

Spectral analysis

Spectral analysis is perhaps the most important of the EEG processing methods in clinical anesthesia because most inhaled and intravenous general anesthetics result in a generalized "slowing" of the raw EEG waveform, wherein the waveform exhibits increased power in lower frequency bands. The slowing of the raw EEG waveform can be characterized using spectral analysis. Applying Fourier's theorem using a fast Fourier transform, spectral analysis is a mathematical technique used to separate a complex sine wave (like the raw EEG) into its component sine waves, thereby generating a power versus frequency histogram. Drugs used for general anesthesia, such as isoflurane or propofol, characteristically produce a leftward shift in the power versus frequency histogram. This leftward shift is reflected in a lower median frequency (i.e., frequency in the power versus frequency histogram in which 50% of the power is lower and 50% is higher) and a lower spectral edge frequency (frequency below which 95% of the power in the power versus frequency histogram is found).

Spectrogram

In addition to numerical parameters such as the median frequency and spectral edge frequency, the results of spectral analysis can also be visualized in the form of a spectrogram. A spectrogram plots the power across a spectrum of frequencies as they change over time [5]. Time is displayed along one axis and frequency and power along the opposite axis (some commercial devices plot time on the horizontal axis, others plot time on the vertical axis). The frequency typically ranges from 0–30 Hz. Applying a "heat map" approach, the power is presented using colors from blue (–40 dB) to red (15 dB). The "warmer" the color, the greater the power (e.g., blue represents lower power, red represents higher power). The spectrogram is intended to reduce the cognitive workload required for EEG interpretation, making it easier to visualize where most of the power in the EEG signal resides [6]. Fig. 1 presents differences in the alpha band power between two patients.

Burst suppression

When anesthetic concentrations (e.g., halogenated agents, propofol, etomidate, and thiopental) reach sufficiently high levels, periods of isoelectricity are generated in the raw EEG. These periods of isoelectricity are typically interspersed with "bursts" of EEG activity. Higher concentrations of anesthesia can result in complete burst suppression, wherein the EEG is completely isoelectric. Computed as part of a signal processing technique known as aperiodic analysis, the burst suppression ratio is the proportion of time in which the EEG is isoelectric over a specified length of time (usually 15–60 s). Other conditions can also result in burst suppression or isoelectricity, including hypothermia and cerebral

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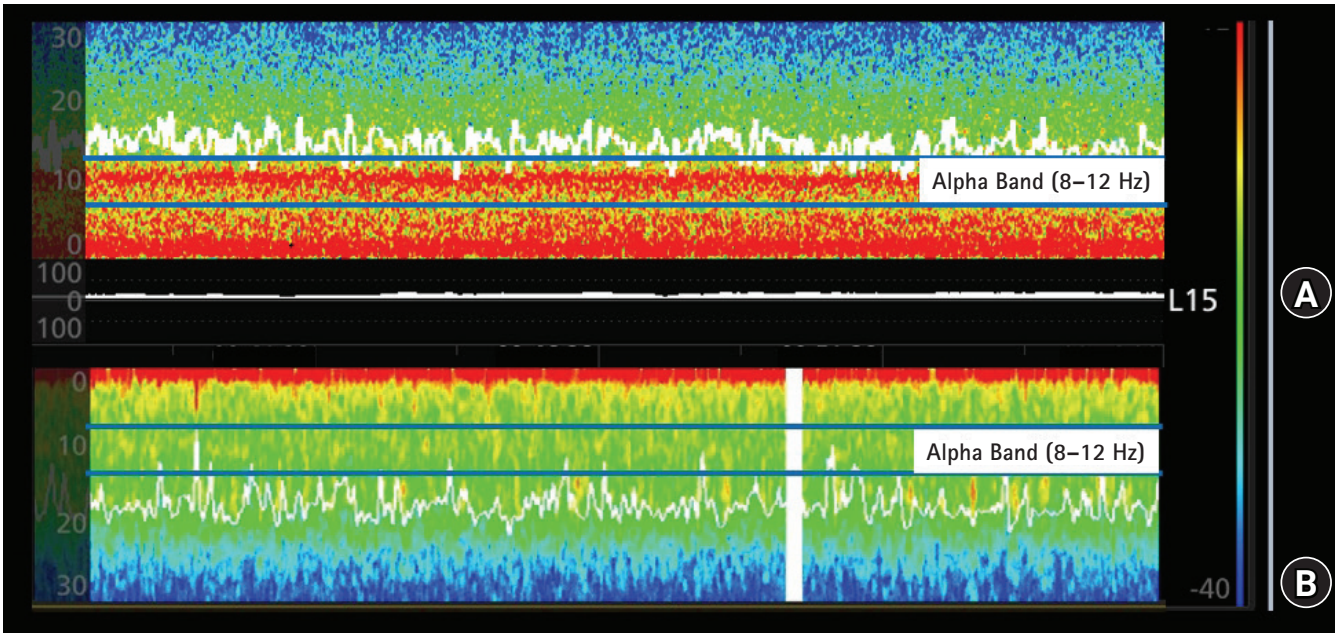

Fig. 1. Examples of (A) high and (B) low alpha power within a left frontal spectral display. The left vertical axis is frequency (Hz). The right vertical axis is power (dB). The cooler and warmer colors represent low and high power, respectively. The horizontal axis is time (min). The dark blue horizontal lines present the alpha band range (8–12 Hz).

ischemia. Advanced age is associated with burst suppression at lower anesthetic concentrations.

Alpha power

The alpha band is of particular interest since it changes with general anesthesia and declines with age more than other frequency bands [7]. Alpha power is thought to originate from thalamocortical electrical activity, which plays a role in integrating sensory information and synchronizing different cortical regions of the brain [8]. Therefore, alpha band power has been the subject of several studies exploring its potential utility as a biomarker of brain health in the perioperative period [9].

The vulnerable brain

The term "vulnerable brain" has emerged as a description of patients who may exhibit increased sensitivity to anesthesia and/or may develop adverse neurocognitive effects after receiving anesthesia. Patients with advanced age, neurovascular disease, intracranial pathology, traumatic brain injury, or an overwhelming infectious or metabolic disorder are some potential examples.

Neuroscientists suggest that neurons in vulnerable brains have a lower mitochondrial production of energy substrates, which reduces neuronal electrical activity and synaptic neurotransmission [10]. Significant cerebral ischemia or hypoperfusion during anesthesia can be detected using EEG changes. Particularly during stable anesthesia, a sudden alteration in the EEG (i.e., a shift in power to lower frequency ranges, decrease in amplitude, periods of burst suppression, isoelectricity, and/or a drop in the pEEG index) may indicate incidental cerebral ischemia.

A large body of work has explored pEEG-guided titration of anesthesia to improve clinical outcomes associated with the vulnerable brain, including postoperative delirium (POD), postoperative cognitive dysfunction (POCD), and mortality. Table 1 presents a summary of results from four randomized controlled trials (RCTs) exploring the effect of pEEG-guided anesthesia delivery on the incidence of POD and POCD.

In a recently published large RCT, the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) trial [11], the authors compared pEEG-guided (target bispectral index [BIS] value ≥ 40) with routine anesthesia delivery. The main finding was that pEEG-guided anesthesia did not decrease the incidence of POD, despite a modest reduction in anesthetic exposure (a decrease in the median end-tidal anesthesia concentration from 0.8 to 0.7 minimum alveolar concentration [MAC]) and a reduction in the duration of EEG suppression (the median duration of time with a BIS value < 40 decreased from 60 min to 32 min) (Table 1).

In an independent analysis of the ENGAGES trial data, Ackland and Pryor [12] importantly identified that prior retrospective observational studies have established that EEG burst suppression

Table 1. Select Randomized Controlled Trials Comparing pEEG-guided to Routine or End-tidal-guided Anesthetic Delivery on POD and POCD

Study name	Experimental design	Results	Conclusions
Cognitive dysfunction after anesthesia	· Demographics: aged ≥ 60, ASA ≥ 3 (16%), 61% male · Non-cardiac and non-neurosurgical	· Median BIS values in the pEEG-guided and routine care groups were 53 and 36, respectively · pEEG-guided anesthesia reduced the amount of propofol and inhaled anesthetic drugs by 21% and 30%, respectively.	· The authors estimate that for every 1,000 elderly patients undergoing major surgery, titration to a BIS between 40 and 60 prevented 23 and 83 patients from developing POCD and POD, respectively.
Chan et al. 2013 [47]	· Anesthetic technique: 11% TIVA & 89% inhaled agents · pEEG-guided group: target BIS 40–60 in 462 patients · Routine care in 459 patients. · Primary outcome: incidence of POCD 3 months after surgery. · Secondary outcome: incidence of POCD and POD one week after surgery.	· Primary outcome: At three months, there was a 4.5% reduction in the incidence of POCD in the pEEG-guided group compared to the routine care group. · Secondary outcome: One week after surgery, there was no difference in the incidence of POCD, but an 8.5% decrease in the incidence of POD.	
Monitoring depth of anesthesia decreases the rate of POD but not POCD	· Demographics: aged ≥ 60, ASA ≥ 3 (48%), 54% male · Non-cardiac surgery	· Mean average BIS values in the pEEG guided and routine care group were 39.0 and 38.7 respectively · Primary outcome: 16.7% developed POD in the BIS-guided group and 21.4% in the routine care group. No difference in POCD was found between the groups	· Intraoperative pEEG monitoring may provide anesthesia care providers with a tool to influence one of many factors that lead to POD.
Radtke et al. 2013 [48]	· Anesthetic technique: 35% TIVA & 65% inhaled agents · pEEG-guided group: target BIS 40–60 in 575 patients · Routine care in 580 patients. · Primary outcome: POD & POCD at baseline, 1 week, and 3 months post-operation.	· pEEG-guided anesthesia reduced the occurrence of extremely low BIS values (< 20) and burst suppression, possibly decreasing the incidence of POD.	
Postoperative delirium in a sub-study of cardiothoracic surgical patients in the BAG-RECALL clinical trial	· Demographics: aged ≥ 60, ASA ≥ 3 (100%), 63% male · Cardiothoracic surgery	· Primary outcome: 19% in the BIS group and 28% in the end-tidal-guided group developed POD, a 9% non-significant reduction in the BIS-guided group. · Independent predictors of POD included low anesthesia dose, intraoperative transfusion, & ASA physical status.	· A larger RCT is warranted to further explore the role of pEEG-guided versus end-tidal-guided anesthesia delivery on POD after cardiothoracic surgery. · Patients in poor health may be more sensitive to anesthesia and have a higher risk of developing POD.
Whitlock et al. 2014 [13]	· Anesthetic technique: inhaled agents · pEEG-guided group: target BIS 40–60 in 149 patients · End-tidal-guided group: target between 0.7 and 1.3 MAC in 161 patients · Patients screened twice a day for POD using the CAM-ICU · Primary outcome: incidence of POD		· Given the association between POD and poor patient outcomes, development of methods to minimize POD should be prioritized.

(Continued to the next page)

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Table 1. Continued

Study name	Experimental design	Results	Conclusions
The ENGAGES trial	· Demographics: aged ≥ 60, ASA ≥ 3 (34%), 54.3% male	· Primary outcome: 26% in the pEEG group and 23% in the routine care group developed POD.	· pEEG-guided anesthesia delivery did not decrease the incidence of POD compared with routine care.
	· Major surgery (cardiac and non-cardiac)	· Intraoperative measures: median end-tidal anesthetic concentration was lower in the pEEG-guided group (0.69 vs. 0.80 MAC). Median duration of EEG suppression was less in the pEEG-guided group (SR > 1%: 7 vs. 13 min, BIS < 40: 32 vs. 60 min). No differences in MAP < 60 mmHg (7 min for both groups).	· Median end-tidal anesthetic concentration and median cumulative time with EEG suppression was significantly less in the pEEG-guided group.
Wildes et al. 2019 [11]	· Anesthetic technique: inhaled agents	· Adverse events: No reported awareness with recall in either group. Death within 30 days: < 1% in the pEEG-guided group and 3% in the routine care group.	
	· pEEG-guided group (BIS ≥ 40): 614 patients		
	· Routine care: 618 patients		
	· Patients screened for POD using the CAM-ICU		
	· Primary outcome: incidence of POD on postoperative days 1–5		
	· Intraoperative measures: end-tidal anesthetic concentration, duration of EEG suppression (SR > 1% & time with BIS < 40), and hypotension (MAP < 60 mmHg).		
	· Adverse events: awareness with recall, death within 30 days.		

ASA: American Society of Anesthesiologists, BIS: bispectral index, TIVA: total intravenous anesthesia, pEEG: processed electroencephalography, POCD: postoperative cognitive dysfunction. Assessed using the selected tools. Some examples include the cognitive failure questionnaire to indicate potential subjective problems with perception, memory, and motor function, and neuropsychological tests, such as the verbal fluency test, verbal learning test, and color trail making test; POD: postoperative delirium. Assessed using the selected tools. Examples include the CAM-ICU; BAG-RECALL: BIS or Anesthesia Gas to Reduce Explicit Recall. This was a prospective, multi-center, randomized controlled trial to determine whether a bispectral index-guided protocol is superior to an anesthesia gas-guided protocol in reducing intraoperative awareness with explicit recall in high-risk surgical patients, RCT: randomized clinical trial, MAC: minimum alveolar concentration, CAM-ICU: Confusion Assessment Method for the intensive care unit, ENGAGES: Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes, SR: suppression ratio, MAP: mean arterial pressure.

in the presence of low anesthesia concentrations is associated with a higher incidence of POD [13]. They also found that the published threshold for increased risk of POD is a burst suppression duration ≥ 4 min. In the ENGAGES trial, the median EEG burst suppression duration was 7 and 13 min in the pEEG-guided and control groups, respectively. The duration for both groups exceeded the threshold for increased delirium risk. They suggested that with the burst suppression duration above the threshold for POD, it was difficult to draw any conclusions about the utility of pEEG-guided anesthesia delivery for reducing the incidence of POD.

To synthesize a consensus from this body of work, meta-analyses have systematically found that pEEG-guided anesthesia has the potential to reduce the incidence of POD and POCD. Punjasawadwong et al. [14] analyzed data from three RCTs to explore the incidence of POD and POCD in combined cohorts of 2,529 and 2,051 patients, respectively. They reported a reduction in the incidence of POD in patients aged > 60 years undergoing non-cardiac and non-neurosurgical procedures from 21% without to 15% with pEEG monitoring. They also reported a small reduction in the incidence of POCD at three months post-operation from 9% to 6% with pEEG monitoring [14]. In another meta-analysis of five RCTs, which included 2,654 patients, MacKenzie et al. [15] determined that the use of a pEEG monitor was associated with a 38% reduction in the odds of developing POD but data were insufficient to assess the relationship between pEEG and POCD.

Expanding this line of investigation, researchers have identified select measurements for neuronal electrical activity, burst suppression, and changes in the alpha band that may serve as an electrophysiological phenotype of the vulnerable brain [9]. Both are available with newer conventional pEEG monitors; however, they do require some expertise for proper interpretation at the point of care.

Many studies have suggested that anesthesia-induced burst suppression is a risk factor for POD [7,16–19]. For example, Purdon et al. [7], in their study of EEG changes in patients aged 18–90 years who received either propofol or sevoflurane as a maintenance anesthetic, found decreased power in all EEG frequency bands with increasing age. Alpha power was found to decrease more than the other frequency bands and burst suppression was more evident in elderly patients.

In an observational cohort analysis, Fritz et al. [18] enrolled 619 patients who underwent general anesthesia with planned intensive care unit (ICU) admission after surgery. They assessed delirium using the Confusion Assessment Method (CAM) for the ICU and measured the burst suppression. They found that 162 patients developed POD and that patients with more burst suppression were more likely to develop delirium. Approximately 15% of patients who developed POD had no burst suppression; however, 35% of those with ≥ 18 min of burst suppression developed POD. These authors also reported a similar finding, with a BIS value < 20, and found that those patients who received fewer intraoperative opioids were likely to experience more burst suppression. Similar findings have been reported in patients following cardiac surgery [19]. In a retrospective analysis of the same patient cohort, Fritz et al. [16] explored patient sensitivity to inhaled anesthetics. They found that patients who experienced burst suppression at lower concentrations of inhaled anesthesia had a higher incidence of POD and concluded that burst suppression in the presence of low concentrations of inhaled anesthesia may serve as a phenotype of anesthetic sensitivity, increasing their risk for poor cognitive outcomes.

Giattino et al. [20] studied 15 patients who underwent a preoperative neurocognitive assessment and then measured alpha power among other EEG metrics during anesthesia and surgery. They found a correlation between frontal alpha-band activity and preoperative cognitive function that was not present in other EEG frequency bands such as delta, theta, or beta [20]. The authors concluded that lower intraoperative frontal alpha power may be useful for identifying patients with poor cognitive function before surgery who may benefit from practices that minimize or prevent POD and POCD.

In a large multicenter trial, Hesse et al. [17] studied EEG changes during emergence from anesthesia and the development of delirium in the post-anesthesia care unit (PACU). They characterized a set of seven different EEG patterns during emergence from anesthesia, defined as emergence trajectories. Emergence trajectories were compared with the power in the alpha band and other EEG frequency bands. Patients with the various emergence trajectories who did not develop oscillations in alpha power were at a higher risk for POD in the PACU [17]. Of note, this phenomenon was more pronounced in patients who received ketamine or nitrous oxide.

Taking this concept one step further, Shao et al. [9] demonstrated an important relationship between changes in alpha band power and burst suppression. These authors analyzed EEG data for the presence of burst suppression and diminished alpha band power in patients maintained with either propofol or sevoflurane. They characterized the relationship between burst suppression and alpha power using logistic regression and found that for each dB decrease in frontal alpha power, the odds of experiencing burst suppression increased 1.33-fold. From their analysis, they proposed that these findings represent an EEG phenotype of the vulnerable brain.

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Although these findings may allow for the early detection of patients who are vulnerable to adverse neurocognitive outcomes, their clinical value requires further investigation and will likely be part of a comprehensive approach to brain health in the perioperative period. In addition to monitoring EEG values, anesthesia care providers will likely have to utilize more refined approaches to anesthesia titration, implement tools to assess cognitive function throughout the perioperative period, and implement postoperative patient care pathways that minimize adverse outcomes [21,22]. Implementing these patient care adjuncts will likely unveil gaps in anesthesia care providers' experience in conducting a preoperative cognitive assessment and awareness of the adverse consequences of their anesthetic technique on long-term brain health because of limited follow-up with their patients during a period when neurocognitive deficits may appear after surgery.

Recent consensus guidelines from the Periopeartive Quality Initiative (POQI) report insufficient evidence to recommend the use of pEEG monitoring to minimize the risk of POD and POCD in older high-risk patients undergoing general anesthesia [23]. It is important to emphasize, however, that the POQI group of experts noted that three large, randomized trials demonstrated a decrease in POD with EEG-guided general anesthesia, while only the ENGAGES trial showed no effect. We anticipate that future work will explore the use of pEEG monitoring to detect unintended burst suppression that includes recommendations on spectral displays and alpha band power that clinicians can easily interpret to guide anesthetic delivery in the vulnerable brain population.

In summary, when determining which anesthetic approach to use with a patient who is known to have or suspected of having vulnerable brain, EEG monitoring with focused attention on the suppression ratio, alpha band power, and pEEG indices, along with other measures, may prove useful to minimize postoperative neurocognitive decline. Avoiding excessive anesthesia and the use of anesthetics known to increase POD and providing prompt treatment of physiological and metabolic disorders (e.g., low hematocrit, hyponatremia, acidosis, etc.) are also important for minimizing POD.

Reducing awareness during total intravenous anesthesia

There are no monitors available for measuring the concentrations of exhaled drugs when administering total intravenous anesthesia (TIVA). TIVAs commonly consists of a continuous infusion of propofol in combination with bolus administrations or a continuous infusion of an opioid. Anesthesia care providers rely on clinical signs of an adequate depth of anesthesia to ensure continuous delivery of intravenous drugs. This is in stark contrast to potent inhaled agents, for which continuous monitoring of exhaled drug concentrations is routine. Anesthetic drug delivery is confirmed by the presence of exhaled drug concentrations. Another sign of inadequate anesthesia is patient movement. When a neuromuscular blockade is used, which removes patient movement as a sign of inadequate anesthesia, the risk of awareness is higher with TIVA.

Investigators have explored the incidence of awareness with varied results. In a retrospective observational study conducted by the Fifth National Audit Project (NAP5), over 2.8 million patient records over a 12-month period were reviewed to explore the incidence of accidental awareness as spontaneously reported by patients during general anesthesia [24]. The authors reported that 147 patients experienced accidental awareness with an overall incidence of 1 : 19,000 or 0.005%. However, the incidence of awareness varied according to the anesthetic technique. Twenty-eight patients undergoing TIVA reported awareness. TIVA was found to have a higher incidence of 1 : 14,000 or 0.007%, which increased to 1 : 8,333 or 0.012% when it was combined with a neuromuscular blockade. The NAP5 report emphasized that, compared to other anesthetic techniques, awareness with TIVA was largely avoidable and likely related to inadequate drug delivery. In the absence of monitoring to confirm propofol concentrations, the authors suggested that the use of pEEG monitors may help prevent awareness when using TIVA in combination with a neuromuscular blockade. This recommendation is especially important when considering propofol as the maintenance anesthesia. Variability in propofol effects is substantial and requires careful titration to achieve the desired effects while avoiding the adverse effects. For example, recommended target concentrations have been found to range from 3 to 6 μg/ml with target-controlled infusions and can vary further depending on the co-administration of opioids and patient traits such as anxiety or frailty in elderly patients [25].

Exploring a similar question, Errando et al. [26] conducted a prospective single-center observational study investigating the incidence of awareness using a structured interview in the PACU. Investigators, blinded to the anesthetic technique, interviewed 4,001 patients who received anesthesia from 42 different anesthesia care providers. Of these, over 1,200 patients received TIVA and the overall incidence of awareness was 1 : 100 or 1%. According to the anesthetic technique, the incidence with potent inhaled agents was 1 : 167 or 0.6% and with TIVA it was 1 : 91 or 1.1%. The authors found that the incidence was higher in younger patients, with emergency procedures, and with anesthesia delivery at night and the incidence was lower in patients who were premedicated

with a benzodiazepine.

The large difference in the incidence of awareness reported in these two studies is likely due to differences in the detection of awareness. The NAP5 study relied on patients' self-reporting, followed by documentation that could be identified in their retrospective analysis. In the prospective observational study, all patients were interviewed about awareness in the PACU and those that reported events consistent with awareness had follow-up interviews 7 and 30 days later. As such, the methodology used to report awareness likely played a significant role in the reported rates. With a larger patient population, it is more difficult to employ thorough reporting methods.

Many investigators have explored whether pEEG monitoring can be used to detect brain electrical activity associated with awareness [27–29]. Although laudable, this effort is hampered by studying an adverse event that rarely occurs using a monitor that characterizes brain electrical activity but is not a direct measure of patient responsiveness or consciousness. As such, the notion that pEEG monitors could be reliable monitors of awareness remains somewhat controversial. Nevertheless, experts have recommended "the use of end-tidal anesthesia gas monitoring with alarms or pEEG to reduce the risk of awareness with recall in patients receiving general anesthesia" [23].

In summary, when administering anesthesia to patients who may benefit from TIVA and require a moderate-to-deep neuromuscular blockade (e.g., patients with a history of severe postoperative nausea and vomiting undergoing a laparoscope procedure), pEEG monitoring and vigilant attention to intravenous drug administration may minimize the risk of awareness.

Anesthetic titration in patients with hemodynamic instability

Discovering an optimal approach for managing intraoperative hemodynamic instability can be difficult. For example, the best initial treatment of high or low blood pressure may be adjusting the anesthetic dose, administrating a vasoactive agent, or both. However, the most prudent choice is not always evident. As suggested by Fehr et al. [30], pEEG monitors may offer information that would clarify which treatment to apply. However, there is a paucity of research exploring their benefits in this setting. Researchers have explored how pEEG indices in combination with hemodynamic and anesthetic dosing levels may predict adverse outcomes and mortality with inconsistent results [31–34].

As an example, in a large retrospective single-center analysis conducted by Sessler et al. [35], the authors described a triple low phenomenon that consisted of a mean arterial pressure < 80 mmHg, BIS value < 40, and MAC < 0.8, which served as a strong predictor of 30-days mortality. The authors concluded that the triple low was a promising triad, but additional studies are warranted to confirm it is a predictor of perioperative mortality. Follow-up prospective validation comparing mortality between two patient groups exhibiting triple low physiology was conducted. In one group, anesthesia care providers were advised via the electronic anesthetic record to "consider hemodynamic support," while in the control group, no warning was offered. An effective response to the warning was to administer a vasoactive agent within 5 min of the warning or decrease the end tidal anesthesia by more than 20%. They found that the warning did not change 90-days mortality. The anesthesia care providers, however, had ignored the warning approximately half of the time, which was unanticipated. The authors had anticipated that anesthesia care providers in the advisory group would respond more frequently and fewer would respond in the non-advisory group. They concluded that their data were inadequate to properly explore whether a triple low advisory would improve outcomes [36].

We suggest that this unanticipated finding may represent an education gap among anesthesia care providers. Specifically, anesthesia care providers may lack an understanding of how pEEG indices in combination with other physiologic measures can be used to improve outcomes and address hemodynamic perturbations. We propose that pEEG monitoring could contribute to an adequate discrimination between the need for a vasoactive agent, volume resuscitation, or an adjustment in the anesthesia in a variety of clinical scenarios. As an example, we considered the hemodynamic pEEG profiles that inform intraoperative management. Fig. 2 presents options for normal, low, and high blood pressure conditions versus normal, low, and high pEEG indices.

For example, if a patient exhibits high blood pressure but has a low pEEG index (e.g., a BIS value ≤ 40), even though increasing the anesthesia is likely effective at lowering the blood pressure, it may lead to excessive anesthesia and prolonged emergence. Therefore, antihypertensive agents may be more appropriate. In this scenario, the likely source of high blood pressure is essential hypertension and not inadequate anesthesia. Considering hypertension in the context of pEEG values is useful when caring for patients for whom unnecessary administration of anesthetics may increase the risk of worrisome postoperative adverse events [30].

Under select conditions of mild-to-moderate low blood pressure, in addition to administering vasopressors, inotropic agents, and intravenous fluids, pEEG monitoring may inform appropriate adjustments of the anesthetic. For example, if a patient exhibits mild hypotension and low pEEG indices, corrective actions include reducing the anesthetic and administering vasoactive drugs

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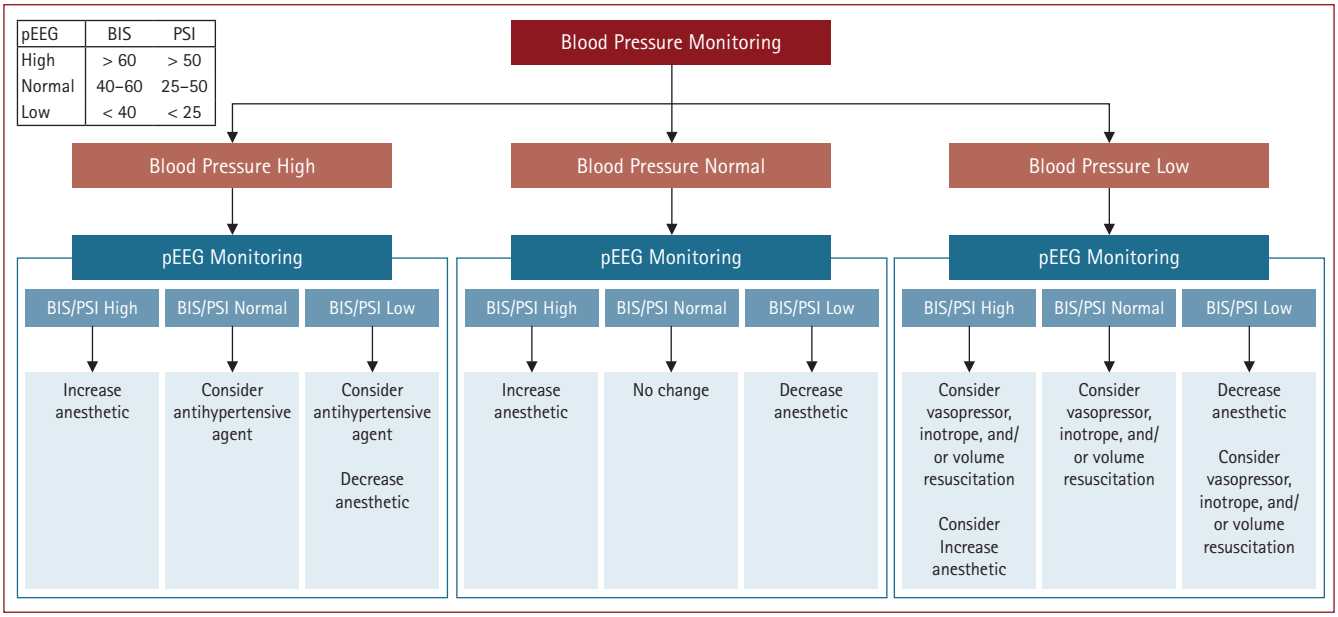

Fig. 2. Intraoperative hemodynamic-processed electroencephalography decision matrix for choosing between altering anesthetic depth versus administering vasoactive agents and fluid administration. BIS: bispectral index, pEEG: processed electroencephalography, PSI: patient state index.

and intravenous fluids. Although less likely, if a patient exhibits hypotension and high pEEG indices, it may be prudent to restore the blood pressure with vasoactive agents and intravenous fluids before reducing the anesthesia.

In instances of severe hypotension due to blood loss, pEEG monitoring may be especially helpful. Hemorrhagic shock results in an increase in the concentration of intravenous anesthesia due to altered distribution and metabolism. The increased drug levels produce a more pronounced anesthetic effect that is reflected in lower pEEG indices, providing a rational basis for anesthesia administration [37]. Cardiac output is reduced by altering the pharmacokinetics of anesthetic drugs. As the volume of distribution contracts, conventional dosing can lead to elevated blood and effect-site drug concentrations with pronounced effects. When managing an anesthesia under these conditions, anesthesia providers often decrease drug delivery.

An example of this phenomenon was presented in a case report describing the blood pressure and BIS values resulting from significant blood loss in a 70-year-old woman who underwent abdominal aneurysm repair [38]. The patient was anesthetized with propofol-alfentanil (TIVA). Notably, the hemorrhage-associated drop in blood pressure was preceded by a drop in the BIS. The authors suggested that pEEG values may serve as an early warning of altered drug pharmacokinetics due to severe blood loss.

In summary, we suggest that pEEG monitoring may play a role in anesthesia and resuscitative management when faced with adverse changes in blood pressure. We also suggest addressing education gaps that exist in clinicians' understanding of how pEEG monitoring in combination with conventional physiological monitors may be used to improve intraoperative and long-term patient outcomes.

Patients with a history of substance abuse

Formulating an appropriate anesthetic dose in patients with a history of substance abuse to achieve the desired level of sedation, analgesia, and immobility presents challenges. Prolonged exposure to opioids, alcohol, and stimulants or the use of drugs to treat opioid use disorders may make it difficult to find an appropriate anesthetic dose. The primary concern is the risk of unintended awareness during general anesthesia [39]. Prior work exploring the scientific foundation behind this concern is limited, but that which exists is interesting and perhaps unexpected. The selected substances are briefly discussed below.

Researchers have studied how painful stimuli processing is altered in chronic pain. Chronic opioid use differentially affects the level of consciousness and spinal cord responses to surgical stimulation. For example, Oh et al. [40] measured end-tidal sevoflurane concentrations needed to maintain a BIS value < 50 ($SEVO_{BIS50}$) in both chronic opioid users and opioid-naïve patients. They defined chronic opioid users as those who received a stable dose of oral morphine of at least 60 mg per day for at least 4 weeks. The $SEVO_{BIS50}$ was determined using Dixon's up-down method and probit analysis. The predetermined consistent end-tidal sevoflu-

rane concentration was confirmed and maintained for 15 min to ensure equilibrium in end-tidal and effect site concentrations. Subsequently, BIS values were obtained for 1 min at 10-s intervals in the absence of a surgical stimulus. If the average of the five values was < 50, the authors decreased the sevoflurane by 0.2% for the next patient, and if the average was > 50, the authors increased the sevoflurane by 0.2% for the next patient. They reported a modest decrease in the $SEVO_{BIS50}$ levels for chronic opioid users compared to opioid-naïve patients (0.84 [95% CI: 0.58, 1.11] and 1.18% [95% CI: 0.96, 1.40], respectively). Although not intuitive, patients who chronically consume opioids may require less maintenance anesthesia.

The mechanism behind this observation is not well understood; however, it may be a function of how the data were collected and how the results were interpreted. $SEVO_{BIS50}$ is not defined in the same manner as the MAC. The MAC is defined as the concentration needed to blunt a response to a standard stimulus such as surgical incision in 50% of patients, whereas the BIS is a pEEG index of brain electrical activity suppression. Although the authors did not explore changes in the MAC of sevoflurane due to chronic opioid use, they did evaluate how chronic opioid use influences brain electrical activity under general anesthesia. A limitation of this approach was that the $SEVO_{BIS50}$ was not evaluated in the presence of a nociceptive stimulus. Unlike with MAC studies, the impact of sevoflurane on spinal cord transmission from nociceptive stimuli has not been determined.

As with the vulnerable brain, patients with chronic pain exhibit unique characteristics in the spectral display. Specifically, patients with chronic pain exhibit changes in the theta frequency band (3–8 Hz) that are not observed in opioid-naïve patients [41]. The clinical implications of these changes are yet to be elucidated. Future work is warranted to explore how changes in the theta frequency band can be used to titrate anesthetic delivery to this patient population.

In response to the opioid epidemic, buprenorphine has been used to manage patients with opioid use disorders and chronic pain. Buprenorphine is a partial opioid mu receptor agonist and an opioid kappa and a delta receptor antagonist. It has a much higher affinity for mu receptors than several commonly used opioids, such as fentanyl, hydrocodone, oxycodone, and morphine, but has a similar affinity as hydromorphone [42]. With a higher affinity, it displaces opioid agonists and competitively occupies up to 80%–95% of receptors at clinical doses. As a partial agonist, it is considered safer since there is an associated ceiling effect on ventilatory depression, although the analgesic effect may be less pronounced [43]. Conflicting concerns have emerged regarding its use during the perioperative period, such as a concern for inadequate acute pain control because buprenorphine occupies mu receptors, displacing pure opioid agonists. Conversely, cessation of buprenorphine increases the risk of opioid use disorder relapse and is associated with adverse outcomes.

Recent recommendations propose maintaining buprenorphine at preoperative doses throughout the perioperative period [43,44]. Under select conditions, reducing the buprenorphine dosage may be considered with procedures associated with significant pain. This is done to allow for more receptors to be occupied by full opioid agonists.

Although these guidelines focus on the challenges of providing adequate and safe perioperative care, they are based on lower levels of evidence, such as case series, case reports, observational studies, studies without control groups, and expert consensus. Future work is therefore warranted to establish evidence on how to best manage buprenorphine administration during the perioperative period. Therefore, when determining the appropriate anesthesia for patients receiving buprenorphine, the anesthesia and the dose require individualized and timely adjustments to achieve the desired effects. Opioid analgesic efficacy and interactions with sedatives and potent inhaled agents are likely altered, making conventional approaches to dosing challenging and even inadequate. Using pEEG indices and end-tidal inhaled agent concentrations may prove useful in titrating anesthetic delivery in this patient group.

Alcoholics can have varied anesthesia requirements based on the state of inebriation. If acutely intoxicated, they require less anesthesia, and if sober, they can have increased anesthesia requirements. Acute alcohol intoxication slows the EEG and may influence BIS values. Gerstman et al. [45] found a moderate correlation between BIS values and venous blood alcohol concentration ($r = -0.49$, $P = 0.029$) in healthy young adults. In their study, 21 participants consumed a median of 90 g of alcohol over a 3-hour period. The authors concluded that BIS values may decrease in the presence of alcohol.

Fassoulaki et al. [46] compared the induction and maintenance propofol dose requirements in alcoholics and non-alcoholics. They defined chronic alcoholics as those who had consumed an average of 40 g/day of ethanol for at least 2 years. They defined non-alcoholics as those who consumed alcohol only occasionally or not at all. They found that with induction, the mean propofol dose required for loss of responsiveness was modestly increased in alcoholics compared to non-alcoholics (2.7 ± 0.4 vs. 2.2 ± 0.4 mg/kg, respectively). Similarly, when using propofol as the maintenance anesthesia, the total amount was increased in alcoholics compared to non-alcoholics (4.2 ± 1.0 vs. 3.2 ± 0.8 mg/kg, respectively) [46].

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In summary, providing anesthesia to patients with known or suspected substance use is difficult, since they may have unanticipated increased or decreased requirements. The use of pEEG monitoring with attentive hemodynamic monitoring may be better for identifying anesthesia requirements and guiding anesthetic titration to avoid excessive or inadequate anesthesia administration.

In conclusion, advances in understanding the nuances in intraoperative EEG monitoring at the point of care are emerging to better guide anesthesia delivery in select patient populations. In this article, we reviewed well-supported, but perhaps poorly appreciated, key features of EEG waveforms, and their clinical implications. These key features include EEG waveform morphology, spectral analysis, burst suppression, and alpha power. We recommend anesthesia providers receive education to increase awareness of the clinical utility of these key EEG features at the point of care. This review article also posits that in select patient groups and anesthetic techniques, pEEG monitors can improve patient outcomes and minimize adverse events.

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Conflicts of Interest

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

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References

1. Chen X, Tang J, White PF, Wender RH, Ma H, Sloninsky A, et al. A comparison of patient state index and bispectral index values during the perioperative period. Anesth Analg 2002; 95: 1669-74.
2. Prichep LS, Gugino LD, John ER, Chabot RJ, Howard B, Merkin H, et al. The Patient State Index as an indicator of the level of hypnosis under general anaesthesia. Br J Anaesth 2004; 92: 393-9.
3. Puri GD, Mathew PJ, Sethu Madhavan J, Hegde HV, Fiehn A. Bi-spectral index, entropy and predicted plasma propofol concentrations with target controlled infusions in Indian patients. J Clin Monit Comput 2011; 25: 309-14.
4. Pilge S, Zanner R, Schneider G, Blum J, Kreuzer M, Kochs EF. Time delay of index calculation: analysis of cerebral state, bispectral, and narcotrend indices. Anesthesiology 2006; 104: 488-94.
5. Purdon PL, Sampson A, Pavone KJ, Brown EN. Clinical electroencephalography for anesthesiologists: part i: background and basic signatures. Anesthesiology 2015; 123: 937-60.
6. Babadi B, Brown EN. A review of multitaper spectral analysis. IEEE Trans Biomed Eng 2014; 61: 1555-64.
7. Purdon PL, Pavone KJ, Akeju O, Smith AC, Sampson AL, Lee J, et al. The ageing brain: age-dependent changes in the electroencephalogram during propofol and sevoflurane general anaesthesia. Br J Anaesth 2015; 115 Suppl 1(Suppl 1): i46-57.
8. Bollimunta A, Mo J, Schroeder CE, Ding M. Neuronal mechanisms and attentional modulation of corticothalamic α oscillations. J Neurosci 2011; 31: 4935-43.
9. Shao YR, Kahali P, Houle TT, Deng H, Colvin C, Dickerson BC, et al. Low frontal alpha power is associated with the propensity for burst suppression: an electroencephalogram phenotype for a "vulnerable brain". Anesth Analg 2020; 131: 1529-39.
10. Jung H, Kim SY, Canbakis Cecen FS, Cho Y, Kwon SK. Dysfunction of mitochondrial Ca2+ regulatory machineries in brain aging and neurodegenerative diseases. Front Cell Dev Biol 2020; 8: 599792.
11. Wildes TS, Mickle AM, Ben Abdallah A, Maybrier HR, Oberhaus J, Budelier TP, et al. Effect of electroencephalography-guided anesthetic administration on postoperative delirium among older adults undergoing major surgery: the engages randomized clinical trial. JAMA 2019; 321: 473-83.
12. Ackland GL, Pryor KO. Electroencephalography-guided anaesthetic administration does not impact postoperative delirium among older adults undergoing major surgery: an independent discussion of the ENGAGES trial. Br J Anaesth 2019; 123: 112-7.
13. Whitlock EL, Torres BA, Lin N, Helsten DL, Nadelson MR, Mashour GA, et al. Postoperative delirium in a substudy of cardiothoracic surgical patients in the BAG-RECALL clinical trial. Anesth Analg 2014; 118: 809-17.

14. Punjasawadwong Y, Chau-In W, Laopaiboon M, Punjasawadwong S, Pin-On P. Processed electroencephalogram and evoked potential techniques for amelioration of postoperative delirium and cognitive dysfunction following non-cardiac and non-neurosurgical procedures in adults. Cochrane Database Syst Rev 2018; 5: CD011283.
15. MacKenzie KK, Britt-Spells AM, Sands LP, Leung JM. Processed electroencephalogram monitoring and postoperative delirium: a systematic review and meta-analysis. Anesthesiology 2018; 129: 417-27.
16. Fritz BA, Maybrier HR, Avidan MS. Intraoperative electroencephalogram suppression at lower volatile anaesthetic concentrations predicts postoperative delirium occurring in the intensive care unit. Br J Anaesth 2018; 121: 241-8.
17. Hesse S, Kreuzer M, Hight D, Gaskell A, Devari P, Singh D, et al. Association of electroencephalogram trajectories during emergence from anaesthesia with delirium in the postanaesthesia care unit: an early sign of postoperative complications. Br J Anaesth 2019; 122: 622-34.
18. Fritz BA, Kalarickal PL, Maybrier HR, Muench MR, Dearth D, Chen Y, et al. Intraoperative Electroencephalogram Suppression Predicts Postoperative Delirium. Anesth Analg 2016; 122: 234-42.
19. Soehle M, Dittmann A, Ellerkmann RK, Baumgarten G, Putensen C, Guenther U. Intraoperative burst suppression is associated with postoperative delirium following cardiac surgery: a prospective, observational study. BMC Anesthesiol 2015; 15: 61.
20. Giattino CM, Gardner JE, Sbahi FM, Roberts KC, Cooter M, Moretti E, et al. Intraoperative frontal alpha-band power correlates with preoperative neurocognitive function in older adults. Front Syst Neurosci 2017; 11: 24.
21. Berger M, Schenning KJ, Brown CH 4th, Deiner SG, Whittington RA, Eckenhoff RG, et al. Best practices for postoperative brain health: recommendations from the fifth international perioperative neurotoxicity working group. Anesth Analg 2018; 127: 1406-13.
22. Mahanna-Gabrielli E, Schenning KJ, Eriksson LI, Browndyke JN, Wright CB, Culley DJ, et al. State of the clinical science of perioperative brain health: report from the American Society of Anesthesiologists Brain Health Initiative Summit 2018. Br J Anaesth 2019; 123: 464-78.
23. Chan MT, Hedrick TL, Egan TD, García PS, Koch S, Purdon PL, et al. American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on the role of neuromonitoring in perioperative outcomes: electroencephalography. Anesth Analg 2020; 130: 1278-91.
24. Pandit JJ, Andrade J, Bogod DG, Hitchman JM, Jonker WR, Lucas N, et al. 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: summary of main findings and risk factors. Br J Anaesth 2014; 113: 549-59.
25. Nimmo AF, Absalom AR, Bagshaw O, Biswas A, Cook TM, Costello A, et al. Guidelines for the safe practice of total intravenous anaesthesia (TIVA): Joint Guidelines from the Association of Anaesthetists and the Society for Intravenous Anaesthesia. Anaesthesia 2019; 74: 211-24.
26. Errando CL, Sigl JC, Robles M, Calabuig E, García J, Arocas F, et al. Awareness with recall during general anaesthesia: a prospective observational evaluation of 4001 patients. Br J Anaesth 2008; 101: 178-85.
27. Myles PS, Leslie K, McNeil J, Forbes A, Chan MT. Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial. Lancet 2004; 363: 1757-63.
28. Avidan MS, Zhang L, Burnside BA, Finkel KJ, Searleman AC, Selvidge JA, et al. Anesthesia awareness and the bispectral index. N Engl J Med 2008; 358: 1097-108.
29. Mashour GA, Shanks A, Tremper KK, Kheterpal S, Turner CR, Ramachandran SK, et al. Prevention of intraoperative awareness with explicit recall in an unselected surgical population: a randomized comparative effectiveness trial. Anesthesiology 2012; 117: 717-25.
30. Fehr SB, Zalunardo MP, Seifert B, Rentsch KM, Rohling RG, Pasch T, et al. Clonidine decreases propofol requirements during anaesthesia: effect on bispectral index. Br J Anaesth 2001; 86: 627-32.
31. Monk TG, Saini V, Weldon BC, Sigl JC. Anesthetic management and one-year mortality after noncardiac surgery. Anesth Analg 2005; 100: 4-10.
32. Leslie K, Myles PS, Forbes A, Chan MT. The effect of bispectral index monitoring on long-term survival in the B-aware trial. Anesth Analg 2010; 110: 816-22.
33. Kertai MD, Pal N, Palanca BJ, Lin N, Searleman SA, Zhang L, et al. Association of perioperative risk factors and cumulative duration of low bispectral index with intermediate-term mortality after cardiac surgery in the B-Unaware Trial. Anesthesiology 2010; 112: 1116-27.
34. Kertai MD, Palanca BJ, Pal N, Burnside BA, Zhang L, Sadiq F, et al. Bispectral index monitoring, duration of bispectral index below 45, patient risk factors, and intermediate-term mortality after noncardiac surgery in the B-Unaware Trial. Anesthesiology 2011; 114: 545-56.
35. Sessler DI, Sigl JC, Kelley SD, Chamoun NG, Manberg PJ, Saager L, et al. Hospital stay and mortality are increased in patients having a "triple low" of low blood pressure, low bispectral index,

https://doi.org/10.4097/kja.21349

and low minimum alveolar concentration of volatile anesthesia. Anesthesiology 2012; 116: 1195-203.
36. Sessler DI, Turan A, Stapelfeldt WH, Mascha EJ, Yang D, Farag E, et al. Triple-low Alerts Do Not Reduce Mortality: A Real-time Randomized Trial. Anesthesiology 2019; 130: 72-82.
37. Egan ED, Johnson KB. The influence of hemorrhagic shock on the disposition and effects of intravenous anesthetics: a narrative review. Anesth Analg 2020; 130: 1320-30.
38. Honan DM, Breen PJ, Boylan JF, McDonald NJ, Egan TD. Decrease in bispectral index preceding intraoperative hemodynamic crisis: evidence of acute alteration of propofol pharmacokinetics. Anesthesiology 2002; 97: 1303-5.
39. National Institute for Health and Care Excellence. Depth of anaesthesia monitors - bispectral index (BIS), E-Entropy, and Narcotrend-Compact M. Diagnostics guidance [DG6] [Internet]. London: NICE; 2012 Nov 21 [cited 2021 Aug 12]. Available from www.nice.org.uk/guidance/dg6
40. Oh TK, Eom W, Yim J, Kim N, Kwon K, Kim SE, et al. The effect of chronic opioid use on end-tidal concentration of sevoflurane necessary to maintain a bispectral index below 50: a prospective, single-blind study. Anesth Analg 2017; 125: 156-61.
41. Ploner M, May ES. Electroencephalography and magnetoencephalography in pain research-current state and future perspectives. Pain 2018; 159: 206-11.
42. Volpe DA, McMahon Tobin GA, Mellon RD, Katki AG, Parker RJ, Colatsky T, et al. Uniform assessment and ranking of opioid μ receptor binding constants for selected opioid drugs. Regul Toxicol Pharmacol 2011; 59: 385-90.
43. Warner NS, Warner MA, Cunningham JL, Gazelka HM, Hooten WM, Kolla BP, et al. A practical approach for the management of the mixed opioid agonist-antagonist buprenorphine during acute pain and surgery. Mayo Clin Proc 2020; 95: 1253-67.
44. Goel A, Azargive S, Weissman JS, Shanthanna H, Hanlon JG, Samman B, et al. Perioperative Pain and Addiction Interdisciplinary Network (PAIN) clinical practice advisory for perioperative management of buprenorphine: results of a modified Delphi process. Br J Anaesth 2019; 123: e333-42.
45. Gerstman MD, Merry AF, McIlroy DR, Hannam JA, Mitchell SJ, Myles PS. Acute alcohol intoxication and bispectral index monitoring. Acta Anaesthesiol Scand 2015; 59: 1015-21.
46. Fassoulaki A, Farinotti R, Servin F, Desmonts JM. Chronic alcoholism increases the induction dose of propofol in humans. Anesth Analg 1993; 77: 553-6.
47. Chan MT, Cheng BC, Lee TM, Gin T; CODA Trial Group. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. J Neurosurg Anesthesiol 2013; 25: 33-42.
48. Radtke FM, Franck M, Lendner J, Krüger S, Wernecke KD, Spies CD. Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. Br J Anaesth 2013; 110 Suppl 1: i98-105.

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Obesity and anesthetic pharmacology: simulation of target-controlled infusion models of propofol and remifentanil

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Review Article

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The prevalence of obesity is increasing, resulting in an increase in the number of surgeries performed to treat obesity and diseases induced by obesity. The associated comorbidities as well as the pharmacokinetic and pharmacodynamic changes that occur in obese patients make it difficult to control the appropriate dose of anesthetic agents. Factors that affect pharmacokinetic changes include the increase in adipose tissue, lean body weight, extracellular fluid, and cardiac output associated with obesity. These physiological and body compositional changes cause changes in the pharmacokinetic and pharmacodynamic parameters. The increased central volume of distribution and alterations in the clearance of drugs affect the plasma concentration of propofol and remifentanil in the obese population. Additionally, obesity can affect pharmacodynamic properties, such as the 50% of maximal effective concentration and the effect-site equilibration rate constant (ke0). Conducting a simulation of target-controlled infusions based on pharmacokinetic and pharmacodynamic models that include patients that are obese can help clinicians better understand the pharmacokinetic and pharmacodynamic changes of anesthetic drugs associated with this population.

Keywords: Cardiac output; Computer simulation; Ideal body weight; Metabolic clearance rate; Obesity; Pharmacokinetics.

Introduction

The prevalence of obesity is increasing annually worldwide. According to the WHO report [1], 13% of the world's adult population is obese, and the number has been growing steadily. In 2016, obesity was approximately three times what it was in 1975. In particular, the morbidly obese population, with a body mass index (BMI) > 40 kg/m^2, is on the rise. Given the increase in the number of surgeries performed to treat obesity and associated diseases and the comorbidities present in this population, anesthesiologists are having an increasingly difficult time managing these patients. During surgery, anesthesiologists may have trouble with intubation and airway management before and after surgery, mechanical ventilation, control of diabetes and hypertension, obstructive sleep apnea, and cardiopulmonary disease.

In addition, pharmacokinetic and pharmacodynamic changes of anesthetic drugs in obese patients make it difficult to control the appropriate dose of anesthetic agents. The increase in body mass and changes of its composition influences pharmacokinetic parameters such as distribution volume, clearance, and elimination half-life. Comorbidities in obese patients, such as obstructive sleep apnea, may also cause narrowing of the therapeutic dynamic range of anesthetic drugs.

This review will include a discussion about the changes in various anesthetic drugs' pharmacokinetic and pharmacodynamic behaviors that result from the increase in body mass and compositional changes that occur in obese patients based on published articles.

Changes in body mass composition

In obese individuals, the lean body mass, which includes vessel-rich organs and the tissues where drugs act, does not usually increase proportionally to the increase in total body mass. Rather, as the body weight increases, the blood volume, fat mass, lean body mass, and extracellular water volume increase along with the increase in total body weight (TBW); however, the composition of the mass does not always increase in proportion to the total body mass. The fat mass tends to increase along with the TBW; however, lean body mass does not. The ratio of lean body weight (LBW) to TBW decreases as the TBW increases. The proportion of LBW, which explains the increase in TBW, is approximately 20%–40% [2].

When a drug dosage is determined, it is usually scaled based on the TBW. However, administering drugs scaled simply using the TBW in obese patients would result in an overdose. Therefore, obese individuals need other mass scalars to calculate the appropriate dose, such as LBW, ideal body weight (IBW), and fat-free mass. Various mass scalars have been introduced, each with their own characteristic features and equations (Table 1).

Total body weight

Dosing based on the TBW is valid for people with a normal weight. In obese patients, however, the lean tissue, which is where most cardiac output is delivered, does not increase in proportion to the TBW; therefore, the use of the TBW to determine the dose in obese patients would result in an overdose. Other mass scalars must therefore be considered.

Ideal body weight

Numerous equations have been introduced to calculate the IBW [3]. The disadvantage of this mass scalar is that individuals who have the same sex and height receive the same dose regardless of obesity and body mass composition.

Lean body weight

The LBW is the body mass without fat or adipose tissue. For the past several decades, James' equation has frequently been used to calculate the LBW [4]; however, it has serious limitations for the obese population. The equation underestimates the LBW of morbidly obese individuals and even yields a flawed negative LBW. In 2005, Janmahasatian et al. [5] suggested another equation be used to overcome the limitations of James' formula. This equation is derived from dual-energy X-ray absorptiometry measured in men and women of various body weights and heights. Most metabolic activities occur in the lean body mass, and an increase in cardiac output is closely correlated with an increase in the LBW. Therefore, the early distribution kinetics of the drug and clearance are influenced by cardiac output.

Adjusted body weight

The adjusted body weight (ABW) is defined as the IBW plus a proportion (40%) of the excess TBW compared to the IBW. The ABW is calculated as the IBW + 0.4 × (TBW – IBW).

Table 1. Common Dosing Scalars

Dosing scalar	Equation
Ideal body weight	Males: 50 kg + 2.3 kg for each 2.54 cm (1 in) over 152 cm (5 ft)
	Females: 45.5 kg + 2.3 kg for each 2.54 cm (1 in) over 152 cm (5 ft)
Lean body weight	Males: $1.1 \times TBW - 128 \times (TBW / Ht)^2$
	Females: $1.07 \times TBW - 148 \times (TBW / Ht)^2$
Fat-free mass [5]	Males: $(9.27 \times 10^3 \times TBW) / (6.68 \times 10^3 + 216 \times BMI)$
	Females: $(9.27 \times 10^3 \times TBW) / (8.78 \times 10^3 + 244 \times BMI)$
Body surface area (Mosteller's adaptation) [6]	$[(height [cm] - TBW) / 3600]^{1/2}$
Pharmacokinetic mass [7,51]	$52 / [1 + (196.4 \times e^{-0.025 TBW} - 53.66) / 100]$ (fentanyl only)
Corrected body weight or Adjusted body weight [17,34]	IBW + 0.4 × (TBW – IBW)
Allometric scaling	With allometric coefficient alpha, clearance = beta × $(TBW)^{alpha}$

BMI: body mass index, FFM: fat-free mass, Ht: height (cm), IBW: ideal body weight, LBW: lean body weight, TBW: total body weight (kg).

Body mass index

The BMI is widely used to determine the degree of obesity and is calculated as the ratio of the body weight (kg) to the height (m) squared. However, the BMI does not consider the body mass composition.

Body surface area

The body surface area (BSA) has been primarily used as a dosing scalar for chemotherapeutic agents. The equations derived by Mosteller [6] are widely used. However, the BSA does not discriminate between fat and lean body mass.

Pharmacokinetic mass

Due to the non-linear relationship between fentanyl clearance and the TBW, if fentanyl was administered based on the TBW, obese patients would be overdosed. Shibutani et al. [7] therefore devised a modified weight called pharmacokinetic mass, in which the mass scalar increases in proportion to the increase in clearance. The 'pharmacokinetic mass' is reported to be highly correlated with the LBW.

Allometric scaling

Allometric scaling is a method that establishes a relationship between the body mass and pharmacokinetic or pharmacodynamic parameters with a certain fixed exponent constant α, calculated as follows: Clearance = $\beta \times (TBW)^{\alpha}$. Alpha is usually called the allometric coefficient. Allometric scaling is designed to apply animal experiment results to humans or to assume pediatric doses from adult data [8–10]. Allometric scaling can sometimes be useful in determining the drug dosages for obese patients. However, extrapolating analyzed data out of the range, such as data from non-obese to obese populations, has inherent problems.

Changes in pharmacokinetic properties

The various physiological and anthropometric changes that occur in obese patients affect pharmacokinetic parameters, such as distribution volume and clearance, which are used to determine drug concentration and dosage. The characteristic changes in patients with obesity that affect pharmacokinetic parameters, which are not present for those with a normal weight, include an increase in lean body mass, muscle mass, fat mass, circulatory blood volume, and total body water. In addition, changes in the lipophilicity or hydrophilicity and protein binding of drugs affect pharmacokinetic parameters in obese patients [11,12].

The increase in fat mass associated with obesity increases the distribution volume of lipophilic drugs [13–15]. In a study of thiopental, which has high lipophilicity, the steady-state distribution volume and the elimination half-life in obese patients was found be considerably higher. [16]. A study of propofol also showed that the volume of distribution increases in proportion to the increase in the TBW [17]. While the volume of distribution of this lipophilic drug does increase as fat mass increases, it does not increase proportionally. The reason for this is related to changes in blood flow to the adipose tissue, which accounts for 5% of cardiac output in non-obese patients, but it is reduced to 2% in obese patients [18].

The increase in the central volume of distribution associated with obese individuals leads to a rapid decrease in concentration during the initial distribution phase. The loading dose is mainly determined by the size of the central volume of distribution, which determines the changes in the initial concentration after administration. In addition, the increase in cardiac output, which is a commonly observed physiological change in obese patients, is another factor explaining low plasma concentrations in the distributive period [19,20].

Increased cardiac output plays an important role in the increase in the overall clearance of drugs, thus lowering the elimination half-life of the drug. The increase in cardiac output in patients with obesity is highly correlated with the increase in the LBW [21,22]. Increased cardiac output and increased LBW are associated with increased renal and hepatic blood flow, which in turn increase the overall clearance and initial distributive clearance [23,24].

The increase in cholesterol levels and free fatty acids in obese patients has been found to inhibit the binding of drugs to plasma proteins, such as albumin. There is also a disagreement, however, as binding of the drug to plasma proteins increases due to increased levels of α-acid glycoproteins in obese patients [25–28].

Changes of pharmacodynamic properties

Excess fat caused by obesity leads to disturbances in body metabolism and inflammatory reactions and increases drug sensitivity [29,30]. Some studies have shown that obesity increases pain sensitivity, while other studies have found no adverse or pharmacodynamic effects [31–33]. Cortinez et al. [34] did not find any changes in the pharmacodynamic parameters in obese patients. Dong et al. [35], however, reported a decrease in the 50% of maximal effective concentration in obese patients and an increased

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sensitivity to propofol.

Considering that obesity affects both pharmacokinetics and pharmacodynamics, determining the dose of propofol based on the EEG processed monitor (e.g., BIS, entropy) should be considered. Subramani et al. [36] reported that the induction dose of propofol based on the BIS index was different from the induction dose based on LBW in morbid obese patients. In this study, compared to the amount of propofol administered based on the LBW, a larger amount was administered when the dose was based on the BIS. These authors also reported that for those who were administered propofol based on the LBW, 60% of them required an additional dose of propofol to obtain a sufficient depth of anesthesia. The Eleveld model also suggests that the effect-site equilibration rate constant (ke0) changes as the body weight changes, using the equation $0.146 \times (\text{weight [kg]} / 70)^{-0.25}$.

Target-controlled infusion model for the obese population

Studies on a target-controlled infusion (TCI) model for the obese population have been conducted using several drugs, including propofol and remifentanil [37–42]. If the obese population was not included in the process of building a TCI model and not equipped into the anesthetic delivery pump, the exact target effect concentration cannot be obtained by calculating doses simply based on the TBW of an obese patient.

However, some reports have stated that changing the weight scalar of the known TCI model to something other than the TBW improves the performance of the model in obese patients. Cortinez et al. [43] reported an improvement in the performance of the TCI model by simply switching the original weight scalar with an alternative weight scalar. They stated that the performances of the Shnider and Marsh models were dramatically improved after substituting the TBW with the ABW. La Colla et al. [40] proposed using a fictitious height, or an adjusted height, for the Minto model to offset the inaccurate influence of the LBW when the model is applied to obese individuals.

However, these types of proposed shortcuts are not a definitive solution. Constructing a new pharmacokinetic model that includes data obtained from obese patients would be a more desirable approach. Eleveld et al. [44] and Kim et al. [42] presented integrative models for propofol and remifentanil, respectively, by gathering data from various pharmacokinetic studies that included obese patients.

Simulations

Before administering drugs to obese patients, simulations based on pharmacokinetic or pharmacodynamic models are helpful for planning drug administration. A simulation model that includes the obese population would help clinicians discover unexpected errors and prepare for them in advance. Therefore, the Eleveld and Kim models were simulated to discover the differences in the pharmacokinetics of propofol and remifentanil between obese and non-obese individuals.

It is clinically impractical to administer propofol and remifentanil independently at each target concentration without consideration of the interaction. The interaction between propofol and remifentanil, therefore, should be considered in the simulation of obese patients. The target concentration of propofol and remifentanil should be adjusted to reflect a real clinical situation in which an interaction of the drugs occurs.

For this interaction, the hierarchical model proposed by Bouillon et al. [45] was referenced. The target concentration for induction and maintenance of anesthesia was maintained at the target concentration combinations of the two drugs, achieving a rate of 95% no response to laryngoscope intubation or hypnosis (Fig. 1). The resultant predicted concentration of each drug simulated by the scenario is plotted in Fig. 2.

The Eleveld and Schnider models were compared for the propofol simulation, while the Minto and Kim models were compared for the remifentanil simulation. In the Eleveld model, various covariates are used to determine the pharmacokinetic and pharmacodynamic parameters. These covariates include the co-administration of opioids and the participant's health status (patient or healthy volunteer), among others. While all cases could not be covered by this simulation, the influences of weight and age were simulated. A simulation was performed for a healthy volunteer who was administered an opioid and remifentanil and was 170 cm in height. The ke0 from the Minto model was used as a reference for the Kim model, since it does not include the ke0. The purpose of the simulation was to show the changes in the total cumulative dose and infusion rate according to various BMIs and ages.

The cumulative dose of the Eleveld model was larger than that of the Schnider model early in the TCI. This was because the Schnider model has a small and fixed central compartment volume, while the Eleveld model has a relatively larger central compartment volume, which requires a relatively larger amount of propofol at the beginning of the TCI to maintain the same target concentration (Fig. 3A).

Later in the TCI infusion, however, the cumulative dose of the

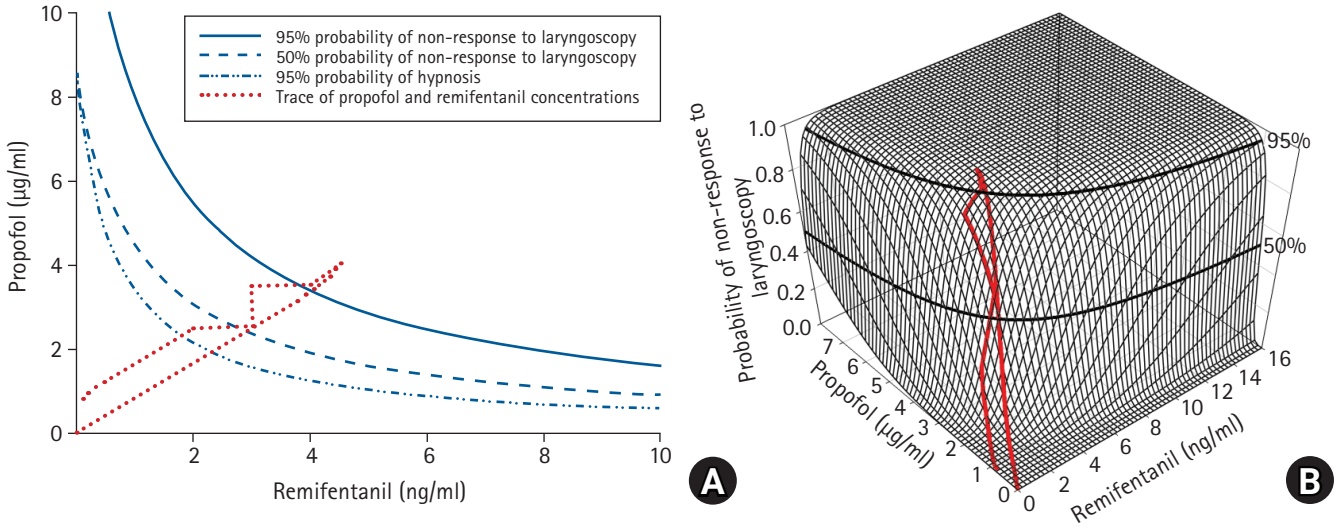

Fig. 1. Planning of the simulation based on loss of responsiveness predictions. (A) Isoboles are presented on top-down view. Isoboles of 95% and 50% non-response to laryngoscope and hypnosis are presented. The inward bow of the isoboles indicates that the interaction is synergistic. (B) Simulated target concentrations are plotted on the interaction surface.

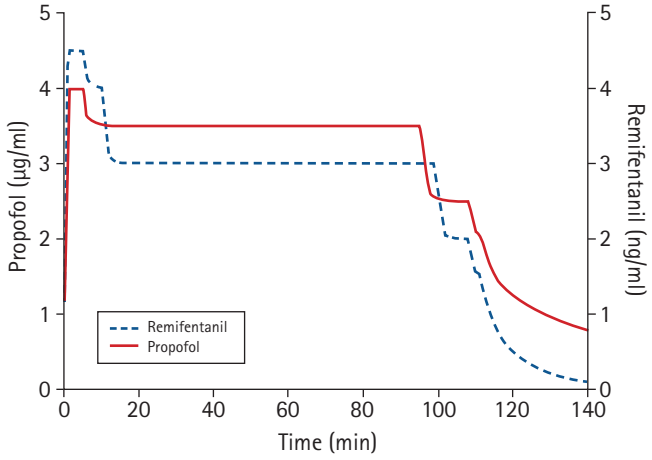

Fig. 2. Resultant effect-site concentrations of propofol and remifentanil. Target concentration of propofol and remifentanil are predicted according to the simulated scenario.

Schnider model was found to increase more than that of the Eleveld model. As the BMI increased, however, the clearance of the Schnider model increased much more than that of the Eleveld model (Fig. 3B). The explanation for this finding is that with a relatively high clearance, a higher dose of the drug is needed to maintain the same target concentration. This trend was significantly more prominent in obese than in non-obese individuals (Fig. 4A). Therefore, when TCI is performed with the same target concentration, the initial infusion rate of the Eleveld model was faster but gradually decreased over time since the clearance was lower than that of the Schnider model (Fig. 4B).

When the Minto and Kim models for remifentanil were compared for people with a normal BMI, the central compartment volume and clearance did not appear to be different between the models. However, as the BMI increased, the central compartment volume and clearance according to the Minto model did not increase in proportion to the BMI because the LBW of James' equation was installed in every parameter of the Minto model. In James' equation, LBW decreases with increasing body weight in morbidly obese individuals (Fig. 3C). However, the central compartment volume and clearance using the Kim model increased according to the increase in the BMI. The Kim model does not use James' equation but rather applies the fat-free mass from the Janmahasatian equation, which is used to calculate the fast-peripheral compartment volume. The central compartment volume and clearance with the Kim model are generally predicted to be larger than those with the Minto model. As the BMI increased, the difference in the central compartment volume and clearance between the two models increased (Fig. 3D). Therefore, when a TCI is performed using the Kim model, the cumulative dose is predicted to be larger over time than that using the Minto model. The difference in the cumulative dose between the two models was larger in obese patients (Fig. 4C). The infusion rate was also higher in the Kim model, but both models showed similar trends throughout the simulation (Fig. 4D).

An additional simulation considering the influence of age showed that the difference in the cumulative dose of propofol between the models increased with age. In the case of remifentanil, however, the difference in the cumulative dose between the two models remained constant for all age groups (Fig. 5).

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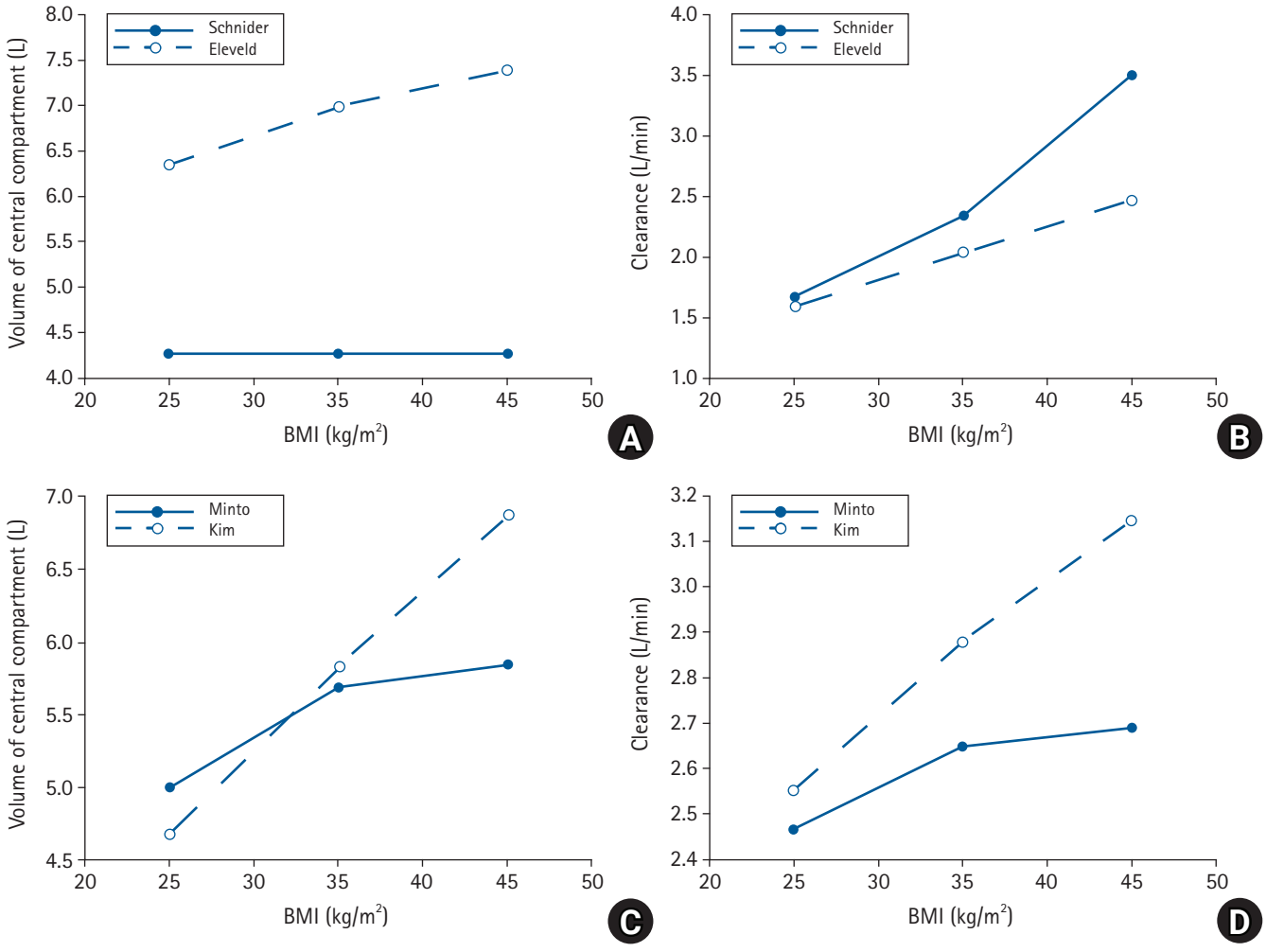

Fig. 3. Comparison of distribution volumes and clearance. Central volumes of distribution and clearance are compared between the pharmacokinetic models by changing the BMI. (A) Central volume of distribution changes in propofol models, (B) Clearance changes in propofol models, (C) Central volume of distribution changes in remifentanil models, (D) Clearance changes in remifentanil models. BMI: body mass index.

Discussion

Regardless of applying an appropriate mass scalar for induction and maintenance of anesthesia, the target concentration cannot be guaranteed by manual administration using a simple calculation of the dose. In other words, a holistic TCI device equipped with an appropriate pharmacokinetic and pharmacodynamic model is needed to control the concentration of anesthetic drugs. Drug infusions through the TCI system is theoretically the most accurate and fastest way to reach the target concentration, but it requires an accurate model to support it. Many pharmacokinetic and pharmacodynamic models, however, were created from data that did not include information of obese patients, and therefore cannot accurately predict concentrations of drug in blood in these patients. Recently, a few models have been introduced that can be applied to both obese patients and general patients [42,44].

The Eleveld model is a well-constructed model that can be used to administer more accurate concentrations of drugs to individual patients through the inclusion of various covariates relevant to actual clinical situations. Since the Eleveld model includes the use of opioids as a covariate, among others, this model may be a more practical model. When propofol is administered in clinical practice, opioids such as remifentanil are almost always administered together, and the two drugs may affect each other pharmacokinetically and/or pharmacodynamically [46]. The propofol simulation conducted for this review also included covariates for opioid use to reflect the effect of co-administration of remifentanil.

Based on the Eleveld model, the central compartment volume does not increase significantly (16.2%) with an increase in BMI. The clearance of obese patients, however, increases as the BMI or

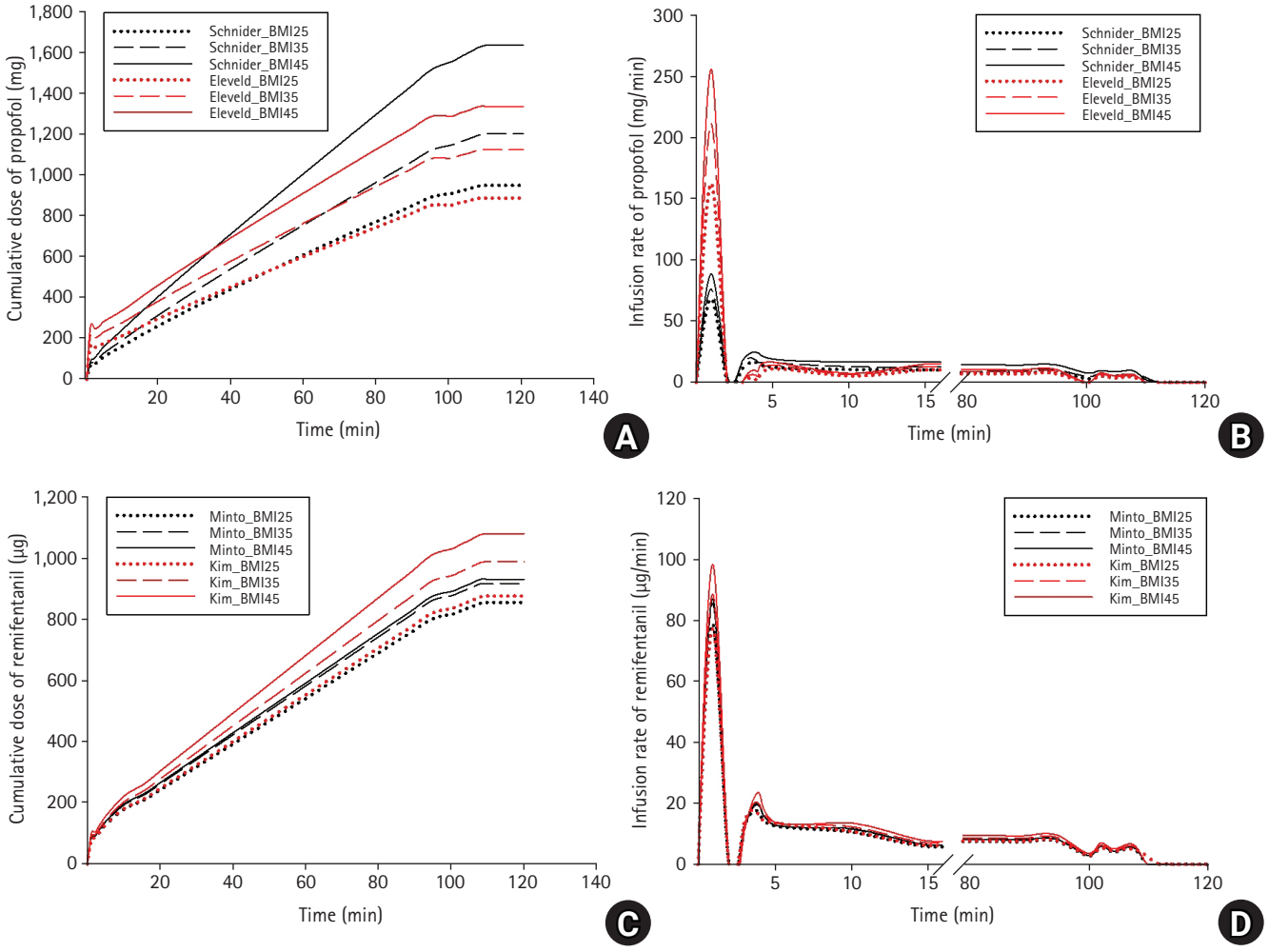

Fig. 4. Comparison of cumulative doses and infusion rates. The cumulative doses and infusion rates are presented by altering the BMI, at a fixed age of 50 years. (A) Cumulative doses of propofol models, (B) Infusion rates of propofol models, (C) Cumulative doses of remifentanil models, (D) Infusion rates of remifentanil models. BMI: body mass index.

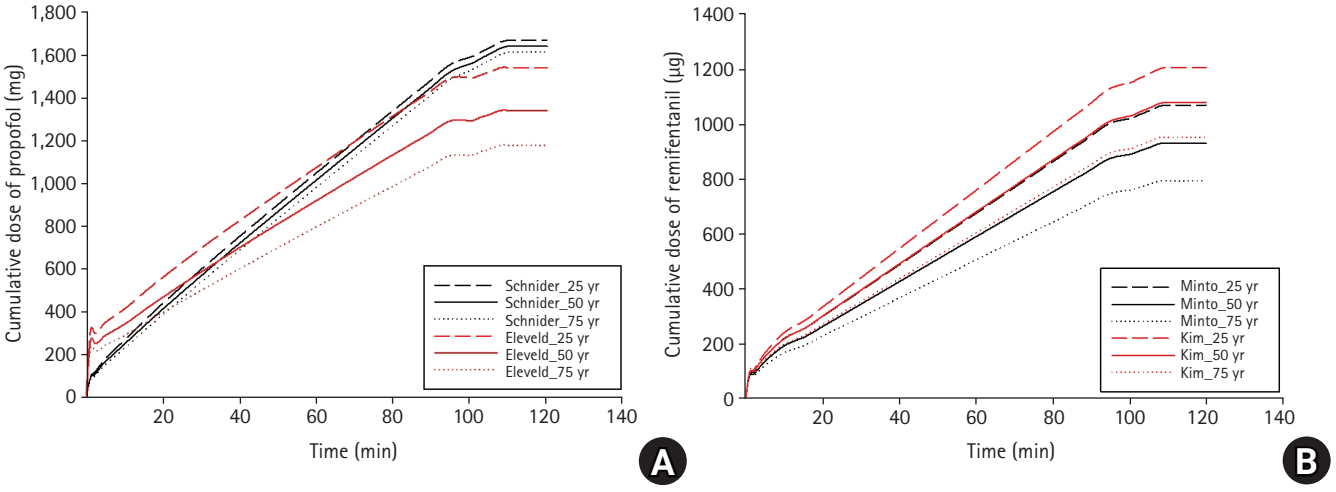

Fig. 5. Comparison of the cumulative doses. The cumulative doses are presented by varying the age, with a fixed BMI of 45 kg/m^2. (A) Cumulative doses of the propofol models, (B) Cumulative doses of the remifentanil models. BMI: body mass index.

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weight increases (54.9%). Clinically, this means that if propofol is administered to obese patients during anesthesia induction with a bolus dose based on the TBW, an overdose may occur because of relatively small increase of central compartment volume. In the case of continuous infusions, however, TBW could be adopted as a dosing scalar for anesthesia even for obese patient as the clearance of obese patient increase enough with the increase of TBW [17,34]. These observations are consistent with previous reports which have found that the increase in the volume of distribution is relatively small while the increase in clearance is prominent in obese [18,23,24].

Even though the best model can accurately predict concentrations, it cannot take all clinical situations into account. Pharmacokinetic changes in propofol can be influenced by various factors, such as very lean or underweight body types, laparoscopic surgery, and a prone posture [47–50]. Propofol itself can cause pharmacokinetic changes. The cardiac depression caused by propofol affects its own distribution and clearance. Therefore, rather than trying to discover every variable that may affect pharmacokinetics and create endless new models, it is essential that patients monitoring, such as the BIS, be used to confirm whether the purpose of the drug is achieved.

However, how many models are currently available for TCIs? Most commercial infusion pumps are not equipped with the new models that have been built for obese patients. To apply a new TCI model suitable for obese patients, an infusion pump must be connected to a computer with TCI software, through which a pharmacokinetic/pharmacodynamic model suitable for obese patients can be run. Another method is to apply an appropriately modified scalar instead of using the patient's actual height or weight in the model already installed in a commercial TCI pump. Through using the ABW instead of the TBW for the traditional Schnider and Marsh models, or inputting a fictitious height for the Minto model, replacing true patient data is a possible solution; however, modified scalars are not a perfect solution.

In conclusion, simply administering an anesthetic drug based on body weight to obese patients is associated with a high risk of overdosing. Comorbidities associated with obesity can further increase the risk of overdosing. To determine the appropriate dose for obese patients, it is important to understand how the pharmacokinetics and pharmacodynamics change as the body weight increases. Factors that affect the pharmacokinetic changes in obese individuals include an increase in adipose tissue, LBW, extracellular fluid, and cardiac output.

Several mass scalars, including the IBW and LBW, have been introduced to more appropriately calculate drug dosages for obese patients; however, there are no mass scalars that can be applied to all drugs and individuals. Therefore, it is important to carefully monitor the effects and side effects of the drugs during administration.

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Conflicts of Interest

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

References

1. WHO. Obesity [Internet]. Geneva: World Health Organization [cited 2021 Aug 9]. Available from https://www.who.int/health-topics/obesity#tab=tab_1
2. Cheymol G. Effects of obesity on pharmacokinetics implications for drug therapy. Clin Pharmacokinet 2000; 39: 215-31.
3. Pai MP, Paloucek FP. The origin of the "ideal" body weight equations. Ann Pharmacother 2000; 34: 1066-9.
4. James WP. Research on obesity. London, Her Majesty's Stationery Office. 1976.
5. Janmahasatian S, Duffull SB, Ash S, Ward LC, Byrne NM, Green B. Quantification of lean bodyweight. Clin Pharmacokinet 2005; 44: 1051-65.
6. Mosteller RD. Simplified calculation of body-surface area. N Engl J Med 1987; 317: 1098.
7. Shibutani K, Inchiosa MA Jr, Sawada K, Bairamian M. Accuracy of pharmacokinetic models for predicting plasma fentanyl concentrations in lean and obese surgical patients: derivation of dosing weight ("pharmacokinetic mass"). Anesthesiology 2004; 101: 603-13.
8. Abernethy DR, Burckart GJ. Pediatric dose selection. Clin Pharmacol Ther 2010; 87: 270-1.
9. Mahmood I. Prediction of clearance, volume of distribution and half-life by allometric scaling and by use of plasma concentrations predicted from pharmacokinetic constants: a comparative study. J Pharm Pharmacol 1999; 51: 905-10.
10. Mahmood I. Prediction of drug clearance in children: impact of allometric exponents, body weight, and age. Ther Drug Monit 2007; 29: 271-8.
11. Adams JP, Murphy PG. Obesity in anaesthesia and intensive care. Br J Anaesth 2000; 85: 91-108.
12. Shenkman Z, Shir Y, Brodsky JB. Perioperative management of

the obese patient. Br J Anaesth 1993; 70: 349-59.
13. Casati A, Putzu M. Anesthesia in the obese patient: pharmacokinetic considerations. J Clin Anesth 2005; 17: 134-45.
14. Kendrick JG, Carr RR, Ensom MH. Pharmacokinetics and drug dosing in obese children. J Pediatr Pharmacol Ther 2010; 15: 94-109.
15. Shi S, Klotz U. Age-related changes in pharmacokinetics. Curr Drug Metab 2011; 12: 601-10.
16. Jung D, Mayersohn M, Perrier D, Calkins J, Saunders R. Thiopental disposition in lean and obese patients undergoing surgery. Anesthesiology 1982; 56: 269-74.
17. Servin F, Farinotti R, Haberer JP, Desmonts JM. Propofol infusion for maintenance of anesthesia in morbidly obese patients receiving nitrous oxide. A clinical and pharmacokinetic study. Anesthesiology 1993; 78: 657-65.
18. Lesser GT, Deutsch S. Measurement of adipose tissue blood flow and perfusion in man by uptake of 85Kr. J Appl Physiol 1967; 23: 621-30.
19. Björkman S, Wada DR, Stanski DR. Application of physiologic models to predict the influence of changes in body composition and blood flows on the pharmacokinetics of fentanyl and alfentanil in patients. Anesthesiology 1998; 88: 657-67.
20. Avram MJ, Krejcie TC. Using front-end kinetics to optimize target-controlled drug infusions. Anesthesiology 2003; 99: 1078-86.
21. Collis T, Devereux RB, Roman MJ, de Simone G, Yeh J, Howard BV, et al. Relations of stroke volume and cardiac output to body composition: the strong heart study. Circulation 2001; 103: 820-5.
22. Abernethy DR, Greenblatt DJ, Divoll M, Smith RB, Shader RI. The influence of obesity on the pharmacokinetics of oral alprazolam and triazolam. Clin Pharmacokinet 1984; 9: 177-83.
23. Salazar DE, Corcoran GB. Predicting creatinine clearance and renal drug clearance in obese patients from estimated fat-free body mass. Am J Med 1988; 84: 1053-60.
24. Stokholm KH, Brøchner-Mortensen J, Hoilund-Carlsen PF. Increased glomerular filtration rate and adrenocortical function in obese women. Int J Obes 1980; 4: 57-63.
25. Benedek IH, Fiske WD 3rd, Griffen WO, Bell RM, Blouin RA, McNamara PJ. Serum alpha 1-acid glycoprotein and the binding of drugs in obesity. Br J Clin Pharmacol 1983; 16: 751-4.
26. Barbeau P, Litaker MS, Woods KF, Lemmon CR, Humphries MC, Owens S, et al. Hemostatic and inflammatory markers in obese youths: effects of exercise and adiposity. J Pediatr 2002; 141: 415-20.
27. Derry CL, Kroboth PD, Pittenger AL, Kroboth FJ, Corey SE, Smith RB. Pharmacokinetics and pharmacodynamics of triazolam after two intermittent doses in obese and normal-weight men. J Clin Psychopharmacol 1995; 15: 197-205.
28. Wasan KM, Lopez-Berestein G. The influence of serum lipoproteins on the pharmacokinetics and pharmacodynamics of lipophilic drugs and drug carriers. Arch Med Res 1993; 24: 395-401.
29. Lloret Linares C, Declèves X, Oppert JM, Basdevant A, Clement K, Bardin C, et al. Pharmacology of morphine in obese patients: clinical implications. Clin Pharmacokinet 2009; 48: 635-51.
30. Ramzan I, Wong BK, Corcoran GB. Pain sensitivity in dietary-induced obese rats. Physiol Behav 1993; 54: 433-5.
31. Maffiuletti NA, Morelli A, Martin A, Duclay J, Billot M, Jubeau M, et al. Effect of gender and obesity on electrical current thresholds. Muscle Nerve 2011; 44: 202-7.
32. McVinnie DS. Obesity and pain. Br J Pain 2013; 7: 163-70.
33. Majchrzak M, Brzecka A, Daroszewski C, Błasiak P, Rzechonek A, Tarasov VV, et al. Increased pain sensitivity in obese patients after lung cancer surgery. Front Pharmacol 2019; 10: 626.
34. Cortínez LI, Anderson BJ, Penna A, Olivares L, Muñoz HR, Holford NH, et al. Influence of obesity on propofol pharmacokinetics: derivation of a pharmacokinetic model. Br J Anaesth 2010; 105: 448-56.
35. Dong D, Peng X, Liu J, Qian H, Li J, Wu B. Morbid obesity alters both pharmacokinetics and pharmacodynamics of propofol: dosing recommendation for anesthesia induction. Drug Metab Dispos 2016; 44: 1579-83.
36. Subramani Y, Riad W, Chung F, Wong J. Optimal propofol induction dose in morbidly obese patients: A randomized controlled trial comparing the bispectral index and lean body weight scalar. Can J Anaesth 2017; 64: 471-9.
37. Cortínez LI, Anderson BJ. Advances in pharmacokinetic modeling: target controlled infusions in the obese. Curr Opin Anaesthesiol 2018; 31: 415-22.
38. Eleveld DJ, Proost JH, Cortínez LI, Absalom AR, Struys MM. A general purpose pharmacokinetic model for propofol. Anesth Analg 2014; 118: 1221-37.
39. Vereecke HE, Eleveld DJ, Colin P, Struys MM. Performance of the Eleveld pharmacokinetic model to titrate propofol in an obese Japanese patient population. Eur J Anaesthesiol 2016; 33: 58-9.
40. Aldegheri G, Di Candia D, Gigli F. Predictive performance of the 'Minto' remifentanil pharmacokinetic parameter set in morbidly obese patients ensuing from a new method for calculating lean body mass. Clin Pharmacokinet 2010; 49: 131-9.
41. La Colla L, Albertin A, La Colla G. Pharmacokinetic model-driven remifentanil administration in the morbidly obese: the 'critical weight' and the 'fictitious height', a possible solution to an unsolved problem? Clin Pharmacokinet 2009; 48: 397-8.
42. Kim TK, Obara S, Egan TD, Minto CF, La Colla L, Drover DR, et

https://doi.org/10.4097/kja.21345

al. Disposition of remifentanil in obesity: a new pharmacokinetic model incorporating the influence of body mass. Anesthesiology 2017; 126: 1019-32.
43. Cortínez LI, De la Fuente N, Eleveld DJ, Oliveros A, Crovari F, Sepulveda P, et al. Performance of propofol target-controlled infusion models in the obese: pharmacokinetic and pharmacodynamic analysis. Anesth Analg 2014; 119: 302-10.
44. Eleveld DJ, Colin P, Absalom AR, Struys MM. Pharmacokinetic-pharmacodynamic model for propofol for broad application in anaesthesia and sedation. Br J Anaesth 2018; 120: 942-59.
45. Bouillon TW, Bruhn J, Radulescu L, Andresen C, Shafer TJ, Cohane C, et al. Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. Anesthesiology 2004; 100: 1353-72.
46. Yufune S, Takamatsu I, Masui K, Kazama T. Effect of remifentanil on plasma propofol concentration and bispectral index during propofol anaesthesia. Br J Anaesth 2011; 106: 208-14.
47. Yi JM, Doh I, Lee SH, Kim SY, Lee YH, Lee EK, et al. Predictive performance of a new pharmacokinetic model for propofol in underweight patients during target-controlled infusion. Acta Anaesthesiol Scand 2019; 63: 448-54.
48. Gutt CN, Oniu T, Mehrabi A, Schemmer P, Kashfi A, Kraus T, et al. Circulatory and respiratory complications of carbon dioxide insufflation. Dig Surg 2004; 21: 95-105.
49. Nguyen NT, Ho HS, Fleming NW, Moore P, Lee SJ, Goldman CD, et al. Cardiac function during laparoscopic vs open gastric bypass. Surg Endosc 2002; 16: 78-83.
50. Perilli V, Sollazzi L, Modesti C, Annetta MG, Sacco T, Bocci MG, et al. Comparison of positive end-expiratory pressure with reverse Trendelenburg position in morbidly obese patients undergoing bariatric surgery: effects on hemodynamics and pulmonary gas exchange. Obes Surg 2003; 13: 605-9.
51. Shibutani K, Inchiosa MA Jr, Sawada K, Bairamian M. Pharmacokinetic mass of fentanyl for postoperative analgesia in lean and obese patients. Br J Anaesth 2005; 95: 377-83.

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Transparency considerations for describing statistical analyses in research

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Researchers who use the results of statistical analyses to draw conclusions about collected data must write a statistical analysis section in their manuscript. Describing statistical analyses in precise detail is as important as presenting the dosages of drugs and methodology of interventions. It is also essential for scientific accuracy and transparency in scientific research. We evaluated the quality of the statistical analysis sections of clinical research articles published in the *Korean Journal of Anesthesiology* between February 2020 and February 2021. Using a Likert scale where 1, 2, and 3 represented "not described at all," "partially described," and "fully described," respectively, the following 6 items were assessed: 1) stating of the statistical analysis methods used, 2) rationale for and detailed description of the statistical analysis methods used, 3) parameters derived from the statistical analyses, 4) type and version of the statistical software package used, 5) significance level, and 6) sidedness of the test (one-sided vs. two-sided). The first 3 items evaluate issues directly related to the statistical analysis methods used and last 3 are indirectly related items. In all the included articles, the statistical analysis methods used were stated (score of 3). However, only 4 articles (12.9%) fully described the sidedness of the test (score of 3). Authors tend not to describe the sidedness of statistical analysis tests in the methodology section of clinical research articles. It is essential that the sidedness be described in research studies.

Keywords: Data analysis; Probability; Research; Software; Statistical data interpretation; Statistics.

Statistical Round

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Introduction

Depending on the type of data presented and the hypothesis of a study, a variety of statistical methods are used for analyzing clinical data. In particular, several journals require authors to be vigilant not only about performing statistical analyses, but also about providing raw data for their research. Therefore, it is necessary to describe clearly and specifically the statistical analysis methods used, how they were used, and the parameters derived from the statistical analysis methods. Accordingly, researchers must describe the statistical analyses in detail in the methods section of research proposals, results reports, theses, or articles. By reading the statistical analyses described in the methods section, readers should be able to understand what statistical analysis methods were used in the study, the reasons they were used, and the parameters presented as results. The statistical analysis software used, pre-set significance level, and sidedness of the test (two-sided or one-sided) should also be easily determinable by the readers. Readers should be able to reproduce the statistical analysis of a study if the raw data are provided. The statistical analysis section should therefore include the following: 1) stating of the statistical analysis methods used, 2) rationale for and detailed description of these statistical analysis methods, 3) presentation of the statistical parameters produced by the statistical analysis

methods, 4) type and version of the statistical software package used, 5) significance level, and 6) sidedness of the statistical test (one-sided vs. two-sided).

In this study, the statistical analysis sections of 31 clinical research papers published in the *Korean Journal of Anesthesiology* (KJA) between February 2020 and February 2021 were evaluated using the above-mentioned 6 items. Through this process, practical ways of increasing the transparency of research to build scientific evidence are presented.

Materials and Methods

In this study, the statistical analysis sections of clinical research papers published in the KJA between February 2020 and February 2021 were evaluated. The sample size calculation was not assessed. Editorials, review articles, statistical round articles, case reports, letters to the editor, and corrigendum, all of which do not include statistical analysis sections, were excluded from the analysis. Additionally, the statistical analysis sections of experimental studies were not evaluated.

Evaluation items directly related to statistical analyses

Stating the statistical analysis methods used

Statistical analyses are used to calculate the significance probability (probability value) of the test statistic (estimated based on the probability distribution corresponding to the statistical analysis method used) to test the hypothesis of a study. There are various probability distributions of test statistics, including t distribution, F distribution, and chi-square distribution. For example, if the distribution of the test statistic is a t-distribution, the statistical analysis method is called a t-test. However, various statistical analysis methods use the t distribution: a one-sample t-test, an independent two-sample t-test, and a paired t-test. Therefore, the name of the statistical analysis methods used should be specifically and accurately presented.

Rationale for and detailed description of the statistical analysis methods used

Although the general descriptions of statistical analysis methods are readily available in related books, finding the best statistical analysis methods consistent with the research design and hypothesis is another issue. Hence, the rationale for using the statistical analysis methods should be clearly described in the statistical analysis section. If a t-test is used to assess the probability of the t-statistic calculated from the mean difference between 2 independent groups, researchers can simply state that the t-test was used to evaluate the statistical significance of the mean difference of the quantitative data between the 2 groups. However, some complicated statistical analysis methods require several steps and require the consideration of various factors. For example, when performing multiple linear regression or multiple logistic regression analyses, the variable selection method should be specified. If a principal component analysis is performed, the factor rotation method should be clear. Additionally, to fully and accurately describe propensity score matching, the adjustment method, caliper value, and ratio of pair-matching must be stated. Therefore, the statistical analysis section should describe in detail the rationale and steps taken for the statistical analysis methods used.

Parameters derived from statistical analysis methods

To test the hypothesis of a research study, statistics are estimated by a statistical analysis method. Statistics are used as the results of data analyses and determine whether the hypothesis is correct. For example, if a t-test is used to test whether there is a significant difference in means between 2 independent groups, the means and standard deviations of each group and the probability value that determines the significance of the mean difference are presented. The mean difference between the 2 groups and pooled standard deviation should be presented. If a logistic regression analysis is performed, the following parameters can be presented: the odds ratios of each variable with their 95% CIs and the probability value that determines whether the odds ratios are statistically different from 1, that is, whether the odds ratios are significant or not. Therefore, the parameters that are derived from statistical analysis methods and used as the results of a study, need to be presented in detail.

Evaluation items indirectly related to statistical analysis methods

Type and version of statistical software package used

Various statistical software packages are available, such as IBM SPSS Statistics (www.ibm.com/products/spss-statistics), R (www.r-project.org), SAS (www.sas.com), Minitab (www.minitab.com), MedCalc (www.medcalc.org), NCSS (www.ncss.com/software), and Excel (www.microsoft.com/en-us/microsoft-365/excel). The versions of these software packages are updated as new functions are added or old functions are upgraded. Since they have different manufacturers, the algorithms or methods used for the statistical analyses may be different. That is, the common statistical analyses with common data performed by different statistical software packages can produce results that are different from each other. Therefore, information regarding the software and the version

used for statistical analyses should be clearly stated in the statistical analysis section.

Significance level

It is mandatory to include the significance level for statistical hypothesis testing since conclusions are directly drawn from it. The significance level is the maximum probability that a type I error (an error of rejecting the null hypothesis even though the null hypothesis is correct) is tolerable. In a statistical hypothesis test, the calculated probability value is compared with the significance level set by the researcher to determine whether the null hypothesis can be rejected. The significance level was set at 0.05 (5%) in all 31 articles analyzed in this study. If the significance level is set at a relatively high value, such as 20% or 30%, rather than 5%, the results of the study may be unreliable. Therefore, the significance level is generally set no higher than 5%. Occasionally, the significance level is set at 1%. This does not mean that setting a significance level of 10% is incorrect. The authors should only clearly state that the significance level was set at 10%. Therefore, the significance level should be explicitly presented in the statistical analysis section.

Sidedness of the test (one-sided vs. two-sided)

Statistical hypothesis testing builds null and alternative hypotheses and is used to determine whether to reject the null hypothesis through a series of processes. To indicate inequality when formulating an alternative hypothesis, the symbol, "≠" should be used if the test is two-sided and "＞" or "＜" should be used if the test is one-sided. For example, if a two-sided t-test is used to determine whether the mean difference between 2 independent groups (A and B) is significant, the null hypothesis (H_0) and the alternative hypothesis (H_a) are as follows:

(1)

$$H_0 : \mu_A = \mu_B \text{ vs. } H_a : \mu_A \neq \mu_B$$

where μ_A is the population mean of group A, and μ_B is the population mean of group B.

If a one-sided t-test is used to test whether the mean of one of 2 independent groups is significantly greater or less than the other, H_0 and H_a are shown as follows:

(2)

$$H_0 : \mu_A = \mu_B \text{ vs. } H_a : \mu_A > \mu_B \text{ or } H_0 : \mu_A = \mu_B \text{ vs. } H_a : \mu_A < \mu_B$$

The range of the t-statistic to determine statistical significance depends on the sidedness of the test. Likewise, different probability values are calculated according to the sidedness of the test. The probability value of a two-sided test is 2 times that of a one-sided test. Since statistical software packages give the results from two-sided tests by default, the setting of the sidedness of the tests should be changed for one-sided tests. Therefore, the sidedness of tests (two-sided or one-sided) should be accurately described in the statistical analysis section.

Assessment of each evaluation item

A 3-level Likert scale was used to score the above-mentioned 6 items. Each item received a score of 3 (★★★) if they were fully described, 2 (★★) if they were partially described, or 1 (★) if they were not described at all. Two researchers independently conducted the evaluation. In the event of a disagreement between the 2 researchers, a consensus was achieved by discussion and through referring to the original text.

Example assessments of well-written statistical analysis sections

In the study conducted by Makarem et al. [1], the statistical analysis section stated the following:

"This study was conducted as a prospective observational study. Three emergence groups were defined as agitated, normal, and hypoactive. Demographic and descriptive data analyses were done for the study population and the 3 groups above. Frequencies were expressed as counts (percentage) and continuous variables as mean with standard deviation (SD). After testing the normality with the Kolmogorov-Smirnov test, we used the Student's t-test and the chi-squared test for univariate analysis. We performed multivariate analyses using a backward binary stepwise logistic regression to examine and determine the odds ratios (OR) of the risk factors for inadequate emergence, with 95% confidence for the CI. Furthermore, the statistical analyses (both univariate and multivariate) were also conducted in the subgroup of patients with a history of substance dependence. We made no adjustments for multiple testing in all these exploratory data analyses. SPSS ver. 22.0 software (IBM Corp., USA) was used for analyses, and the study considered $P < 0.05$ (two-sided) as significant."

The statistical analysis methods that the authors used in this study were the Kolmogorov-Smirnov test, Student's t-test, chi-squared test, and binary stepwise logistic regression (3 points). Concerning the rationale of each statistical analysis method, the Kolmogorov-Smirnov test was used to test the normality of the data, the Student's t-test and chi-squared test were used for the univariate analysis, and the binary stepwise logistic regression was

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performed to determine the odds ratios of the risk factors for inadequate emergence. In particular, the variable selection method for binary logistic regression was stepwise selection[1] (3 points). According to the type of data or statistical analysis methods used, the statistics were presented as counts (percentages) for frequencies, mean with standard deviation for continuous variables, and odds ratio (95% CI) for the logistic regression analysis results (3 points). The statistical analysis software package used was SPSS software ver. 22.0 (IBM Corp., USA) (3 points), the significance level was set at 0.05 (3 points), and a two-sided test was used (3 points).

Another example of a statistical analysis section, taken from a study conducted by Kaur et al. [2], is as follows:

"The normality of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed continuous variables are presented as the mean ± SD, whereas ordinal variables (NRS score) are presented as the mean ± SD (median). Means were also used to describe the ordinal data along with median. A one-way analysis of variance was used to compare the means among the three independent groups. The Kruskal-Wallis test was used followed by multiple comparisons (Bonferroni test) to compare the distribution of the NRS pain scores among the three study groups. A paired sample t-test was used to test the change in means between the pre to post observations. Fisher's exact test was used to compare the proportions between the groups. A two-sided P value of < 0.05 was considered statistically significant. Statistical Package for Social Sciences, version 23 (SPSS-23, IBM Corp., USA) was used for data analysis."

The statistical analysis methods used in this study were the Shapiro-Wilk test, one-way analysis of variance, Kruskal-Wallis test, paired sample t-test, and Fisher's exact test (3 points). With regard to the rationale for each statistical analysis method used, the Shapiro-Wilk test was used to test the normality of the data, the one-way analysis of variance was used to compare the means among the 3 independent groups, the Kruskal Wallis test was used to compare the distribution of the NRS pain scores among the 3 study groups, the paired sample t-test was used to test the change in means between the pre- and post-observations, Fisher's exact test was used to compare the proportions between the groups, and the Bonferroni test was used to adjust the probability values for multiple comparisons (3 points). According to the type of data, the statistics were presented as means ± standard deviations for normally distributed continuous variables and means ± standard deviations (median) for ordinal variables (3 points). The statistical analysis software package used was Statistical Package for Social Sciences version 23 (SPSS v.23, IBM Corp., USA) (3 points), the significance level was set at 0.05 (3 points), and two-sided tests were used (3 points).

The above methodology was applied to assess the statistical analysis sections of the remaining articles.

Results

From February 2020 to February 2021, a total of 111 papers were published in the KJA. Among them, 31 clinical research articles were included in the analysis after 10 editorials, 16 review articles, 5 statistical round articles, 15 case reports, 30 letters to editor, and 4 experimental studies were excluded.

The evaluation items, from highest to lowest rankings, are as follows: stating of the statistical analysis methods used, type and version of statistical software package, significance level, parameters derived from statistical analysis methods, rationale for and detailed description of the statistical analysis methods used, and sidedness of statistical tests (Table 1). All 31 articles stated the statistical analysis methods used appropriately (score of 3). Of the 31 articles, 29 (93.5%) presented the type and version of the statistical software package used (score of 3). The number (percentage) of the articles that received a score of 3 for the two items (parameters derived from statistical analysis methods and rationale for and details of statistical analysis methods) was 24 (77.4%) and 23 (74.2%), respectively. The studies by Lee et al. [3] and Hervás et al. [4] received scores of 2 for the "rationale for and details of the statistical analysis methods used" item because, although they stated that they used propensity score matching, no descriptions of the adjustment method, caliper value, or the ratio of pair-matching were found, which would significantly affect the results of the subsequent statistical analysis. Likewise, the papers by Lim et al. [5] and Tamboli et al. [6] reported performing statistical analyses without describing the rationale for and details of the statistical analysis methods used. Thus, they each received a score of 2 for this item. Lastly, the sidedness of statistical tests (one-sided vs. two-sided) was explicitly described in only 4 (12.9%) of the 31 articles, which was the lowest ranked evaluation item.

Discussion

Surprisingly, most of the articles did not specify the sidedness of the statistical tests used. The KJA author guidelines do not explicitly request the sidedness of statistical tests be included. However, it requires that probability values should be two-tailed except

[1]It is unclear whether the authors performed backward elimination or stepwise selection to select the variables to be included in the regression model because they used the unclear term, "backward binary stepwise logistic regression."

Table 1. Assessment of Statistical Analysis Sections of 31 Clinical Research Articles Published in the Korean Journal of Anesthesiology between February 2020 and February 2021

No.	Last name of first author	Year	Volume	Issue	Evaluation items					
					1	2	3	4	5	6
1	Gautam [7]	2021	74	1	★★★	★★★	★	★★★	★★★	★
2	Lee [3]	2021	74	1	★★★	★★	★★★	★★★	★★★	★
3	Hervás [4]	2021	74	1	★★★	★★	★★★	★★★	★	★
4	Choi [8]	2021	74	1	★★★	★★★	★★★	★★★	★★★	★
5	Burton [9]	2021	74	1	★★★	★★★	★★★	★★★	★★★	★
6	Lee [10]	2020	73	6	★★★	★★★	★★★	★★★	★★★	★
7	Efremov [11]	2020	73	6	★★★	★★★	★★★	★★★	★★★	★
8	Lee [12]	2020	73	6	★★★	★★★	★★★	★★★	★★★	★
9	Ashoor [13]	2020	73	6	★★★	★	★★★	★★★	★★★	★
10	Ryu [14]	2020	73	6	★★★	★★★	★★★	★★★	★★★	★
11	Kaur [2]	2020	73	5	★★★	★★★	★★★	★★★	★★★	★★★
12	Gadsden [15]	2020	73	5	★★★	★★★	★★★	★★★	★★★	★
13	Lim [5]	2020	73	5	★★★	★★	★★★	★★★	★★★	★★★
14	Tamboli [6]	2020	73	5	★★★	★★	★★★	★★★	★★★	★
15	Aoyama [16]	2020	73	4	★★★	★★	★★★	★★★	★★★	★
16	Chadha [17]	2020	73	4	★★★	★★★	★	★★★	★	★★★
17	Banik [18]	2020	73	4	★★★	★	★★★	★	★★★	★
18	Makarem [1]	2020	73	4	★★★	★★★	★★★	★★★	★★★	★★★
19	Udupi [19]	2020	73	3	★★★	★★★	★	★★★	★★★	★
20	Boscolo [20]	2020	73	3	★★★	★★★	★★	★★★	★	★
21	Said [21]	2020	73	3	★★★	★★★	★★	★★★	★★★	★
22	Azemati [22]	2020	73	3	★★★	★★★	★★★	★★★	★★★	★
23	Srivastava [23]	2020	73	2	★★★	★★★	★	★★★	★★★	★
24	An [24]	2020	73	2	★★★	★★★	★	★	★	★
25	Na [25]	2020	73	2	★★★	★★★	★★★	★★★	★★★	★
26	Salama [26]	2020	73	2	★★★	★	★★★	★★★	★★★	★
27	Doo [27]	2020	73	1	★★★	★★★	★★★	★★★	★★★	★
28	Park [28]	2020	73	1	★★★	★★★	★★★	★★★	★★★	★
29	Ökmen [29]	2020	73	1	★★★	★★★	★★★	★★★	★★★	★
30	Choi [30]	2020	73	1	★★★	★★★	★★★	★★★	★★★	★
31	Danforth [31]	2020	73	1	★★★	★★★	★★★	★★★	★★★	★
Number (percentage) of each score										
★					0 (0.0)	3 (9.7)	5 (16.1)	2 (6.5)	4 (12.9)	27 (87.1)
★★					0 (0.0)	5 (16.1)	2 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)
★★★					31 (100)	23 (74.2)	24 (77.4)	29 (93.5)	27 (87.1)	4 (12.9)

[Evaluation items]

1 Stating the statistical analysis methods used

2 Rationale for and detailed description of statistical analysis methods used

3 Parameters derived from statistical analysis methods

4 Type and version of statistical software package used

5 Significance level

6 Sidedness of statistical test (one-sided vs. two-sided)

[Symbols]

★: not described at all

★★: partially described

★★★: fully described

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for study designs that require a one-tailed test. Since most of the authors of clinical research articles perform two-tailed tests, the readers are likely to think that the tests are two-tailed unless otherwise specified. However, it is not best practice to omit important information conventionally in scientific papers that must provide accurate information.

There are several important reasons why statistical analysis sections should include information on the 6 items mentioned in this article. First, scientific evidence should be available to support the appropriate use of statistical methods to test the research hypothesis. For example, it is inappropriate to perform parametric tests using data that do not fulfill the normality assumption. Instead, non-parametric tests should be performed for non-normally distributed data. Performing a t-test twice (A vs. B and A vs. C) or 3 times (A vs. B, A vs. C, and B vs. C) to compare the means of 3 independent groups (A, B, and C) is also inappropriate. One-way analysis of variance should be used to test the null hypothesis regarding the difference in means of 3 groups. If the null hypothesis is rejected, a post-hoc test is necessary. Second, the transparency of a study can be ensured by describing how the statistical analysis method was performed with the type and version of the statistical software package, significance level, and the sidedness of statistical tests used. For example, when performing logistic regression analyses, whether covariates are included (and if so, which covariates) and the significance level of the univariate analyses, which is used to determine which independent variables to include in the multivariable analysis, should be described. In propensity score matching, the results of the analysis vary depending on the propensity score correction method, caliper value, and the ratio of pair-matching, and thus these should be described in detail. The type and version of the statistical software package, significance level, and sidedness of the tests should also be presented. Third, describing the rationale or purpose for choosing the selected analysis methods provides evidence that the analyses were appropriate to reveal the causal relationship between the variables measured in the study, making it scientific. For example, when an independent two-sample t-test is used, a statement such as "After the normality assumption had been met by the Kolmogorov-Smirnov test, independent two-sample t-test was used to compare the pain scores between the 2 analgesics" could be used.

However, an important limitation of this study should be considered. We did not check whether the results of all the statistical analyses described in the statistical analysis section were presented clearly in the results section. It is therefore unclear whether the results of the statistical analyses that were not described in the statistical analysis section are presented in the results section. However, we believe that the peer review system of this journal has already resolved this issue.

Researchers need to recognize what should be included when describing statistical analyses in research proposals, results reports, theses, and articles. The inclusion of the above-mentioned items, which are directly and indirectly related to statistical analyses, in the methodology section improves the transparency and scientific nature of a study. In particular, for complicated analyses or the use of multiple statistical analyses, more effort to describe the essential points we have proposed is needed to clarify how the presented results were obtained. While it is difficult to generalize our results since we did not assess all articles that have been published, we emphasize that researchers should pay particular attention to the items that were rated poorly in this study (sidedness of statistical tests [one-sided vs. two-sided], rationale for and details of the statistical analysis methods used, and parameters derived from statistical analysis methods) and should describe them clearly in their statistical analysis sections.

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Conflicts of Interest

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

Author Contributions

Sang Kyu Kwak (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Supervision; Validation; Writing – original draft; Writing – review & editing)
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References

1. Makarem J, Larijani AH, Eslami B, Jafarzadeh A, Karvandian K, Mireskandari SM. Risk factors of inadequate emergence following general anesthesia with an emphasis on patients with sub-

stance dependence history. Korean J Anesthesiol 2020; 73: 302-10.
2. Kaur U, Shamshery C, Agarwal A, Prakash N, Valiveru RC, Mishra P. Evaluation of postoperative pain in patients undergoing modified radical mastectomy with pectoralis or serratus-intercostal fascial plane blocks. Korean J Anesthesiol 2020; 73: 425-33.
3. Lee JH, Heo HJ, Kim YY, Baek SM, Kim KM, Jung DW. The effect of interscalene brachial plexus block with propofol sedation on preventing perioperative hypothermia during arthroscopic shoulder surgery. Korean J Anesthesiol 2021; 74: 53-8.
4. Hervás MS, Játiva-Porcar R, Robles-Hernández D, Rubert AS, Segarra B, Oliva C, et al. Evaluation of the relationship between lactacidemia and postoperative complications after surgery for peritoneal carcinomatosis. Korean J Anesthesiol 2021; 74: 45-52.
5. Lim YC, Koo ZK, Ho VW, Chang SS, Manohara S, Tong QJ. Randomized, controlled trial comparing respiratory and analgesic effects of interscalene, anterior suprascapular, and posterior suprascapular nerve blocks for arthroscopic shoulder surgery. Korean J Anesthesiol 2020; 73: 408-16.
6. Tamboli M, Leng JC, Hunter OO, Kou A, Mudumbai SC, Memtsoudis SG, et al. Five-year follow-up to assess long-term sustainability of changing clinical practice regarding anesthesia and regional analgesia for lower extremity arthroplasty. Korean J Anesthesiol 2020; 73: 401-7.
7. Gautam S, Agarwal A, Das PK, Khuba S, Kumar S. Prevention of epidural catheter migration: a comparative evaluation of two tunneling techniques. Korean J Anesthesiol 2021; 74: 59-64.
8. Choi JW, Kim DK, Jeong HJ, Kim YR, Chung YJ, Son YH. Risk factors associated with hypotensive bradycardic events during open shoulder surgery in the beach chair position. Korean J Anesthesiol 2021; 74: 38-44.
9. Burton BN, Finneran JJ, Angerstein A, Ross E, Mitchell A, Waterman RS, et al. Demographic and clinical factors associated with same-day discharge and unplanned readmission following shoulder arthroplasty: a retrospective cohort study. Korean J Anesthesiol 2021; 74: 30-7.
10. Lee JH, Kim Y, Mun J, Lee J, Ko S. Effects of hypercarbia on arterial oxygenation during one-lung ventilation: prospective randomized crossover study. Korean J Anesthesiol 2020; 73: 534-41.
11. Efremov SM, Kozireva VS, Moroz GB, Abubakirov MN, Shkoda OS, Shilova AN, et al. The immunosuppressive effects of volatile versus intravenous anesthesia combined with epidural analgesia on kidney cancer: a pilot randomized controlled trial. Korean J Anesthesiol 2020; 73: 525-33.
12. Lee JH, Yoon DH, Heo BH. Incidence of newly developed postoperative low back pain with median versus paramedian approach for spinal anesthesia. Korean J Anesthesiol 2020; 73: 518-24.
13. Ashoor TM, Hasseb AM, Esmat IM. Nebulized heparin and salbutamol versus salbutamol alone in acute exacerbations of chronic obstructive pulmonary disease requiring mechanical ventilation: a double-blind randomized controlled trial. Korean J Anesthesiol 2020; 73: 509-17.
14. Ryu T, Kim BJ, Woo SJ, Lee SY, Lim JA, Kwak SG, et al. Retrospective analysis of risk factors of hypotensive bradycardic events during shoulder arthroscopic surgery under interscalene blockade in the sitting position. Korean J Anesthesiol 2020; 73: 542-9.
15. Gadsden JC, Sata S, Bullock WM, Kumar AH, Grant SA, Dooley JR. The relative analgesic value of a femoral nerve block versus adductor canal block following total knee arthroplasty: a randomized, controlled, double-blinded study. Korean J Anesthesiol 2020; 73: 417-24.
16. Aoyama Y, Sakura S, Abe S, Wada M, Saito Y. Analgesic effects and distribution of cutaneous sensory blockade of quadratus lumborum block type 2 and posterior transversus abdominis plane block: an observational comparative study. Korean J Anesthesiol 2020; 73: 326-33.
17. Chadha RM, Dexter F, Brull SJ. Lack of recall after sedation for cataract surgery and its effect on the validity of measuring patient satisfaction. Korean J Anesthesiol 2020; 73: 319-25.
18. Banik S, Rath GP, Lamsal R, Bithal PK. Effect of dexmedetomidine on dynamic cerebral autoregulation and carbon dioxide reactivity during sevoflurane anesthesia in healthy patients. Korean J Anesthesiol 2020; 73: 311-8.
19. Udupi S, Puri K. A novel approach to bedside pretransfusion identity check of blood and its components: the Sandesh Positive-Negative protocol. Korean J Anesthesiol 2020; 73: 232-8.
20. Boscolo A, Spiezia L, Campello E, Bertini D, Lucchetta V, Piasentini E, et al. Whole-blood hypocoagulable profile correlates with a greater risk of death within 28 days in patients with severe sepsis. Korean J Anesthesiol 2020; 73: 224-31.
21. Said ET, Sztain JF, Martin EI, Abramson WB, Meineke MN, Furnish TJ, et al. Association of trainee involvement in an acute pain service with postoperative opioid use in patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. Korean J Anesthesiol 2020; 73: 219-23.
22. Azemati S, Pourali A, Aghazadeh S. Effects of adding dexmedetomidine to local infiltration of bupivacaine on postoperative pain in pediatric herniorrhaphy: a randomized clinical trial. Korean J Anesthesiol 2020; 73: 212-8.
23. Srivastava VK, Agrawal S, Deshmukh SA, Noushad F, Khan S, Kumar R. Efficacy of trospium for prevention of catheter-related bladder discomfort: a prospective, randomized, placebo-con-

https://doi.org/10.4097/kja.21203

trolled, double-blind study. Korean J Anesthesiol 2020; 73: 145-50.
24. An J, Noh H, Kim E, Lee J, Woo K, Kim H. Neuromuscular blockade reversal with sugammadex versus pyridostigmine/glycopyrrolate in laparoscopic cholecystectomy: a randomized trial of effects on postoperative gastrointestinal motility. Korean J Anesthesiol 2020; 73: 137-44.
25. Na SH, Shin CS, Kim GH, Kim JH, Lee JS. Long-term mortality of patients discharged from the hospital after successful critical care in the ICU in Korea: a retrospective observational study in a single tertiary care teaching hospital. Korean J Anesthesiol 2020; 73: 129-36.
26. Salama ER. Ultrasound-guided bilateral quadratus lumborum block vs. intrathecal morphine for postoperative analgesia after cesarean section: a randomized controlled trial. Korean J Anesthesiol 2020; 73: 121-8.
27. Doo AR, Kang S, Kim YS, Lee TW, Lee JR, Kim DC. The effect of the type of anesthesia on the quality of postoperative recovery after orthopedic forearm surgery. Korean J Anesthesiol 2020; 73: 58-66.
28. Park SH, Park S, Lee S, Choi JI, Bae HB, You Y, et al. Effect of transportation method on preoperative anxiety in children: a randomized controlled trial. Korean J Anesthesiol 2020; 73: 51-7.
29. Ökmen K, Ökmen BM. Ultrasound-guided anterior quadratus lumborum block for postoperative pain after percutaneous nephrolithotomy: a randomized controlled trial. Korean J Anesthesiol 2020; 73: 44-50.
30. Choi EJ, Choi YJ, Lee SW, Choi YM, Ri HS, Park JY, et al. Effect of anesthetic method on incidence of delirium after total hip replacement arthroplasty in South Korea: a population-based study using National Health Insurance claims data. Korean J Anesthesiol 2020; 73: 36-43.
31. Danforth D, Gabriel RA, Clark AI, Newhouse B, Khoche S, Vig S, et al. Preoperative risk factors for massive transfusion, prolonged ventilation requirements, and mortality in patients undergoing liver transplantation. Korean J Anesthesiol 2020; 73: 30-5.

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The analgesic efficacy of anterior femoral cutaneous nerve block in combination with femoral triangle block in total knee arthroplasty: a randomized controlled trial

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Background: Ultrasound-guided femoral triangle block (FTB) can provide motor-sparing anterior knee analgesia. However, it may not completely anesthetize the anterior femoral cutaneous nerve (AFCN). We hypothesized that an AFCN block (AFCNB) in combination with an FTB would decrease pain during movement in the immediate 12 h postoperative period compared with an FTB alone.
Methods: Eighty patients scheduled to undergo total knee arthroplasty were randomized to receive either FTB alone (FTB group) or AFCNB with FTB (AFCNB + FTB group) as part of the multimodal analgesic regimen. The primary outcome was pain during movement at 12 h postoperatively. Secondary outcomes included numeric rating scale (NRS) pain scores, incidence of surgical incision site pain, intravenous morphine consumption, immediate functional performance, patient satisfaction, and length of hospital stay.
Results: The NRS pain scores on movement 12 h postoperatively were significantly lower in the AFCNB + FTB group than in the FTB group (mean difference: −2.02, 95% CI: −3.14, −0.89, $P < 0.001$). The incidence of pain at the surgical incision site at 24 h postoperatively and morphine consumption within 48 h postoperatively were significantly lower ($P < 0.001$), and quadriceps muscle strength at 0° immediately after surgery was significantly greater in the AFCNB + FTB group ($P = 0.04$).
Conclusions: The addition of ultrasound-guided AFCNB to FTB provided more effective analgesia and decreased opioid requirement compared to FTB alone after total knee arthroplasty and may enhance immediate functional performance on the day of surgery.

Keywords: Arthroplasty; Knee; Nerve block; Peripheral nerves; Postoperative pain; Ultrasonography.

Introduction

Motor-sparing anterior knee analgesia as part of a multimodal protocol for total knee arthroplasty (TKA) is popular and preferred because it enhances patient recovery and satisfaction and reduces the length of hospital stay [1,2]. Adductor canal block (ACB) is an essential component of motor-sparing anterior knee analgesia, as it provides sensory

blockade with minimal effect on quadriceps muscle strength compared with a traditional femoral nerve block [3,4]. Moreover, supplemental infiltration of the space between the popliteal artery and posterior capsule of the knee (IPACK block) is effective in achieving motor-sparing posterior knee analgesia [5,6].

Manickam et al. [7] first described the ultrasound-guided ACB, in which local anesthetic was injected into the distal adductor canal to block the saphenous nerve. Since then, several approaches to anterior knee analgesia have been developed. The operator relies on the position of the sartorius muscle (SM) and subsartorial or superficial femoral artery (SFA), which courses from the apex of the femoral triangle along the adductor canal to the adductor hiatus in an ultrasound image, and new terminologies have been developed to define each injection point [8–10]. A needle injection point at the position where the SFA lies inferior or medial to the SM in the ultrasound image (femoral triangle block [FTB] or proximal ACB) is the most common [10–12]. Analgesia following FTB or proximal ACB is superior to that of other approaches, as the corresponding site is closer to the apex of the femoral triangle and can involve other branches of the femoral nerve, such as the vastus medialis nerve and infrapatellar branch of the saphenous nerve, and possibly the medial cutaneous nerve of the thigh, comprising the majority of nerve supply to the anteromedial knee joint [11,13].

The most commonly used surgical approach for TKA is the medial parapatellar approach, which exposes most structures in the anteromedial aspect of the knee. Therefore, the additional analgesic effect due to the blockade of the lateral femoral cutaneous nerve is minimized, as it mainly innervates the skin in the anterolateral part of the thigh and knee [14]. The anteromedial cutaneous regions of the distal thigh and knee are innervated by the anterior division of the sensory branch of the femoral nerve, called the anterior femoral cutaneous nerve (AFCN), which consists of the intermediate and medial cutaneous nerves of the thigh (ICNT and MCNT) [12,15]. The FTB may not completely anesthetize these nerves. The AFCN block (AFCNB) is used for postoperative pain relief after TKA [16,17]. However, the analgesic efficacy of combined AFCNB and FTB has not been compared with that of FTB alone.

Hence, the purpose of this study was to compare the postoperative analgesic effect of AFCNB combined with FTB with that of FTB alone in patients undergoing TKA as part of a multimodal analgesic regimen including continuous ACB (CACB) and IPACK block. We hypothesized that AFCNB + FTB would significantly lower pain scores during movement in the immediate 12 h postoperative period when compared with FTB alone.

Materials and Methods

This study was approved by the Institutional Review Board of Chulalongkorn University (Ref no. 781/62), and written informed consent was obtained from all participants. The trial was registered prior to patient enrollment at clinicaltrials.in.th (TCTR2019 1209004, Principal investigator: W. K., date of registration: December 9, 2019). This clinical research was done following the ethical principles for medical research involving human subjects in accordance with the Helsinki Declaration 2013 and this manuscript adheres to the applicable Consolidated Standards of Reporting Trials guidelines.

Owing to the variable courses and patterns of the ICNT and MCNT, as demonstrated in previous cadaveric studies [18–20], we first selected five soft embalmed cadavers donated for scientific research at the Department of Anatomy, Chulalongkorn University, to explore the anatomical structure of the AFCN (ICNT and MCNT) and to determine the needle injection point in ultrasound-guided AFCNB (Figs. 1A and 1B). We found that the ICNT pierces the SM and fascia lata distal to the inguinal crease or courses between the SM and fascia lata before perforating the fascia lata at the level of the femoral triangle and reaching the subcutaneous fat with descending branches along the forepart of the thigh. The MCNT has a variable course and pattern and medially overlays the course of the ICNT [19,20]. We found several branches that descended anteromedially to the femoral artery in the area of the femoral triangle and reached superficial layers of the SM by coursing distally and medially to the medial border of the SM or penetrating the medial border of the SM at the apex of the femoral triangle. Therefore, the site of the SFA beneath the medial border of the SM was determined as the needle injection point for ultrasound-guided AFCNB.

Thereafter, this prospective, double-blind, randomized controlled trial was conducted from January 2020 to August 2020. Adult patients (aged ≤ 80 years) with American Society of Anesthesiologists classification status I to III and body mass index between 18 and 40 kg/m^2 scheduled for elective primary TKA due to osteoarthritis were considered for enrollment in the study. The exclusion criteria included a varus-valgus deformity > 20°, knee flexion deformity > 30°, receiving any type of intraoperative periarticular infiltration (PAI) of local anesthetic by the surgeons, known allergy to study drugs, contraindication to neuraxial or regional anesthesia, chronic opioid use (daily or almost daily use of opioids for ≥ 3 months or morphine use ≥ 60 mg/day for ≥ 1 month), and inability to cooperate or unwillingness to provide informed consent. All eligible patients were interviewed and provided with information on the day of the preoperative admission.

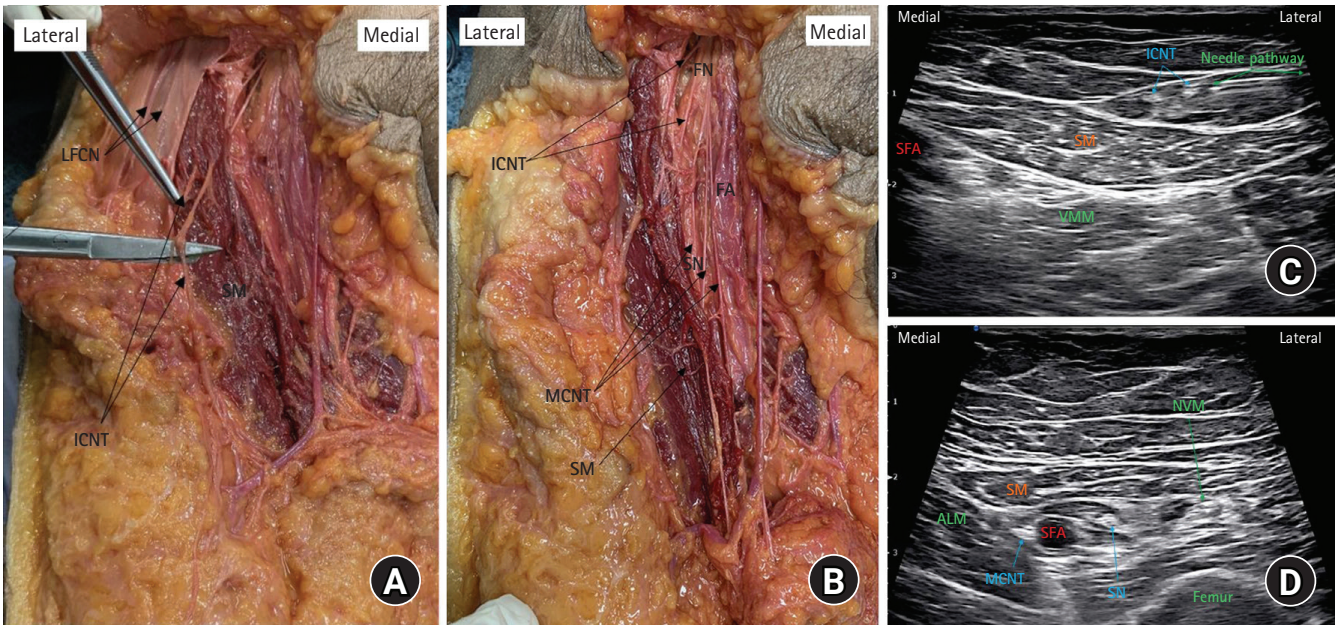

Fig. 1. A and B: Illustrations of anatomical dissection delineating the trajectories of the anterior femoral cutaneous nerve and its branches (the ICNT and MCNT). (A) The ICNT pierces the fascia lata just below the inguinal crease and descends anterior to the fascia lata along the forepart of the thigh. (B) The MCNT branches descend along the medial border of the SM. C and D: Illustrations of ultrasound views for the anterior femoral cutaneous nerve block. (C) Ultrasound image of the path traced by the needle while injecting the local anesthetic mixture anterior to the FL that covers the SM and the ICNT as seen after hydrodissection. (D) Ultrasound image of the branch of the MCNT around the SFA and the SN lateral to the SFA after injection of the local anesthetic mixture. ALM: adductor longus muscle, FA: femoral artery, FL: fascia lata, FN: femoral nerve, ICNT: intermediate cutaneous nerve of the thigh, LFCN: lateral femoral cutaneous nerve, MCNT: medial cutaneous nerve of the thigh, NVM: nerve to vastus medialis, SFA: superficial femoral artery, SM: sartorius muscle, SN: saphenous nerve, VMM: vastus medialis muscle.

Demographic data, preoperative pain scores, and functional performance results (timed up and go [TUG] test, five times sit-to-stand test [FTSST], quadriceps muscle strength [QMS], and knee range of motion [ROM]) were obtained on the day before the surgery by a blinded research assistant. All patients were provided with instructions to assess pain intensity using the numeric rating scale (NRS) for the area where the TKA would be performed.

Treatment allocation and blinding

After providing informed consent, all patients were randomly assigned to either the FTB alone group (FTB group; n = 40) or the AFCNB and FTB combination group (AFCNB + FTB group; n = 40) using computer-generated block randomization in a 1 : 1 ratio (blocks of 4 and 6) by a statistician not involved in the study. Treatment allocation was concealed using consecutively numbered, sealed, opaque envelopes that were opened by the nurse anesthetist before the patient's arrival in the room where the nerve blocks were performed. All nerve blocks were performed by a single, experienced, regional anesthesiologist (W.K.) with a nurse anesthetist; both were uninvolved in any other study phases, thus eliminating performance bias. All surgeons, research assistants, operating room and floor nurses, patients, and statisticians were blinded to group allocation.

Preoperative and block procedures

All patients received multimodal analgesia, including oral acetaminophen (650 mg) 30 min before surgery. After standard noninvasive monitoring was initiated, peripheral intravenous (IV) catheters were applied, the patient was placed in a supine position with the legs slightly abducted, and the procedural area was cleaned. A high-frequency linear-array transducer (L11-3, Sonimage® HS1, Konica Minolta, Japan) used for ultrasonography was also disinfected. A titrated anxiolytic 1–2 mg IV dose of midazolam was administered to the patient. Sterile mixtures of local anesthetic solution consisted of 100 mg levobupivacaine (20 ml of 0.5% levobupivacaine) with 0.2 mg epinephrine and 30 mg ketorolac in 20 ml normal saline (total 40 ml divided by 2; syringes of 20 ml each) and 20 ml normal saline for the sham AFCNB in the FTB group, and 150 mg levobupivacaine (30 ml of 0.5% levobupivacaine) with 0.3 mg epinephrine and 30 mg ketorolac in 30 ml normal saline (total 60 ml divided by 3; syringes of 20 ml each) in the AFCNB + FTB group.

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Under sterile conditions, ultrasound-guided AFCNB was performed by placing the transducer along the upper to middle third of the thigh. After identifying the position of the SFA beneath the SM in the ultrasound image, the transducer was moved slightly cephalad to identify the optimal position of the SFA beneath the medial border of the SM in the ultrasound image [11]. After administration of 1–2 ml of 1% lidocaine to anesthetize the skin, a 21-gauge 10-cm stimulating needle (Stimuplex® A100; B. Braun Medical, Inc., USA) was inserted from the lateral-to-medial direction using an "in-plane technique" and was advanced until the needle tip was superficial to the fascia lata at the junction of the sartorius and rectus femoris muscles [16,17]. Thereafter, 10 ml of the local anesthetic mixture was slowly injected with aspiration, while the needle was advanced superficial to the fascia lata covering the SM until it reached the medial border of the SM to block the ICNT (Fig. 1C). The needle was then redirected to pierce the fascia lata [12], and another 10 ml of anesthetic mixture was slowly injected between the fascia lata and SM until the tip of the needle reached the medial border of the SM to block the MCNT branches and ensure adequate spread to the ICNT. In the FTB group, 20 ml of normal saline was injected.

The needle was then advanced through the SM at the same level until the tip of the needle was located beneath the SM and anterolateral to the SFA. In the FTB group, 20 ml of local anesthetic mixture was injected. In the AFCNB + FTB group, the needle was carefully advanced periarterially toward the medial side of the SFA and beneath the medial border of the SM, in order to achieve spread to the MCNT branches (Fig. 1D) [12]. Subsequently, patients in both groups were placed in 90° flexion of the knee to perform the IPACK block under sterile conditions with a 20 ml local anesthetic mixture, as described in a previous study [21].

Intraoperative protocol

All patients received spinal anesthesia with 3 to 3.2 ml of 0.5% hyperbaric bupivacaine. Antiemetic prophylaxis was administered to all patients with 10 mg IV dexamethasone and 4 mg IV ondansetron. Minimally invasive TKA was performed by two surgeons blinded to the group allocation, and the patients did not receive any intraoperative PAI of local anesthetic by the surgeons.

Postoperative protocol

CACBs were performed in the postanesthesia care unit by the regional anesthesiologist team using an 80-mm Touhy needle and Perifix® 18-gauge epidural catheter (B. Braun Medical, Inc., USA) for all patients in their operated extremities. After ultrasound identification of the SFA under the SM and below the apex of the femoral triangle, a Touhy needle was inserted in-plane from the lateral-to-medial direction and advanced until the tip was positioned between the SM and SFA. Thereafter, 5–10 ml of normal saline was injected to confirm the optimal positioning of the catheter and to secure catheter insertion [22]. An ACB catheter was then inserted through the needle and fixed over the skin after the position of the catheter tip was confirmed by ultrasound. Subsequently, levobupivacaine 0.15% was continuously infused at 5 ml/h for 60 h via a disposable infusion pump (Coopdech Syrinjector, Daiken Medical Co., Ltd., Japan). A standardized analgesic protocol comprising two doses of IV parecoxib 20 mg every 12 h, oral acetaminophen 650 mg every 6 h, and oral pregabalin 75 mg and oral celecoxib 400 mg (starting after the last dose of parecoxib) once a day. In addition, for patients with NRS scores ≥ 4, 2 mg IV morphine was administered every 30 min. If a patient continued to exhibit an NRS score ≥ 4 for up to 1 h, patient-controlled anesthesia (PCA) was initiated using morphine (no basal rate; PCA dose, 2 mg; lockout time, 10 min) as a rescue drug. Discharge criteria [23] were assessed by the surgeons blinded to the treatment.

Outcome assessments

All data were collected by a research assistant who was blinded to the group assignment and was not involved in perioperative patient care. The primary outcome was pain score on movement as measured using an NRS (0–10; 0: no pain, 10: worst imaginable pain) in the first 12 h after surgery. The secondary outcomes included the following: pain scores at rest and during movement until 2 months after surgery; the end-of-analgesia time, defined as the time from the end of surgery to the first NRS score ≥ 4; incidence of surgical incision site pain, defined as the proportion of patients who experienced moderate-to-severe pain (NRS score ≥ 4) in the area of the surgical incision in the first 24 h after surgery; IV morphine consumption (in mg; at 12, 24, and 48 h postoperatively); immediate functional performance measures (recorded by a blinded physiotherapist from preoperative to postoperative day [POD] 2) including (i) the TUG test, with results measured in seconds, requiring the patient to stand up from an armchair, walk 3 m, turn, walk back to the chair, and sit down [24]; (ii) the FTSST, with results measured in seconds, requiring the patient to stand and sit five times as quickly as possible without physical assistance [25]; (iii) the QMS, measured using a handheld dynamometer (microFET®2, Hoggan Health Industries, USA), requiring the patient to sit with legs hanging from the bed with 0° and 90° angulations of the knee joint. For each degree, three consecutive measurements were made with 30 s intervening rest periods,

and the average was calculated. (iv) The ROM measured the degree of maximum active flexion and extension of the operated knee. Nausea and vomiting and dizziness scores were assessed on a visual analog scale (0 = none, 10 = severe) until POD 2; patient satisfaction and quality of sleep were recorded on a Likert scale (0–7); length of hospital stay was defined as the time from surgery until discharge; and other postoperative complications included local anesthetic toxicity, motor weakness of the peroneal nerve, and incidence of falls.

Sample size

Sample size was calculated by reviewing the patient records at our institution and was based on the findings of our previous study [22] that NRS pain scores on movement 12 h postoperatively were 3.3 ± 2.8 in patients who had received spinal anesthesia combined with postoperative CACB without intrathecal morphine or PAI. Assuming a standard deviation of 3 points, which corresponds to an effect size of 0.67, with a significance level of 0.05 and 80% power, 36 patients would be required in each group to detect a minimally clinically important difference of 2 points in NRS pain scores on movement 12 h postoperatively between patients receiving AFCNB + FTB and FTB alone. We planned to include 80 patients altogether to compensate for potential dropouts.

Statistical analysis

The primary outcome, pain scores, and functional outcomes measured at a single postoperative time point were compared between the groups using multivariable linear regression. Regression based on a generalized estimating equation (GEE) approach [26] with an unstructured correlation structure was used to compare outcomes measured longitudinally. The GEE method accounts for the correlation between repeated measurements for the same patient. Continuous variables between the groups were compared using the unpaired t test, and categorical variables were analyzed using the chi-square test. All variables were tested for normality using the Shapiro–Wilk test. Data are presented as the mean ± standard deviation with 95% CI, or median (Q1, Q3), according to the normality of data distribution, or as a number (proportion). We did not impute values when data were missing, and an effect was considered statistically significant at $P < 0.05$ (95% CI excluded zero). Statistical analysis was conducted using STATA version 14.0 (STATA Corp., USA).

Results

A total of 80 patients met the inclusion criteria and were enrolled in the study. One patient in the AFCNB + FTB group was withdrawn from the analysis because of protocol violation due to inadvertent intraoperative PAI. The CONSORT diagram for the study is shown in Fig. 2. Preoperative patient characteristics were similar between the two groups (Table 1).

Pain outcomes

Although the mean NRS pain scores in both groups were lower than 4 (Table 2), patients in the AFCNB + FTB group showed sta-

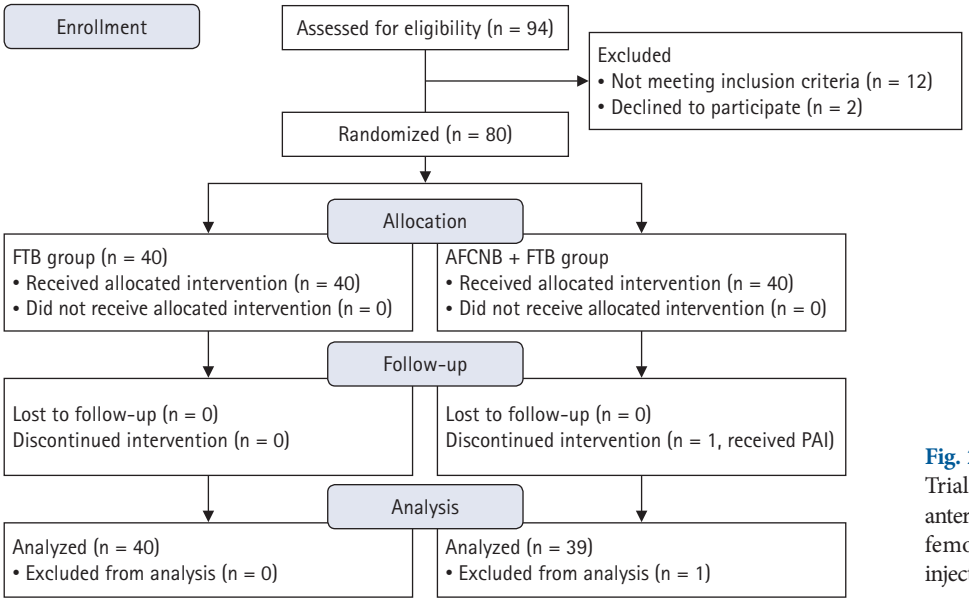

Fig. 2. Consolidated Standards of Reporting Trials (CONSORT) flow diagram. AFCNB: anterior femoral cutaneous nerve block, FTB: femoral triangle block, PAI: periarticular injection.

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Table 1. Baseline Patient Characteristics

Variable	FTB group (n = 40)	AFCNB + FTB group (n = 39)
Sex		
Male	5 (12.5)	4 (10.3)
Female	35 (87.5)	35 (89.7)
Age (yr)	70.9 ± 7.6	71.1 ± 7.5
Weight (kg)	65.2 ± 10.6	61.9 ± 11.2
Height (cm)	153.9 ± 6.9	153.4 ± 6.3
Body mass index (kg/m^2)	27.6 ± 4.2	26.3 ± 4.0
ASA PS (I/II/III)	2/34/4	2/34/3
Preop NRS pain score		
At rest	1.5 ± 2.2	1.0 ± 2.1
During movement	4.4 ± 2.9	4.9 ± 2.3
Preop TUG (s)	24.9 ± 9.4	24.5 ± 11.8
Preop FTSST (s)	25.7 ± 12.2	23.6 ± 10.5
Preop QMS 0 degree (n)	47.6 ± 15.5	51.3 ± 14.6
Preop QMS 90 degree (n)	56.1 ± 24.6	77.9 ± 29.4
Preop active ROM (°)	117.9 ± 17.4	120.4 ± 11.4
Operative side		
Left	14 (35.9)	20 (52.6)
Right	25 (64.1)	18 (47.4)
Duration of surgery (min)	116.3 ± 24.8	115.0 ± 21.6
Duration of anesthesia (min)	150.1 ± 28.2	152.7 ± 24.1

Values are presented as mean ± SD or number (%). AFCNB: anterior femoral cutaneous nerve block, ASA PS: American Society of Anesthesiologists physical status, FTB: femoral triangle block, FTSST: five times sit-to-stand test, NRS: numeric rating scale, Preop: preoperative, QMS: quadriceps strength, ROM: range of motion, TUG: timed up and go.

tistically significant reduction in their scores during movement compared to those in the FTB group 12 h postoperatively (FTB: 2.2 ± 1.8 vs. AFCNB + FTB: 0.8 ± 1.3; mean difference: –2.02, 95 CI: –3.14, –0.89, P < 0.001). In addition, patients in the AFCNB + FTB group revealed significantly lower NRS pain scores at rest 6 h postoperatively (FTB: 2.3 ± 2.9 vs. AFCNB + FTB: 0.2 ± 0.7; mean difference: –1.61, 95% CI: –2.4, –0.81, P < 0.001), and on movement 6 and 24 h postoperatively (FTB: 3.1 ± 3.4 vs. AFCNB + FTB: 0.3 ± 0.8; mean difference: –3.47, 95% CI: –4.59, –2.35, P < 0.001 and FTB: 2.3 ± 2.1 vs. AFCNB + FTB: 1.7 ± 2; mean difference: –1.27, 95% CI: –2.4, –0.15, P = 0.025, respectively). Additionally, the incidence of moderate-to-severe pain at the surgical incision site was significantly lower in these patients than in patients in the FTB group 24 h after surgery (15.8% vs. 41%, P = 0.014).

The end-of-analgesia time (NRS ≥ 4) was significantly longer in the AFCNB + FTB group than in the FTB group (19.6 ± 6.2 vs. 5.4 ± 5.4 h, P < 0.001). The IV morphine consumption was lower in the AFCNB + FTB group than in the FTB group at 12 h (0 [0, 0] vs. 0 [0, 2], P < 0.001), 24 h (0 [0, 0] vs. 0 [0, 2], P < 0.001), and 48 h (0 [0, 0] vs. 2 [0, 4], P < 0.001). However, this difference was not clinically significant. Likewise, no patient in either group required IV PCA.

Performance outcomes

The mean TUG test time on POD 2 in the AFCNB + FTB group was significantly lower than in the FTB group (FTB: 70.2 ± 34.3 s vs. AFCNB + FTB: 50.9 ± 21.4 s; mean difference: –18.95 s, 95% CI: –35.23, –2.67, P = 0.023) (Table 3). The mean QMS in the AFCNB + FTB group on PODs 0–2 was greater in both degrees of knee joint movement than in their FTB group counterparts, and the number of patients able to perform the QMS test in all degrees of knee joint movement on POD 0 was higher in the AFCNB + FTB group (27 vs. 36 in 90°, P = 0.006). However, there was no difference in the mean QMS at 90° between the groups on POD 0 (FTB: 37.6 ± 24.6 vs. AFCNB + FTB: 55.6 ± 28.5; mean difference: –4.8, 95% CI: –14.15, 4.54, P = 0.313), while the FTB group showed significantly reduced QMS at 0° compared to the AFCNB + FTB group on POD 0 (FTB: 26.8 ± 12.2 vs. AFCNB + FTB: 45.3 ± 43.5; mean difference: 11.21, 95% CI: 0.5, 21.89, P = 0.04) (Table 3). There were no significant differences between the two groups in other measures at various time points.

Other outcomes

There were no clinically relevant or statistically significant differences between the two groups in terms of nausea and vomiting, dizziness, quality of sleep, patient satisfaction, and length of hospital stay (FTB: 57 ± 13.5 h vs. AFCNB + FTB: 53.2 ± 7.8 h; P = 0.14). No adverse events occurred in either group.

Discussion

This randomized controlled trial evaluated the effects of AFCNB in combination with FTB as part of a postoperative multimodal analgesia regimen including CACB after TKA. Our results indicated that AFCNB in combination with FTB can provide analgesia superior to that of FTB alone during the first 12 h after surgery. Moreover, it also increased the time to first analgesic request and reduced IV morphine consumption, although the results were not clinically significant.

Furthermore, AFCNB combined with FTB decreased the incidence of moderate-to-severe pain in the surgical incision area during the first 24 h after TKA, in comparison with FTB alone. These results suggest that AFCNB could provide cutaneous anes-

Table 2. Pain Assessment

Time points	FTB group Unadjusted (n = 40)		AFCNB + FTB group Unadjusted (n = 39)		Adjusted difference (95% CI)	P value
NRS at rest						
PACU	40	0.3 ± 0.9	39	0.1 ± 0.4	0.42 (−0.37, 1.21)	0.301
6 h	40	2.3 ± 2.9	39	0.2 ± 0.7	−1.61 (−2.4, −0.81)	< 0.001*
12 h	40	1.3 ± 1.8	39	0.5 ± 0.9	−0.28 (−1.07, 0.52)	0.494
24 h	40	1.0 ± 1.5	39	0.5 ± 0.9	−0.03 (−0.82, 0.76)	0.942
48 h	40	0.6 ± 1.3	39	0.3 ± 0.8	0.23 (−0.56, 1.02)	0.571
5 days	40	0.9 ± 1.1	39	0.8 ± 1.5	0.35 (−0.45, 1.15)	0.392
1 week	40	0.8 ± 1.0	39	0.9 ± 1.7	0.6 (−0.21, 1.4)	0.146
2 weeks	40	0.7 ± 1.3	39	0.6 ± 1.5	0.45 (−0.36, 1.26)	0.274
1 month	40	0.5 ± 1.1	39	0.3 ± 0.9	0.29 (−0.52, 1.1)	0.482
2 months	40	0.3 ± 1.0	39	0.1 ± 0.2	0.26 (−0.56, 1.07)	0.538
NRS during movement						
PACU	40	0.5 ± 1.7	39	0.1 ± 0.5	−0.96 (−2.09, 0.16)	0.093
6 h	40	3.1 ± 3.4	39	0.3 ± 0.8	−3.47 (−4.59, −2.35)	< 0.001*
12 h	40	2.2 ± 1.8	39	0.8 ± 1.3	−2.02 (−3.14, −0.89)	< 0.001*
24 h	40	2.3 ± 2.1	39	1.7 ± 2.0	−1.27 (−2.4, −0.15)	0.025*
48 h	40	2.8 ± 1.9	39	2.3 ± 1.5	−1.1 (−2.22, 0.03)	0.056
5 days	40	2.6 ± 1.9	39	2.8 ± 2.4	-0.52 (-1.65, 0.61)	0.368
1 week	40	2.5 ± 1.4	39	3.3 ± 2.4	0.03 (−1.11, 1.17)	0.959
2 weeks	40	2.3 ± 1.7	39	2.8 ± 2.2	−0.03 (−1.18, 1.11)	0.956
1 month	40	1.5 ± 1.5	39	2.1 ± 2.8	−0.02 (−1.16, 1.13)	0.976
2 months	40	1.4 ± 1.6	39	0.9 ± 1.3	−1.1 (−2.25, 0.06)	0.063

Values are presented as mean ± SD or number. AFCNB: anterior femoral cutaneous nerve block, FTB: femoral triangle block, NRS: numeric rating scale, PACU: postanesthesia care unit. *P value < 0.05.

Table 3. Postoperative Timed Up and Go Test, Five Times Sit-to-stand Test, Quadriceps Strength, and Active Range of Motion

Functional outcomes	FTB group Unadjusted (n = 40)		AFCNB + FTB group Unadjusted (n = 39)		Adjusted difference (95% CI)	P value
TUG (s)						
Day 1	40	93.5 ± 47.6	39	80.5 ± 35.0	−12.91 (−29.19, 3.37)	0.120
Day 2	40	70.2 ± 34.3	39	50.9 ± 21.4	−18.95 (−35.23, −2.67)	0.023*
FTSST (s)						
Day 1	37	53.2 ± 34.9	38	44.1 ± 24.6	−7.12 (−18.21, 3.98)	0.209
Day 2	40	35.4 ± 22.7	39	30.8 ± 13.9	−2.13 (−13.22, 8.97)	0.707
QMS 0° (n)						
Day 0	34	26.8 ± 12.2	36	45.3 ± 43.5	11.21 (0.5, 21.89)	0.040*
Day 1	40	38.7 ± 13.0	39	48.9 ± 17.3	4.36 (−6, 14.72)	0.409
Day 2	40	42.7 ± 15.6	39	49.2 ± 18.9	1.25 (−9.07, 11.61)	0.810
QMS 90° (n)						
Day 0	27	37.6 ± 24.6	36	55.6 ± 28.5	−4.8 (−14.15, 4.54)	0.313
Day 1	40	48.4 ± 25.6	39	68.3 ± 30.0	−7.21 (−15.35, 0.93)	0.083
Day 2	40	56.4 ± 30.3	39	71.1 ± 28.8	−12.19 (−20.33, −4.05)	0.003*
Active ROM (°)						
Day 0	40	124.4 ± 13.1	39	124.9 ± 9.2	−1.6 (−8.19, 4.98)	0.633
Day 1	40	91.8 ± 15.3	39	92.5 ± 11.8	−1.84 (−8.45, 4.78)	0.586
Day 2	40	105.8 ± 15.9	39	101.6 ± 14.2	−6.34 (−12.96, 0.27)	0.060

Values are presented as mean ± SD or number. AFCNB: anterior femoral cutaneous nerve block, FTB: femoral triangle block, FTSST: five times sit-to-stand test, QMS: quadriceps muscle strength, ROM: range of motion, TUG: time up and go. *P value < 0.05.

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thesia in the region of the surgical incision and medial aspect of the knee after TKA, whereas FTB or proximal ACB cannot. Hence, AFCNB can be beneficial for cases in which surgical incisions for TKA are relatively large. However, we were unable to accurately determine the effects of combining AFCNB with FTB on the immediate functional performance outcomes after TKA, because we found a reduction in muscle strength only in the 0° knee joint on POD 0 in the FTB group compared to that in the AFCNB + FTB group. Moreover, there were no significant differences in the other immediate performance test measures, except for the TUG test and QMS results on POD 2. However, patients in the AFCNB + FTB group had lower pain scores and greater cooperation in physical performance measures on POD 0. Therefore, the motor-sparing anterior knee block (AFCNB with FTB) combined with the motor-sparing posterior knee block (IPACK block) may prove effective in cases requiring early ambulation after TKA.

The needle injection point for FTB in our study was located just above the apex of the femoral triangle or the SFA, beneath the medial border of the SM in the ultrasound images. This is the same location as in previous studies, defined as "FTB" and "proximal ACB" [8–11]. Our results and anatomical findings also support the possibility of an analgesic effect in this location extending to the saphenous nerve, infrapatellar branch of the saphenous nerve, vastus medialis nerve, and some branches of the MCNT that course anteromedial to the SFA at this level [18–20], which are not involved in other techniques of motor-sparing anterior knee analgesia. This could be because the FTB or proximal ACB can anesthetize more branches of the femoral nerve than the distal ACB and may lead to quadriceps muscle weakness. However, results of previous studies did not show quadriceps muscle weakness [21,22,27]. The continuous catheter technique at this location should be explored in future studies for longer pain relief after TKA.

To the best of our knowledge, this is the first clinical study to investigate the efficacy of AFCNB in combination with FTB in patients undergoing TKA. Sogbein et al. [16] examined the use of AFCNB as part of motor-sparing knee blocks (including the lateral femoral cutaneous nerve block, AFCNB, ACB, and IPACK block) and demonstrated longer analgesia compared with the PAI technique. However, no ACB or FTB group was defined for direct comparison. Moreover, the trajectory of the ICNT is fairly constant, in contrast to that of the MCNT [18–20]. Therefore, the location of the block of the MCNT varies. Our technique for MCNT block was similar to that used by Johnston et al. [17], who devised it from a literature review of the anatomy and innervation of the knee joint. However, the quantity of local anesthetic used at each injection point in that trial was relatively small. Hence, it might not have been sufficiently distributed to most of the branches of the MCNT. Moreover, we did not inject the local anesthetic between the SM and posterior fascia above the adductor canal (subsartorial space), because local anesthetic distribution by FTB also includes this space. The anatomical and volunteer trial by Bjørn et al. [12] demonstrated a block of the ICNT in which duplication of the fascia lata superficial to the SM can be visualized in ultrasound images and a block of the MCNT by the FTB with the needle tip located only lateral to the femoral artery. In our injection, the needle tip was further advanced anteromedial to the femoral artery for adequate local anesthetic distribution. Further studies are needed to investigate the optimal needle injection point and the required volume of local anesthetic to block the branches of the MCNT.

Our study had several limitations. First, use of the CACB in our postoperative multimodal analgesic regimen might have led to an absence of obvious differences in the pain scores and IV morphine consumption between the two groups. However, the duration of the effect of single-shot ACB is generally 24–36 h [22,28], and breakthrough pain may occur after the effect of a single shot subsides, which can cause delays in the initiation of physical therapy and hospital discharge [29,30]. Second, all preoperative block procedures were performed by a single anesthesiologist who could not be blinded to the study group; therefore, an involuntary bias may have been introduced in the performance of the blocks. However, the minimal pain scores in both groups suggested that both block techniques were comparable. Third, as the patients were under sedation, we could not clearly examine the differences in the anesthetized areas after blocks between the groups. The assessment was performed only by cold sensation on the anteromedial knee 20–30 min after the respective procedures. Lastly, because of the clinical setting and study protocol, we could not assess the efficacy of these blocks in outpatient settings. Future studies on the efficacy of AFCNB combined with FTB in outpatient settings are warranted.

In conclusion, the motor-sparing knee blocks, including the FTB (with or without AFCNB) and IPACK blocks, as part of the multimodal analgesic regimen, provide effective postoperative analgesia in patients undergoing TKA. They also reduce postoperative opioid requirements. Moreover, the addition of AFCNB to FTB decreased pain scores at 12 h after surgery and the incidence of moderate-to-severe surgical incision pain compared to FTB alone, and it could enhance the immediate physical performance of the patients on the day of surgery.

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Conflicts of Interest

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

Author Contributions

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References

1. Oseka L, Pecka S. Anesthetic management in early recovery after surgery protocols for total knee and total hip arthroplasty. AANA J 2018; 86: 32-9.
2. Ellis TA 2nd, Hammoud H, Dela Merced P, Nooli NP, Ghoddoussi F, Kong J, et al. Multimodal clinical pathway with adductor canal block decreases hospital length of stay, improves pain control, and reduces opioid consumption in total knee arthroplasty patients: a retrospective review. J Arthroplasty 2018; 33: 2440-8.
3. Li D, Ma GG. Analgesic efficacy and quadriceps strength of adductor canal block versus femoral nerve block following total knee arthroplasty. Knee Surg Sports Traumatol Arthrosc 2016; 24: 2614-9.
4. Abdallah FW, Whelan DB, Chan VW, Prasad GA, Endersby RV, Theodoropolous J, et al. Adductor canal block provides noninferior analgesia and superior quadriceps strength compared with femoral nerve block in anterior cruciate ligament reconstruction. Anesthesiology 2016; 124: 1053-64.
5. Kandarian B, Indelli PF, Sinha S, Hunter OO, Wang RR, Kim TE, et al. Implementation of the IPACK (infiltration between the popliteal artery and capsule of the knee) block into a multimodal analgesic pathway for total knee replacement. Korean J Anesthesiol 2019; 72: 238-44.
6. Kim DH, Beathe JC, Lin Y, YaDeau JT, Maalouf DB, Goytizolo E, et al. Addition of infiltration between the popliteal artery and the capsule of the posterior knee and adductor canal block to periarticular injection enhances postoperative pain control in total knee arthroplasty: a randomized controlled trial. Anesth Analg 2019; 129: 526-35.
7. Manickam B, Perlas A, Duggan E, Brull R, Chan VW, Ramlogan R. Feasibility and efficacy of ultrasound-guided block of the saphenous nerve in the adductor canal. Reg Anesth Pain Med 2009; 34: 578-80.
8. Bendtsen TF, Moriggl B, Chan V, Børglum J. Basic topography of the saphenous nerve in the femoral triangle and the adductor canal. Reg Anesth Pain Med 2015; 40: 391-2.
9. Cowlishaw P, Kotze P. Adductor canal block--or subsartorial canal block? Reg Anesth Pain Med 2015; 40: 175-6.
10. Wong WY, Bjørn S, Strid JM, Børglum J, Bendtsen TF. Defining the location of the adductor canal using ultrasound. Reg Anesth Pain Med 2017; 42: 241-5.
11. Abdallah FW, Mejia J, Prasad GA, Moga R, Chahal J, Theodoropulos J, et al. Opioid- and motor-sparing with proximal, mid-, and distal locations for adductor canal block in anterior cruciate ligament reconstruction: a randomized clinical trial. Anesthesiology 2019; 131: 619-29.
12. Bjørn S, Nielsen TD, Moriggl B, Hoermann R, Bendtsen TF. Anesthesia of the anterior femoral cutaneous nerves for total knee arthroplasty incision: randomized volunteer trial. Reg Anesth Pain Med 2020; 45: 107-16.
13. Song L, Li Y, Xu Z, Geng ZY, Wang DX. Comparison of the ultrasound-guided single-injection femoral triangle block versus adductor canal block for analgesia following total knee arthroplasty: a randomized, double-blind trial. J Anesth 2020; 34: 702-11.

https://doi.org/10.4097/kja.21120

14. Bendtsen TF, Moriggl B, Chan V, Børglum J. The optimal analgesic block for total knee arthroplasty. Reg Anesth Pain Med 2016; 41: 711-9.
15. Horner G, Dellon AL. Innervation of the human knee joint and implications for surgery. Clin Orthop Relat Res 1994; (301): 221-6.
16. Sogbein OA, Sondekoppam RV, Bryant D, Johnston DF, Vasarhelyi EM, MacDonald S, et al. Ultrasound-guided motor-sparing knee blocks for postoperative analgesia following total knee arthroplasty: a randomized blinded study. J Bone Joint Surg Am 2017; 99: 1274-81.
17. Johnston DF, Sondekoppam RV, Uppal V, Howard JL, Ganapathy S. Hybrid blocks for total knee arthroplasty: a technical description. Clin J Pain 2018; 34: 222-30.
18. Baccarani G, Zanotti G. The innervation of the skin on the antero-medial region of the knee. Ital J Orthop Traumatol 1984; 10: 521-5.
19. Pivec C, Bodner G, Mayer JA, Brugger PC, Paraszti I, Moser V, et al. Novel demonstration of the anterior femoral cutaneous nerves using ultrasound. Ultraschall Med 2018; 39: 318-27.
20. Riegler G, Pivec C, Jengojan S, Mayer JA, Schellen C, Trattnig S, et al. Cutaneous nerve fields of the anteromedial lower limb-Determination with selective ultrasound-guided nerve blockade. Clin Anat 2021; 34: 11-8.
21. Kampitak W, Tanavalee A, Ngarmukos S, Tantavisut S. Motor-sparing effect of iPACK (interspace between the popliteal artery and capsule of the posterior knee) block versus tibial nerve block after total knee arthroplasty: a randomized controlled trial. Reg Anesth Pain Med 2020; 45: 267-76.
22. Kertkiatkachorn W, Kampitak W, Tanavalee A, Ngarmukos S. Adductor canal block combined with iPACK (interspace between the popliteal artery and the capsule of the posterior knee) block vs periarticular injection for analgesia after total knee arthroplasty: a randomized noninferiority trial. J Arthroplasty 2021; 36: 122-9.
23. Kampitak W, Tanavalee A, Ngarmukos S, Amarase C, Songthamwat B, Boonshua A. comparison of adductor canal block versus local infiltration analgesia on postoperative pain and functional outcome after total knee arthroplasty: a randomized controlled trial. Malays Orthop J 2018; 12: 7-14.
24. Bohannon RW. Reference values for the timed up and go test: a descriptive meta-analysis. J Geriatr Phys Ther 2006; 29: 64-8.
25. Alcazar J, Losa-Reyna J, Rodriguez-Lopez C, Alfaro-Acha A, Rodriguez-Mañas L, Ara I, et al. The sit-to-stand muscle power test: an easy, inexpensive and portable procedure to assess muscle power in older people. Exp Gerontol 2018; 112: 38-43.
26. Liu J, Colditz GA. Optimal design of longitudinal data analysis using generalized estimating equation models. Biom J 2017; 59: 315-30.
27. Mariano ER, Kim TE, Wagner MJ, Funck N, Harrison TK, Walters T, et al. A randomized comparison of proximal and distal ultrasound-guided adductor canal catheter insertion sites for knee arthroplasty. J Ultrasound Med 2014; 33: 1653-62.
28. Turner JD, Dobson SW, Henshaw DS, Edwards CJ, Weller RS, Reynolds JW, et al. Single-injection adductor canal block with multiple adjuvants provides equivalent analgesia when compared with continuous adductor canal blockade for primary total knee arthroplasty: a double-blinded, randomized, controlled, equivalency trial. J Arthroplasty 2018; 33: 3160-6.
29. Zhang LK, Zhang BY, Quan RF, Xu H, Sun YJ, Zhou JH. Single shot versus continuous technique adductor canal block for analgesia following total knee arthroplasty: A PRISMA-compliant meta-analysis. Medicine (Baltimore) 2019; 98: e15539.
30. Wang C, Chen Z, Ma X. Continuous adductor canal block is a better choice compared to single shot after primary total knee arthroplasty: a meta-analysis of randomized controlled trials. Int J Surg 2019; 72: 16-24.

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Analysis of endotracheal intubation-related judicial precedents in South Korea

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Background: Medical malpractice during endotracheal intubation can result in catastrophic complications. However, there are no reports on these severe complications in South Korea. We aimed to investigate the severe complications associated with endotracheal intubation occurring in South Korea, via medicolegal analysis.
Methods: We retrospectively analyzed the closed judicial precedents regarding complications related to endotracheal intubation lodged between January 1994 and June 2020, using the database of the Supreme Court of Korea. We collected clinical and judicial characteristics from the judgments and analyzed the medical malpractices related to endotracheal intubation.
Results: Of 220 potential cases, 63 were included in the final analysis. The most common event location was the operating room (n = 20, 31.7%). All but 3 cases were associated with significant permanent or more severe injury, including 31 deaths. The most common problems were failed or delayed intubation (n = 56, 88.9%). Supraglottic airway device was used in 5.2% (n = 3) cases of delayed or failed intubation. Fifty-one (81%) cases were ruled in favor of the plaintiff in the claims for damages, with a median payment of Korean Won 133,897,845 (38,000,000, 308,538,274). The most common malpractice recognized by the court was that of not attempting an alternative airway technique (n = 32, 50.8%), followed by violation of the duty of explanation (n = 10, 15.9%).
Conclusions: Our results could increase physicians' awareness of the major complications related to endotracheal intubation and help ensure patient safety.

Keywords: Airway management; Complications; Emergency treatment; Intratracheal intubation; Medical legislation; Medical liability.

Introduction

Endotracheal intubation is an important airway procedure to secure airway patency and ensure adequate ventilation in patients with respiratory depression or those undergoing general anesthesia [1]. Since a delay of only a few minutes in securing the airway can cause hypoxic brain injury or death, medical malpractice during endotracheal intubation could lead to catastrophic complications.

Previous closed claims analyses related to airway management, including endotracheal intubation, have been mainly performed in the field of anesthesiology [2,3]. According to the closed claims database of the American Society of Anesthesiologists (ASA) since 1990, respiratory complications are the second most common damaging event, and diffi-

cult intubation is the most common respiratory event leading to claims [2]. Another closed claims analysis of the ASA focusing on difficult intubation reported a total of 179 claims related to difficult airway management between 1985 and 1999 and revealed that serious complications, such as brain damage or death, occurred in approximately 63% of these cases [3].

However, to the best of our knowledge, no reports have focused on severe complications resulting from medical malpractice related to endotracheal intubation in South Korea. Therefore, we aimed to examine the rare but severe complications and possible medical malpractice associated with endotracheal intubation via the analysis of medical malpractice legal judgments.

Materials and Methods

Data collection

We analyzed closed judicial precedents from the publicly available judgment database of the Supreme Court of Korea. We searched all civil proceedings that were decided by the court between January 1, 1994 and June 31, 2020 using the following terms: 'endotracheal' and 'intubation.' We included medical malpractice litigation cases related to endotracheal intubation itself. We excluded cases related to airway procedures other than endotracheal intubation. We also excluded cases related to complications that occurred during an intubated state or extubation. The Institutional Review Board of Seoul National University Hospital (No. 02010-075-1163) approved this retrospective study. Since the judgments were provided to the researcher after de-identification, the need for informed consent was waived.

This analysis was conducted in a similar manner as our previous medicolegal studies [4,5]. Each precedent text included detailed clinical information related to the events, the plaintiff's claim, and the court decisions regarding medical malpractice. Three anesthesiologists (HY Cho, SJ Lee, and S Yoon) scrutinized the precedent texts, collecting the following variables: demographics (including age and sex), department of primary defendant physician, type of medical institution (local clinic, hospital), location of event, reason for tracheal intubation, and the types and severities of the complications. The severity of complications was evaluated using the 10-point National Association of Insurance Commissioners (NAIC) scale (0: no obvious injury, 1: emotional only, 2: temporary insignificant, 3: temporary minor, 4: temporary major, 5: permanent minor, 6: permanent significant, 7: permanent major, 8: permanent grave, 9: death) [6]; and classified as low (0–2), medium (3–5), or high (6–9) [5]. During the second review, we investigated the potential predictors of difficult tracheal intubation [7], the number of laryngoscopic attempts, whether or not alternative airway intervention was performed, and the duration from the determination of intubation to intubation (min) in cases associated with delayed intubation. We also collected legal data including the detailed claims of plaintiffs, opinion of the court, and final claimed and awarded amounts. The defendant's allegations were classified into violation of the duty of care and violation of the duty of explanation. The violation of the duty of care was subclassified into the following 8 categories during the second review: no attempt of alternative airway technique, physician inexperience, no confirmation of endotracheal intubation, inappropriate tube size, pulmonary aspiration, upper airway trauma, absence of intubation instruments, and inappropriate management of bronchospasm. The classification process was conducted by 2 anesthesiologists (HY Cho and H-J Lee) independently. In the case of a conflict between the 2 authors, the decision was made after discussion with a third author (SH Shin). Additionally, we performed a subgroup analysis in pediatric patients during the revision process.

Statistical analysis

Descriptive statistical analysis was performed using MedCalc version 19.5.3 (MedCalc Software Ltd., Belgium). We did not perform comparative statistics because our data could not represent all complications caused by endotracheal intubation in South Korea, and we could not know the accurate denominators. Continuous data are described as medians and interquartile ranges, and categorical data are described as numbers and percentages.

Results

A total of 220 cases from 408 judgments were reviewed for eligibility. Among them, 157 were excluded and 63 cases were included in the final analysis. The general characteristics of the cases are presented in Table 1. Intubation was performed for respiratory depression management in 48 (76.2%) cases and for general anesthesia in 15 (23.8%) cases. The NAIC severity level was high (6–9) for 60 (95.2%) claims, with a total of 31 (49.2%) deaths.

The type of problems identified by researchers are provided in Table 2. The most common problem was delayed intubation (n = 56, 88.9%). Failed intubation occurred in 2 patients. In these 2 cases, tracheal intubation was attempted for general anesthesia and the patients were awakened after intubation failure. Accidental bronchial intubation occurred in 2 pediatric patients.

Table 3 presents the detailed information of the cases related to delayed or failed intubation. Predictors of difficult tracheal intu-

Table 1. General Characteristics of the Cases in This Study

Characteristics	Total (n = 63)
Sex (Male/Female/Not described)	25 (39.7)/22 (34.9)/16 (25.4)
Age at the time of event, years	15 (23.8)/3 (4.8)/24 (38.1)/4 (6.3)/17 (27.0)
(< 10/10–19/20–59/ ≥ 60/Not described)	
Institution (Local clinic/Hospital)	8 (12.7)/55 (87.3)
Location of event	
Operating room	20* (31.7)
Emergency room	15 (23.8)
General ward	13 (20.6)
Intensive care unit	9 (14.3)
Diagnostic procedure room	4† (6.3)
Post-Anesthesia Care Unit	2 (3.2)
Cause of intubation (Respiratory depression/General anesthesia)	48 (76.2)/15 (23.8)
Clinical outcomes	
High (NAIC score 6–9)	60‡ (95.2)
Medium (NAIC score 3–5)	2 (3.2)
Low (NAIC score 0–2)	1 (1.6)

Values are presented as number (%). NAIC: National Association of Insurance Commissioners. *Causes of intubation at operating room: general anesthesia, n = 15 (23.8); respiratory depression during local anesthesia, n = 2 (3.2); respiratory depression after extubation, n = 1 (1.6); respiratory depression immediately after birth, n = 2 (3.2). †Esophagogastroduodenoscopy, n = 3 (4.8); bronchoscopy, n = 1 (1.6). ‡This included 31 deaths.

Table 2. Type of Alleged Problems

Classification*	Total (n = 63)
Delayed intubation	56* (88.9)
Aspiration of gastric contents	4 (6.3)
Upper airway trauma	4† (6.3)
Accidental bronchial intubation	2 (3.2)
Failed intubation	2 (3.2)

Values are presented as number (%). *There were 5 cases involving 2 or more events: 3 cases of delayed intubation and aspiration of gastric contents; 1 case of delayed intubation, aspiration of gastric contents, and upper airway trauma; and 1 case of delayed intubation and bronchial intubation. †Tooth injury, n = 2 (3.2); laryngeal injury, n = 1 (1.6); vocal cord injury, n = 1 (1.6).

bation were identified in 43 (74.1%) of these cases. The most common predictor was airway obstruction (n = 33, 56.9%), followed by limited mouth opening (n = 13, 22.4%). In all cases, the initial attempt was direct laryngoscopy, and there were ≥ 3 laryngoscopic attempts in 34 (58.6%) cases. Subsequent alternative airway procedures were performed in 19 (35.8%) cases. The supraglottic airway device (SAD) was used in 5.2% (n = 3) cases of delayed or failed intubation, and all of these were performed by anesthesiologists.

The legal outcomes of the malpractice claims related to intubation are shown in Table 4. A total of 51 (81%) claims resulted in payments to the plaintiffs, with a median payment of Korean Won (KRW) 133,897,845 (38,000,000, 308,538,274). The most common type of violation of the duty of care claimed by the plaintiff was that of no attempt of alternative airway management (n = 47, 74.6%), followed by physician inexperience (n = 15, 23.8%). The most common type of violation of the duty of care recognized by the court was also that of no attempt of alternative airway management (n = 32, 50.8%), followed by physician inexperience (n = 8, 12.7%). All physicians whose inexperience was recognized as malpractice were non- anesthesiologists. Of the cases in which an inappropriate tube size was claimed to be malpractice, 5 were pediatric patients and 2 were adult patients. Violation of the duty of explanation was recognized in 10 cases (15.9%), and among them, there were 2 cases of violation of the duty of explanation alone without violation of the duty of care. The reasons for their recognized malpractices were as follows: no explanation prior to scheduled intubation for general anesthesia (n = 8), explanation by a nurse (n = 1), and insufficient explanation regarding tooth injury by an attending surgeon (n = 1). Supplementary Tables 1–4 show the results of the subgroup analysis in pediatric patients.

Discussion

In this study, we analyzed 63 judicial precedents associated with endotracheal intubation complications in the Korean court system. The main finding was that the majority of cases were related to delayed intubation, and the most common type of malpractice recognized by the court was that of no attempt of alternative air-

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Table 3. Detailed Information of the Cases Related to Delayed or Failed Intubation

Characteristics	Total (n = 58)
Failed intubation	2 (3.4)
Predictors of difficult tracheal intubation	43 (74.1)
Airway obstruction from any cause	33* (56.9)
Limited mouth opening	13 (22.4)
Short neck	12 (20.7)
Secretions/blood in airway	5 (8.6)
History of cervical operation	3 (5.2)
History of cervical irradiation	1 (1.7)
Swollen tongue	2 (3.4)
Mallampati grade III or IV	1 (1.7)
Number of predictors (0/1/≥2)	15 (25.9)/21 (36.2)/ 22 (37.9)
Department of the first intubation attempter (Anesthesiologist/Internal medicine doctor/ Emergency medicine doctor/Pediatrician/Others/Not described)	18[†] (31.0)/10 (17.2)/6 (10.3)/3 (5.2)/9[‡] (15.5)/11 (19.0)
Calling for help	14 (24.1)
Number of endotracheal intubation attempts (1/2/≥3/Not described)	7 (12.1)/14 (24.1)/34 (58.6)/3 (5.2)
Alternative airway intervention (Tracheostomy/Cricothyroidotomy/Supraglottic airway device)	11 (19.0)/5 (8.6)/3 (5.2)
Duration from the determination of intubation to airway securement (min)[§]	20 (14, 35)

Values are presented as median (Q1, Q3) or number (%). *Causes of airway obstruction: upper airway edema, n = 21 (36.2); neck abscess, n = 5 (8.6); neck hematoma, n = 5 (8.6); tracheal stenosis, n = 2 (3.4). [†]Received a request for help in 3 cases. [‡]General physician, n = 4 (6.9); neurosurgeon, n = 2 (3.4); orthopedic surgeon, n = 1 (1.7); obstetrician, n = 1 (1.7); family medicine doctor, n = 1 (1.7). [§]Two failed intubation cases were excluded.

Table 4. Judicial Characteristics

Characteristics	Total (n = 63)
Claim conclusion	
Dismissal/Settlement/Recognition of violation	12 (19.0)/11 (17.5)/40 (63.5)
Violation of the duty of care (contended by plaintiffs/recognized by the court)	
No attempt of alternative airway technique	47 (74.6)/32 (50.8)
Physician inexperience	15 (23.8)/8 (12.7)
No confirmation of endotracheal intubation	9 (14.3)/7 (11.1)
Inappropriate tube size	7 (11.1)/6 (9.5)
Pulmonary aspiration	4 (6.3)/4 (6.3)
Upper airway trauma	4 (6.3)/2 (3.2)
Absence of intubation instruments*	2 (3.2)/1 (1.6)
Inappropriate management of bronchospasm	1 (1.6)/1 (1.6)
Violation of the duty of explanation related to complications following intubation (contended by plaintiffs/recognized by the court)	19 (30.2)/10 (15.9)
Amount for damage—Korean Won	
Claims of plaintiffs (n = 63)	393,759,292 (162,046,444, 699,732,701)
Recognition of the court (n = 51)	133,897,845 (38,000,000, 308,538,274)

Values are presented as median (Q1, Q3) or number (%). *No endotracheal tube, n = 1 (1.6); no endotracheal tube for pediatric patient, n = 1 (1.6).

way technique, followed by violation of the duty of explanation. All but 3 cases were associated with major permanent injuries, and approximately 50% of the patients died. To the best of our knowledge, this is the first study to focus on malpractice cases related to endotracheal intubation in South Korea, providing important information to mitigate medical liability and ensure patient safety.

In South Korea, there have been 2 closed claims analyses related to this issue in the field of anesthesiology. According to the analyses of anesthesia-related medical disputes using the Korean Society of Anesthesiologists database, >50% of the anesthesia-related disputes were associated with airway management [8,9]. However,

only 11 of the 182 cases were associated with endotracheal intubation itself, and no further analysis was performed regarding this issue. Unlike these studies, our study focused on the adverse events related to endotracheal intubation itself, including events occurring in other medical disciplines in addition to anesthesiology, since physicians from any discipline can encounter an emergency situation requiring endotracheal intubation.

In other countries, previous medicolegal studies on malpractice related to endotracheal intubation have been reported [7,10,11]. According to a recent analysis of the anesthesia closed claims database in the United States regarding difficult tracheal intubation between 2000 and 2012, inappropriate management of a difficult airway was identified in 73% (71/97) cases [7]. The malpractices identified in that study were failure to use a supraglottic airway device as a bridge, perseveration (defined as ≥ 2 attempts using the same method), delay in surgical airway management, inadequate preoperative or airway evaluation, and lack of backup plan for difficult tracheal intubation. In a study of the UK national audit database regarding major complications associated with airway management, the majority of cases were found to occur during anesthesia (133/184, 72.3%), while the remaining cases occurred in the intensive care unit and emergency department [10]. In this study, the most common airway problems during anesthesia were related to tracheal intubation including delayed or difficult intubation, failed intubation, and 'can't intubate can't ventilate' (CICV) scenarios, which accounted for 39% of all events [10]. Another closed claims analysis of airway and respiratory complications associated with anesthesia in the UK, between 1995 and 2007, reported that airway-related claims had high fatality rates, and the most common claims were associated with airway trauma, primarily during tracheal intubation [11]. As in previous studies, the cases included in our study showed a high fatality rate, most of which were associated with delayed intubation.

In our study, the most common types of malpractice contended by plaintiffs and recognized by the court were that of no attempt of alternative airway technique. In the cases related to delayed or failed intubation, there were ≥ 3 laryngoscopic attempts in approximately 60% of cases. Repetitive attempts can worsen intubation conditions and delay intubation [12]. Moreover, repetitive attempts are reportedly associated with patient morbidity [13,14]. Therefore, the difficult airway society (DAS) guideline recommends limiting the number of laryngoscopic attempts to 3, suggesting the use of a SAD as the next step [15,16]. SADs can be useful in rescue airway due to their reported high success rate in difficult airway situations [17,18]. However, in our study, a SAD was used or attempted in only 5.2% of cases, which was lower than the rate of surgical airway management. In a large retrospective study using the Danish anesthesia database, it was reported that SADs were only used or attempted in 12.4% of difficult airway situations despite their prominent role in difficult airway management guidelines [19]. In a Japanese nationwide study of the adequacy of resource availability in difficult airway management in the emergency department, SAD availability was approximately 50%, and the main reasons for its limited use were the preference for surgical airway management, lack of familiarity, and the misconception that a SAD would not be useful in an emergency situation [20]. Since our study could not identify the reason for the low rate of SAD use in difficult airway situations, further studies regarding its availability in South Korea are required.

Additionally, if a difficult airway is expected, physicians should be prepared to perform rescue airway techniques following failure of the primary method [12]. Although the predictors of difficult tracheal intubation were noted in 74.1% of the cases related to delayed or failed intubation, alternative airway techniques were used only in approximately 33% of cases, and other instruments such as fiberoptic bronchoscopes and video laryngoscopes, which can be useful in difficult airway situation [21,22], were not used. It is reported that anesthesiologists tend to adhere to the routine method even if difficult tracheal intubation is anticipated, in which case the probability of proceeding to the CICV situation state is > 60% [3,12]. Therefore, along with risk assessment for difficult tracheal intubation, preparation for alternative airway methods is required when difficult tracheal intubation is anticipated. In addition, in hospital, alternative methods such as SADs and cricothyroidotomy kits should be available for emergency situations in which risk assessment might be difficult.

Violations of the duty of explanation was the second most common type of malpractice contended by plaintiffs and recognized by the court. To avoid such malpractice, the anesthesiologist should be aquainted with the following aspects. First, according to the Medical Service Act in Korea, possible complications related to the scheduled procedures should be notified to the patient in advance [23]. Therefore, for scheduled intubation, such as general anesthesia, detailed information of its possible complications should be provided to the patient. Second, medical personnel other than physicians are not allowed to perform the duty of explanation in the place of physicians [23]. Additionally, even if the possible complications are explained by a physician, it could be recognized as a violation of the duty of explanation if the explanation is insufficient. In this study, the explanation of possibile tooth injury without prior dental evaluation and explanation of possible alternative methods to avoid it by an attending surgeon was recog-

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nized as violation of the duty of explanation. Third, the duty of explanation can be exempted in the case of an emergency [23]. In this study, the violation of the duty of explanation was not recognized as malpractice when the endotracheal intubation was conducted in an unexpected emergency.

Physician inexperience was the third most common type of malpractice contended by plaintiffs and recognized by the court. There is a learning curve for successful endotracheal intubation, and previous studies have reported that > 50 endotracheal intubation procedures were required for a success rate of > 90% [24,25]. However, as it is difficult for non-anesthesiologists to gain sufficient experience in tracheal intubation [26], institutional policies such as anesthesiology-based airway training for non-anesthesiologists are needed to compensate for this problem [27]. There is also a need for education on alternative airway techniques such as SADs and videolaryngoscopes that can increase the success rate for inexperienced physicians in difficult airway situations [28,29].

We also performed a subgroup analysis in pediatric patients. The most common types of malpractice contended by plaintiffs and recognized by the court in these patients were that of no attempt of alternative airway techniques and no use of SAD in cases related to delayed intubation. In addition, we were able to identify predictors of difficult tracheal intubation in only about half of pediatric patients. There could be technical airway difficulties in pediatric patients as their airway anatomy is different from that of adults [30]. Therefore, prediction of difficult tracheal intubation might be more important in these patients, and alternative airway techniques such as SADs should be prepared, even if there are no such predictive factors. SADs were also recommended for rescue airway according to the guideline for unanticipated difficult airway in pediatric patients [31].

There are several limitations to this study. First, since our data were skewed toward rare and severe complications due to the nature of the study, our cases did not represent the comprehensive features of endotracheal intubation. Second, the clinical information described in the precedent text was limited, particularly in dismissed cases. Third, despite the relatively long study period (26 years), we could not investigate the temporal trends of malpractices related to tracheal intubation due to the small number of cases. One retrospective study reported the decline in the incidence of difficult tracheal intubation over a 14-year period, and this result might be due to advances in airway management [32]. Fourth, the amount of compensatory damage could not represent the magnitude of the malpractice, since it was determined not only by the degree of disability and malpractice but also by the loss of wages considering a patient's life expectancy and expected salary. Further, it should also be considered that the amount of compensatory damages has been increasing with the recent uplift of the maximum working age (60 to 65 years) and the increase in hospital liability ratio judged by the court [33]. Lastly, since there was no description regarding the CICV state in the judicial precedents, we found it difficult to judge compliance with the DAS guideline in each case [15]. Despite these limitations, our findings provide useful information on rare but severe complications and consequently improve patient safety.

In conclusion, physicians should be prepared to avoid serious adverse events that may arise from delay in or failure of endotracheal intubation. To this end, physicians should be well-acquainted with the latest difficult airway guideline [15], able to predict difficult airways, and proficient in alternative airway methods. Additionally, the necessary infrastructure should be readily available in difficult airway situations. Through this study, we hope to increase physicians' awareness of the severe complications associated with endotracheal intubation to prevent medical liability.

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Conflicts of Interest

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

Author Contributions

Hye-Yeon Cho (Data curation; Formal analysis; Writing – original draft)
SuHwan Shin (Data curation; Formal analysis; Writing – review & editing)
SangJin Lee (Data curation; Formal analysis)
Susie Yoon (Data curation; Writing – review & editing)
Hojin Lee (Conceptualization; Formal analysis; Supervision; Writing – original draft; Writing – review & editing)

Supplementary Materials

Supplementary Table 1. General characteristics of the cases in pediatric patients
Supplementary Table 2. Type of alleged problems in pediatric patients
Supplementary Table 3. Detailed information of the cases related

to delayed or failed intubation in pediatric patients
Supplementary Table 4. Judicial characteristics in pediatric patients

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References

1. Artime CA, Hagberg CA. Airway management in the adult. In: Miller's Anesthesia. 9th ed. Edited by Gropper MA, Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Cohen NH, et al.: Philadelphia, Elsevier. 2019, pp 1373-412.
2. Metzner J, Posner KL, Lam MS, Domino KB. Closed claims' analysis. Best Pract Res Clin Anaesthesiol 2011; 25: 263-76.
3. Peterson GN, Domino KB, Caplan RA, Posner KL, Lee LA, Cheney FW. Management of the difficult airway: a closed claims analysis. Anesthesiology 2005; 103: 33-9.
4. Kim J, Shin S, Jeong Y, Kim SY, Lee HJ. Medicolegal consideration to prevent medical malpractice regarding opioid administration: an analysis of judicial opinion in South Korea. J Pain Res 2020; 13: 1525-32.
5. Cho SI, Shin S, Jung H, Moon JY, Lee HJ. Analysis of judicial precedent cases regarding epidural injection in chronic pain management in Republic of Korea. Reg Anesth Pain Med 2020; 45: 337-43.
6. Sowka MP. The medical malpractice closed claims study. Conducted by the National Association of Insurance Commissioners. Conn Med 1981; 45: 91-101.
7. Joffe AM, Aziz MF, Posner KL, Duggan LV, Mincer SL, Domino KB. Management of difficult tracheal intubation: a closed claims analysis. Anesthesiology 2019; 131: 818-29.
8. Roh WS, Kim DK, Jeon YH, Kim SH, Lee SC, Ko YK, et al. Analysis of anesthesia-related medical disputes in the 2009-2014 period using the Korean Society of Anesthesiologists database. J Korean Med Sci 2015; 30: 207-13.
9. Choi JW, Kim DK, Cho CK, Park SJ, Son YH. Trends in medical disputes involving anesthesia during July 2009-June 2018: an analysis of the Korean Society of Anesthesiologists database. Korean J Anesthesiol 2019; 72: 156-63.
10. Cook TM, Woodall N, Frerk C; Fourth National Audit Project. Major complications of airway management in the UK: results of the Fourth National Audit Project of the Royal College of Anaesthetists and the Difficult Airway Society. Part 1: anaesthesia. Br J Anaesth 2011; 106: 617-31.
11. Cook TM, Scott S, Mihai R. Litigation related to airway and respiratory complications of anaesthesia: an analysis of claims against the NHS in England 1995-2007. Anaesthesia 2010; 65: 556-63.
12. Cook TM, MacDougall-Davis SR. Complications and failure of airway management. Br J Anaesth 2012; 109 Suppl 1: i68-85.
13. Mort TC. Emergency tracheal intubation: complications associated with repeated laryngoscopic attempts. Anesth Analg 2004; 99: 607-13.
14. Bernhard M, Becker TK, Gries A, Knapp J, Wenzel V. the first shot is often the best shot: first-pass intubation success in emergency airway management. Anesth Analg 2015; 121: 1389-93.
15. Frerk C, Mitchell VS, McNarry AF, Mendonca C, Bhagrath R, Patel A, et al. Difficult Airway Society 2015 guidelines for management of unanticipated difficult intubation in adults. Br J Anaesth 2015; 115: 827-48.
16. Higgs A, McGrath BA, Goddard C, Rangasami J, Suntharalingam G, Gale R, et al. Guidelines for the management of tracheal intubation in critically ill adults. Br J Anaesth 2018; 120: 323-52.
17. Parmet JL, Colonna-Romano P, Horrow JC, Miller F, Gonzales J, Rosenberg H. The laryngeal mask airway reliably provides rescue ventilation in cases of unanticipated difficult tracheal intubation along with difficult mask ventilation. Anesth Analg 1998; 87: 661-5.
18. Winterhalter M, Kirchhoff K, Gröschel W, Lüllwitz E, Heermann R, Hoy L, et al. The laryngeal tube for difficult airway management: a prospective investigation in patients with pharyngeal and laryngeal tumours. Eur J Anaesthesiol 2005; 22: 678-82.
19. Thomsen JL, Nørskov AK, Rosenstock CV. Supraglottic airway devices in difficult airway management: a retrospective cohort study of 658,104 general anaesthetics registered in the Danish Anaesthesia Database. Anaesthesia 2019; 74: 151-7.
20. Ono Y, Tanigawa K, Shinohara K, Yano T, Sorimachi K, Inokuchi R, et al. Human and equipment resources for difficult airway management, airway education programs, and capnometry use in Japanese emergency departments: a nationwide cross-sectional study. Int J Emerg Med 2017; 10: 28.
21. Aziz MF, Dillman D, Fu R, Brambrink AM. Comparative effectiveness of the C-MAC video laryngoscope versus direct laryngoscopy in the setting of the predicted difficult airway. Anesthesiology 2012; 116: 629-36.
22. Asai T. Videolaryngoscopes: do they truly have roles in difficult airways? Anesthesiology 2012; 116: 515-7.
23. Korea Ministry of Government Legislation. Easy to find, practi-

https://doi.org/10.4097/kja.21020

cal law: medical disputes [Internet]. Sejong (KR): Korea Ministry of Government Legislation; 2021 Feb 15 [updated 2021 Aug 15; cited 2021 Jan 17]. Available from http://www.easylaw.go.kr/CSP/CnpClsMain.laf?popMenu=ov&csmSeq=567&ccfNo=2&cciNo=2&cnpClsNo=1

24. Mulcaster JT, Mills J, Hung OR, MacQuarrie K, Law JA, Pytka S, et al. Laryngoscopic intubation: learning and performance. Anesthesiology 2003; 98: 23-7.
25. Konrad C, Schüpfer G, Wietlisbach M, Gerber H. Learning manual skills in anesthesiology: is there a recommended number of cases for anesthetic procedures? Anesth Analg 1998; 86: 635-9.
26. Trimmel H, Beywinkler C, Hornung S, Kreutziger J, Voelckel WG. In-hospital airway management training for non-anesthesiologist EMS physicians: a descriptive quality control study. Scand J Trauma Resusc Emerg Med 2017; 25: 45.
27. Grissom TE, Sappenfield J, Galvagno SM Jr, Cherry SV, Chang YC, Hu PF. Performance assessment in airway management training for nonanesthesiology trainees: an analysis of 4,282 airway procedures performed at a level-1 trauma center. Anesthesiology 2014; 120: 185-95.
28. Bielski A, Rivas E, Ruetzler K, Smereka J, Puslecki M, Dabrowski M, et al. Comparison of blind intubation via supraglottic airway devices versus standard intubation during different airway emergency scenarios in inexperienced hand: Randomized, crossover manikin trial. Medicine (Baltimore) 2018; 97: e12593.
29. Stroumpoulis K, Pagoulatou A, Violari M, Ikonomou I, Kalantzi N, Kastrinaki K, et al. Videolaryngoscopy in the management of the difficult airway: a comparison with the Macintosh blade. Eur J Anaesthesiol 2009; 26: 218-22.
30. Vutskits L, Davidson A. Pediatric anesthesia. In: Miller's Anesthesia. 9th ed. Edited by Gropper MA, Miller RD, Eriksson LI, Fleisher LA, Wiener-Kronish JP, Cohen NH, et al.: Philadelphia, Elsevier. 2019, pp 2423-4.
31. Black AE, Flynn PE, Smith HL, Thomas ML, Wilkinson KA; Association of Pediatric Anaesthetists of Great Britain and Ireland. Development of a guideline for the management of the unanticipated difficult airway in pediatric practice. Paediatr Anaesth 2015; 25: 346-62.
32. Schroeder RA, Pollard R, Dhakal I, Cooter M, Aronson S, Grichnik K, et al. Temporal trends in difficult and failed tracheal intubation in a regional community anesthetic practice. Anesthesiology 2018; 128: 502-10.
33. Lee DP. Current status of medical disputes, prospects and cautions. Korean J Med 2019; 94: 231-6.

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A comparison of adductor canal block before and after thigh tourniquet during knee arthroscopy: a randomized, blinded study

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Background: Adductor canal block (ACB) provides effective analgesia after arthroscopic knee surgery. However, there is insufficient data regarding whether ACB should be performed before or after inflation of a thigh tourniquet. We aimed to investigate the efficacy of ACB performed before and after placement of a thigh tourniquet and evaluate associated quadriceps motor weakness.

Methods: ACB was performed before tourniquet inflation in the PreT group, and it was performed after inflation in the PostT group. In the PO group, ACB was performed at the end of surgery after deflation of the tourniquet.

Results: There were no statistically significant differences between the groups in terms of demographic data. There was no statistically significant difference among the three groups in terms of total postoperative opioid consumption (P = 0.513). Patient satisfaction and the amount of rescue analgesia administered were also not significantly different between the groups. There was no significant difference in terms of static and dynamic visual analog scale scores between the groups (for 24 h: P = 0.306 and P = 0.271, respectively). The incidence of motor block was higher in the PreT group (eight patients) than in the PostT group (no patients) and the PO group (one patient) (P = 0.005).

Conclusions: Using a tourniquet before or after ACB did not result in differences in terms of analgesia quality; however, applying a tourniquet immediately after ACB may lead to quadriceps weakness.

Keywords: Conduction anesthesia; Knee joint; Nerve block; Postoperative pain; Tourniquets; Ultrasonography.

Introduction

Arthroscopic knee surgery is a routine orthopedic procedure performed to repair meniscal tears, debride/reshape cartilage flaps, and reconstruct ligaments [1–3]. Although it is a minimally invasive procedure, patients may experience moderate-to-severe pain due to port-site incision and surgical trauma to the knee ligaments [3]. Pain after arthroscopic knee surgery not only results in patient dissatisfaction but may also cause delayed mobilization. Therefore, it is important to effectively manage postoperative pain [3–5]. Analgesia after this type of surgery can be the most effective using a peripheral nerve block as

part of a multimodal analgesia regimen. Peripheral nerve blocks such as femoral nerve blocks or adductor canal blocks (ACBs) may be an option for pain management [6–8]. However, motor blockade of the quadriceps muscle after a femoral nerve block may create a potential risk of falls [9].

The adductor canal is a musculoaponeurotic tunnel that functions as a passageway for neurovascular structures (such as the femoral artery, femoral vein, saphenous nerve, and nerve to the vastus medialis) from the femoral triangle to the adductor hiatus [10]. Selective blockade of the saphenous nerve in the adductor canal provides effective analgesia after surgical knee procedures [4–15]. Because the saphenous nerve is a sensory branch of the femoral nerve, its selective blockade has potential advantages over femoral block by avoiding motor blockade of the quadriceps muscle and providing early ambulation [16].

Thigh tourniquets are commonly used during knee surgeries to reduce intraoperative blood loss and improve surgical outcomes [17–19]. Although a thigh tourniquet was shown to significantly increase the proximal–distal distribution of radiopaque dye within the adductor canal in a cadaver study, there are insufficient data regarding the occurrence of quadriceps weakness after proximal spreading of the local anesthetic agent [18]. We hypothesized whether performing ACB before or after inflation of a thigh tourniquet may also affect the spread of the local anesthetic agent, which may affect analgesia quality and quadriceps weakness. Thus, our study aimed to investigate the ideal timing for ACB and whether it should be performed before or after application of a thigh tourniquet.

Materials and Methods

This randomized, prospective, exploratory study was approved by the ethics and research committee of Istanbul Medipol University (IRB number: 66291034-604.01.01-E.17567). After approval, the study was registered at ClinicalTrials.gov (registration number: NCT04010916). The Consolidated Standards of Reporting Trials (CONSORT) flow diagram was used for patient enrollment (Fig. 1). Written informed consent was obtained from all patients. The study was conducted between July 2019 and October 2020 at Medipol University Hospital. The study was conducted in accordance with the Helsinki Declaration-2013.

Ninety patients aged 18–65 years with American Society of Anesthesiologists (ASA) physical status classification I and II who were scheduled for unilateral arthroscopic knee surgery were enrolled in the study. Patients with a history of bleeding diathesis; patients who were pregnant or breastfeeding; patients with a history of anticoagulant treatment, allergy to local anesthetic or opioids, or infections at the site of block performance; and patients

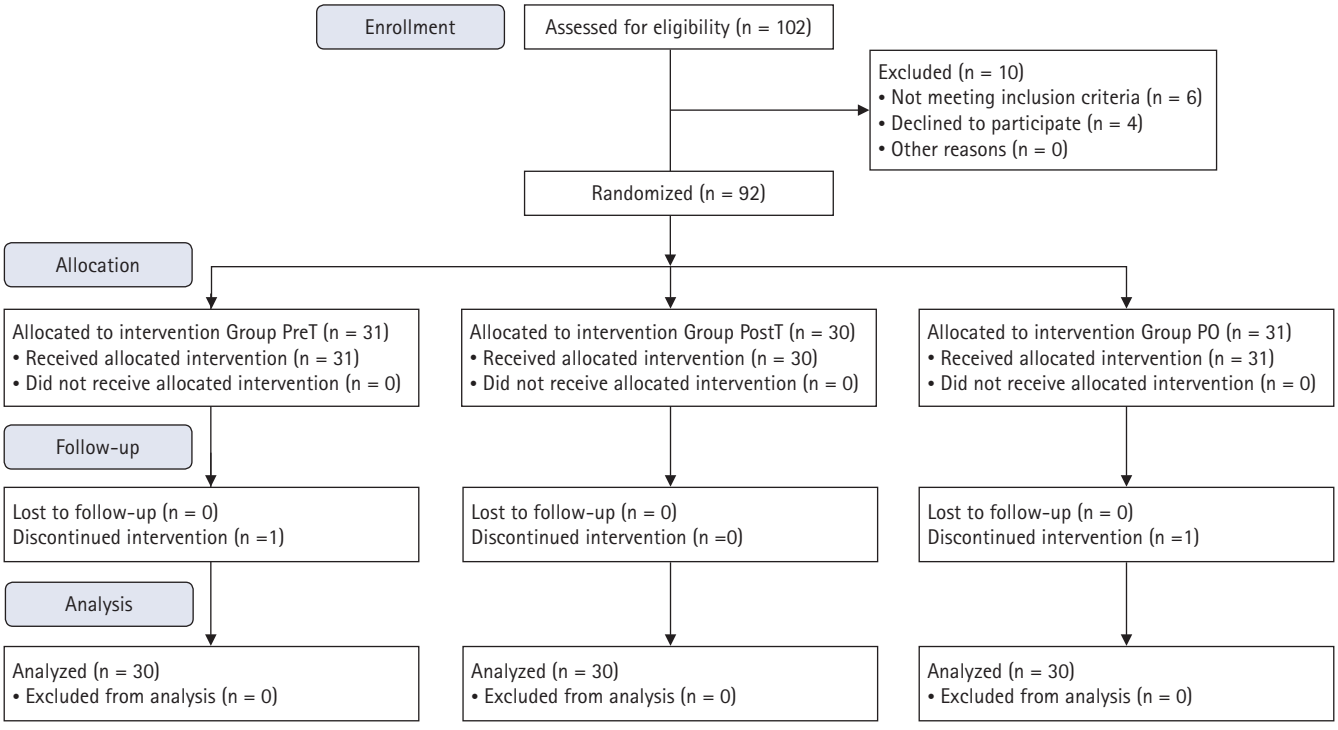

Fig. 1. CONSORT flow diagram of the study.

who refused block performance were excluded from the study. Using a computerized randomization program, the patients were equally divided into three groups (n = 30 in each group) according to the timing of ACB performance—the pre-tourniquet ACB group (PreT group), the after-tourniquet ACB group (PostT group), and the postoperative ACB group (PO group).

General anesthesia

After standard ASA monitoring in the operating room (electrocardiography, noninvasive blood pressure, and pulse oximetry [SpO_2]) and premedication with 2 mg of intravenous (IV) midazolam, anesthesia induction was performed with IV propofol (2–2.5 mg/kg), fentanyl (1–1.5 μg/kg), and rocuronium bromide (0.6 mg/kg). Sevoflurane in a mixture of 50% air–oxygen with 2–3 L/min of fresh gas flow was used to maintain anesthesia. Analgesia was provided with a remifentanil infusion at a rate of 0.01–0.1 μg/kg/min during surgery. In cases of increased heart rate and mean arterial pressure above the baseline level, fentanyl (1 μg/kg) was administered. All personnel in the operating room were blinded to patient randomization. All surgical procedures were performed by the same surgical team using the same technique. At the end of surgery, the neuromuscular blockade was antagonized using IV atropine (0.01 mg/kg) and neostigmine (0.05 mg/kg). The patients were extubated after exhibiting sufficient spontaneous respiration and were transferred to the post-anesthesia care unit (PACU). After attaining a modified Aldrete score of ≥ 9, the patients were discharged from the PACU.

Adductor canal block procedure

After general anesthesia, all blocks were performed under ultrasound (US) guidance (Vivid q US device, GE Healthcare, USA) with a high-frequency (12 mHz) linear US probe and a 22 G, 50 mm block needle Stimuplex Ultra 360; B. Braun, Germany). While ACB was performed before tourniquet inflation in the PreT group, it was performed after inflation of the tourniquet in the PostT group. In the PO group, ACB was performed at the end of surgery after deflation of the tourniquet. The participants were unaware of their group assignments.

- PreT group: ACB was performed preoperatively, before inflation of the tourniquet. The thigh tourniquet was inflated immediately after performing ACB.
- PostT group: ACB was performed preoperatively, after inflation of the tourniquet.
- PO group: ACB was performed postoperatively after deflation of the tourniquet.

The thigh tourniquet was inflated to 250–300 mmHg on the proximal aspect of the thigh using an electronic tourniquet system, supported with an Esmarch bandage, and was applied during surgery [16,17].

The US probe was placed at the mid-thigh, half the distance between the inguinal crease and the patella, and the adductor canal was identified (Fig. 2). After visualization of the pulsatile superficial femoral artery dorsal to the sartorius muscle, the probe was moved distally. At this level, the saphenous nerve was visualized as a hyperechoic structure lateral–anterior to the artery in the

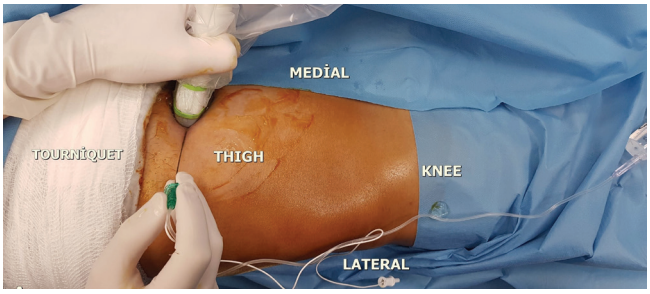

Fig. 2. Probe, needle, tourniquet, and patient position.

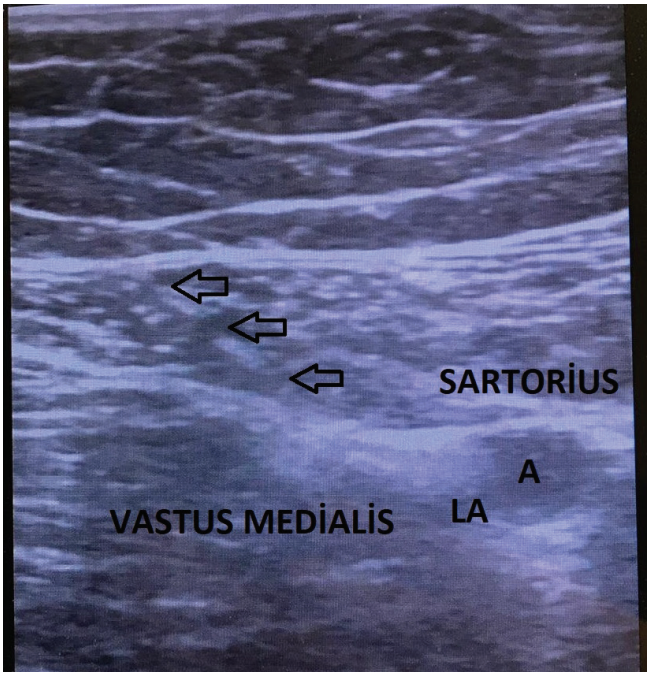

Fig. 3. Sonographic anatomy for block procedure. Needle direction and spread of local anesthetic during block performance. Arrows indicate the needle. A: artery, LA: local anesthetic.

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subsartorial region [4,5,11]. Using the in-plane technique, the injection site was confirmed with an injection of 5 ml of saline, and then 30 ml of 0.25% bupivacaine was injected (Fig. 3).

Outcomes and assessments—postoperative analgesia management, dermatomal testing, and motor block evaluation

The primary outcome was postoperative (24 h) opioid consumption, and the secondary outcomes were postoperative pain scores (visual analog scale [VAS] scores), quadriceps motor blockade, and adverse effects related to opioids (e.g., allergic reaction, nausea, and vomiting).

A standardized postoperative pain management protocol was used in this study. Twenty minutes before the end of surgery, IV ibuprofen 400 mg and IV tramadol 100 mg were administered. IV ibuprofen 400 mg was administered every 8 h in the postoperative period. A patient-controlled analgesia pump administering only fentanyl (10 μg/ml) was provided to all patients with a 2 ml bolus, no background infusion, a lockout time of 20 min, and a 4 h limit. Pain evaluation was performed using the VAS (0 = no pain, 10 = most severe pain). Static (at rest) and dynamic (during mobilization) VAS scores were recorded at 0 (PACU) and 2, 4, 8, 16, and 24 h postoperatively. If the VAS score was ≥ 4 with the routine analgesia protocol, only meperidine (0.5 mg/kg) IV was administered as a rescue analgesic. Postoperative opioid consumption was evaluated and recorded at 0–8, 8–16, and 16–24 h time intervals. Any opioid-related adverse effects, such as nausea, vomiting, or itching, were also recorded. The outcomes were evaluated and recorded by a single pain nurse anesthetist who was blinded to the study.

Dermatomal testing was performed using a pinprick sensation test 20 min after surgery along the field of the saphenous nerve (the medial infrapatellar region and the medial malleolus) by an anesthesiologist who did not participate in the study. The loss of sensation in the corresponding area is considered a successful block [4]. A single motor block evaluation was performed 20 min after surgery by an orthopedic surgeon who was blinded to the study. For motor block evaluation, the patient was asked to extend the knee from full flexion, and the block was classified as grade 0 (normal muscle power), grade I (motor weakness), or grade II (complete motor paralysis) [20].

Sample size calculation and statistical analyses

The primary aim of the study was to compare fentanyl consumption within 24 h postoperatively between the three groups. To determine the required sample size, a preliminary study was performed with 30 patients. While the mean fentanyl consumption was around 48 ± 16.8 μg in the PreT group (n = 10), it was 32 ± 13.9 μg in the PostT group (n = 10) and 36 ± 24.5 μg in the PO group (n = 10). For total opioid consumption, a sample size of 81 was calculated using G*Power (version 3.1.9.2, Germany) with an alpha probability of 0.05, a power of 0.95, and a medium-to-large effect size (0.4) [21]. Considering possible dropouts, we included 30 patients in each group to attain a higher power for a total of 90 patients.

Statistical analysis was performed using IBM SPSS ver. 20.0 (IBM SPSS Statistics Inc., USA) software package. The normality of variable distributions was assessed using the Kolmogorov–Smirnov test and histograms. Descriptive data are expressed as mean ± standard deviation (SD) or median [interquartile range (Q1, Q3)]. Categorical variables were analyzed using the Pearson's chi-square test. Normally distributed data comprising continuous variables were analyzed using one-way analysis of variance, and non-normally distributed data comprising continuous variables were analyzed using the Kruskal–Wallis test to determine differences between groups. A P value of < 0.05 was considered statistically significant.

Results

Fig. 1 shows the CONSORT flow diagram, which describes the patients enrolled in the study. This randomized study included 90 patients, with 30 patients in each of the three groups (PreT, PostT, and PO groups). There were no statistical differences between the groups in terms of demographic data, anesthesia duration, or length of surgery (Table 1). ACB was successfully achieved in all patients.

Opioid consumption, the primary outcome of the study, was not significantly different between the groups at any time interval (for total consumption; P = 0.513). The total consumption was 40 μg (20–60 μg) in the PreT group, 40 μg (20–40 μg) in the PostT group, and 40 μg (20–60 μg) in the PO group. The number of patients who received rescue analgesia (17 patients in the PreT group, 15 patients in the PostT group, and 18 patients in the PO group) and patient satisfaction were also not significantly different between the groups (Table 2). In addition, there was no significant difference in static and dynamic VAS scores between the groups (for 24 h; P = 0.306 and P = 0.271, respectively) (Table 3).

The incidence of motor block grade II was higher in the PreT group (eight patients) than in the PostT group (no patients) and the PO group (one patient; P = 0.005) (Table 4). The postoperative incidence of opioid-related side effects was also not significantly different between the groups (Table 4).

Table 1. Demographic Data and Durations of Surgery/Anesthesia in Different Groups

Variable	PreT group (n = 30)	PostT group (n = 30)	PO group (n = 30)	P value
Age (yr)	40.2 ± 11.30	39.8 ± 9.6	38.7 ± 10.7	0.856
Weight (kg)	77.2 ± 8.2	76.7 ± 10.7	74.4 ± 11.8	0.529
Height (cm)	172.7 ± 6.5	172.4 ± 8.8	168.4 ± 9.7	0.093
Sex (M/F)	18/12	16/14	14/16	0.585
ASA (I/II)	17/13	22/8	17/13	0.307
Duration of surgery (min)	71.4 ± 15.7	70.6 ± 15.8	68.7 ± 19.8	0.819
Duration of anesthesia (min)	81.7 ± 15.2	83.0 ± 18.6	77.6 ± 21.9	0.507

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

Table 2. Comparison of Opioid Consumption and Use of Rescue Analgesia between the Groups

Opioid consumption and patient satisfaction	PreT group (n = 30)	PostT group (n = 30)	PO group (n = 30)	P value
0–8 h (μg)	0 (0, 20)	0 (0, 20)	0 (0, 20)	0.114
8–16 h (μg)	20 (20, 40)	20 (0, 20)	20 (20, 40)	0.221
16–24 h (μg)	0 (0, 20)	0 (0, 20)	0 (0, 20)	0.318
Total consumption (μg)	40 (20, 60)	40 (20, 40)	40 (20, 60)	0.513
Rescue analgesia	17	15	18	0.730
Patient satisfaction (medium/good/excellent)	6/18/6	4/10/16	4/16/10	0.104

Values are presented as median (Q1, Q3) or number of patients.

Table 3. Comparison of Postoperative Resting and Dynamic Visual Analog Scale Scores between the Groups

VAS	PreT group (n = 30)	PostT group (n = 30)	PO group (n = 30)	P value
Rest				
PACU	1 (1, 3)	2 (1, 2)	2 (1, 3)	0.562
2 h	2 (1, 3)	2 (2, 2)	2 (2, 3)	0.146
4 h	1 (1, 2)	2 (1, 2)	2 (1, 2)	0.160
8 h	2 (1, 2)	2 (1, 2)	2 (1, 2)	0.064
16 h	1 (0, 1)	1 (1, 1)	1 (0, 1)	0.286
24 h	0 (0, 1)	0 (0, 1)	0 (0, 0)	0.306
Dynamic				
PACU	2 (2, 4)	3 (2, 3)	3 (2, 4)	0.143
2 h	3 (2, 4)	3 (2, 3)	3 (3, 4)	0.125
4 h	2 (2, 2)	2 (2, 3)	3 (2, 3)	0.071
8 h	3 (2, 4)	3 (3, 4)	3 (2, 4)	0.084
16 h	1 (1, 2)	2 (1, 2)	2 (1, 2)	0.140
24 h	0 (0, 1)	0 (0, 1)	0 (0, 1)	0.271

Values are presented as median (Q1, Q3). VAS: visual analog scale, PACU: post-anesthesia care unit.

Table 4. Comparison of the Incidence of Opioid-related Side Effects and Postoperative Duration of Motor Block between the Groups

Side effects, Motor block	PreT group (n = 30)	PostT group (n = 30)	PO group (n = 30)	P value
Nausea (Y/N)	9/21	5/25	8/22	0.457
Vomiting (Y/N)	3/27	3/27	5/25	0.661
Itching (Y/N)	2/28	1/29	2/28	0.809
Motor block (0/1/2)	15/7/8	23/7/0	21/8/1	0.013

Values are presented as number of patients. Y: yes, N: no. Motor block 0: normal muscle power, 1: motor weakness, 2: complete motor paralysis.

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Discussion

The present study evaluated the efficacy of ACB before and after thigh tourniquet inflation in patients undergoing arthroscopic knee surgery. The results of this study showed no differences between groups in terms of either opioid consumption or pain scores. According to our results, applying a thigh tourniquet immediately after ACB contributes to the occurrence of motor blockade.

Local anesthetic agent distribution through the adductor canal is crucial because it may affect both analgesic efficacy and quadriceps weakness in ACB. The distribution of local anesthetic agents to distal locations (popliteal fossa) through the adductor canal may affect the analgesic efficacy of ACB after knee surgery [22]. The adductor canal extends to the apex of the femoral triangle; therefore, larger volumes of local anesthetic agents or continuous infusion may result in blockade of the femoral nerve [18,23]. The possible predictive factors in the distribution of local anesthetic agents include the injection location, the volume of local anesthetic agent, and whether the local anesthetic agent is given as a bolus or continuous infusion [22,24]. In a study investigating the distribution of the injectate and sensory-motor blockade, Gautier et al. [22] found that 20 ml of the local anesthetic resulted in spread into the popliteal fossa. In contrast, Andersen et al. [19] found that 15 ml of dye was sufficient to spread both proximally and distally through the adductor canal. Jaeger et al. [23] attempted to find the minimum effective volume (dose) of lidocaine 1% to fill the adductor canal and concluded that the minimum effective dose was 20 ml. According to Jaeger et al. [23], there was no correlation between the volume, proximal spread, and muscle strength. Anatomical differences and the fascia associated with the adductor canal may be predictors of the spread of local anesthetics. The similarity between these studies is that none involved the use of a tourniquet. However, the presence of a thigh tourniquet may be another factor that can affect local anesthetic or dye distribution. Nair et al. [18] investigated the effect of a thigh tourniquet on the distribution of local anesthetic within the adductor canal and found a combined superior–inferior dye distribution in cadavers. In the study, Nair et al. injected 25 ml of radio-opaque dye into the adductor canal and applied the tourniquet immediately after the ACB to simulate clinical practice. They found that tourniquets significantly increased the dye distribution proximally and distally. In the cadaveric study, Nair et al. concluded that the pressure created by the tourniquet may have increased the spread of the local anesthetic within the adductor canal.

As an explanation for quadriceps weakness in the PreT group, the pressure of the tourniquet inflated immediately after performing ACB may increase the spread of the local anesthetic within the adductor canal proximally and distally. Our results support the findings of the cadaveric study performed by Nair et al. [18]. This may be a result of the spread of local anesthetic to the motor fibers of the femoral nerve throughout the adductor canal.

This study has some limitations. First, we measured the motor block only once, 20 min after surgery. It would be optimal to determine the duration of motor weakness after surgery. Second, the assessment of motor weakness was subjective in nature. Future studies should utilize objective motor weakness testing. Lastly, because we tested motor function just 20 min after surgery, and the reversal of muscle relaxation was not confirmed, residual relaxation by intraoperatively administered muscle relaxants may have affected the outcome of motor function assessment.

In conclusion, using a tourniquet before or after ACB or performing ACB at the end of surgery after deflation of the tourniquet did not result in differences in terms of analgesia; however, applying a tourniquet immediately after ACB may lead to motor blockade. Further studies with lower volumes of analgesics are required to confirm our findings.

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None.

Conflicts of Interest

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

Author Contributions

Mursel Ekinci (Conceptualization; Investigation; Methodology; Visualization; Writing – original draft)
Bahadır Çiftçi (Conceptualization; Data curation; Investigation; Methodology; Supervision; Visualization; Writing – original draft)
Yavuz Demiraran (Conceptualization; Methodology; Visualization; Writing – review & editing)
Erkan Cem Celik (Conceptualization; Data curation; Formal analysis; Investigation; Software)
Murat Yayik (Conceptualization; Data curation; Investigation; Methodology)
Burak Omur (Conceptualization; Investigation; Methodology)
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References

1. Kim S, Bosque J, Meehan JP, Jamali A, Marder R. Increase in outpatient knee arthroscopy in the United States: a comparison of National Surveys of Ambulatory Surgery, 1996 and 2006. J Bone Joint Surg Am 2011; 93: 994-1000.
2. Lohmander LS, Thorlund JB, Roos EM. Routine knee arthroscopic surgery for the painful knee in middle-aged and old patients--time to abandon ship. Acta Orthop 2016; 87: 2-4.
3. Rahimzadeh P, Faiz HR, Imani F, Hobika GG, Abbasi A, Nader ND. Relieving pain after arthroscopic knee surgery: ultrasound-guided femoral nerve block or adductor canal block? Turk J Anaesthesiol Reanim 2017; 45: 218-24.
4. Hanson NA, Derby RE, Auyong DB, Salinas FV, Delucca C, Nagy R, et al. Ultrasound-guided adductor canal block for arthroscopic medial meniscectomy: a randomized, double-blind trial. Can J Anaesth 2013; 60: 874-80.
5. Kejriwal R, Cooper J, Legg A, Stanley J, Rosenfeldt MP, Walsh SJ. Efficacy of the adductor canal approach to saphenous nerve block for anterior cruciate ligament reconstruction with hamstring autograft: a randomized controlled trial. Orthop J Sports Med 2018; 6: 2325967118800948.
6. Dong CC, Dong SL, He FC. Comparison of adductor canal block and femoral nerve block for postoperative pain in total knee arthroplasty: a systematic review and meta-analysis. Medicine (Baltimore) 2016; 95: e2983.
7. Zhao XQ, Jiang N, Yuan FF, Wang L, Yu B. The comparison of adductor canal block with femoral nerve block following total knee arthroplasty: a systematic review with meta-analysis. J Anesth 2016; 30: 745-54.
8. Li D, Yang Z, Xie X, Zhao J, Kang P. Adductor canal block provides better performance after total knee arthroplasty compared with femoral nerve block: a systematic review and meta-analysis. Int Orthop 2016; 40: 925-33.
9. Ilfeld BM, Duke KB, Donohue MC. The association between lower extremity continuous peripheral nerve blocks and patient falls after knee and hip arthroplasty. Anesth Analg 2010; 111: 1552-4.
10. Burckett-St Laurant D, Peng P, Girón Arango L, Niazi AU, Chan VW, Agur A, et al. The nerves of the adductor canal and the innervation of the knee: an anatomic study. Reg Anesth Pain Med 2016; 41: 321-7.
11. Manickam B, Perlas A, Duggan E, Brull R, Chan VW, Ramlogan R. Feasibility and efficacy of ultrasound-guided block of the saphenous nerve in the adductor canal. Reg Anesth Pain Med 2009; 34: 578-80.
12. Jiang X, Wang QQ, Wu CA, Tian W. Analgesic efficacy of adductor canal block in total knee arthroplasty: a meta-analysis and systematic review. Orthop Surg 2016; 8: 294-300.
13. Lund J, Jenstrup MT, Jaeger P, Sørensen AM, Dahl JB. Continuous adductor-canal-blockade for adjuvant post-operative analgesia after major knee surgery: preliminary results. Acta Anaesthesiol Scand 2011; 55: 14-9.
14. Vora MU, Nicholas TA, Kassel CA, Grant SA. Adductor canal block for knee surgical procedures: review article. J Clin Anesth 2016; 35: 295-303.
15. Arora S, Sadashivappa C, Sen I, Sahni N, Gandhi K, Batra YK, et al. Comparação do bloqueio do canal adutor para analgesia em cirurgia artroscópica com ropivacaína isolada e ropivacaína + clonidina [Comparison of adductor canal block for analgesia in arthroscopic surgery with ropivacaine alone and ropivacaine and clonidine]. Braz J Anesthesiol 2019; 69: 272-8.
16. Jaeger P, Nielsen ZJ, Henningsen MH, Hilsted KL, Mathiesen O, Dahl JB. Adductor canal block versus femoral nerve block and quadriceps strength: a randomized, double-blind, placebo-controlled, crossover study in healthy volunteers. Anesthesiology 2013; 118: 409-15.
17. Andersen LØ, Husted H, Otte KS, Kristensen BB, Kehlet H. A compression bandage improves local infiltration analgesia in total knee arthroplasty. Acta Orthop 2008; 79: 806-11.
18. Nair A, Dolan J, Tanner KE, Kerr CM, Jones B, Pollock PJ, et al. Ultrasound-guided adductor canal block: a cadaver study investigating the effect of a thigh tourniquet. Br J Anaesth 2018; 121: 890-8.
19. Andersen HL, Andersen SL, Tranum-Jensen J. The spread of injectate during saphenous nerve block at the adductor canal: a cadaver study. Acta Anaesthesiol Scand 2015; 59: 238-45.
20. Taha AM, Abd-Elmaksoud AM. Lidocaine use in ultrasound-guided femoral nerve block: what is the minimum effective anaesthetic concentration (MEAC90)? Br J Anaesth 2013;

https://doi.org/10.4097/kja.21040

110: 1040-4.
21. Faul F, Erdfelder E, Lang AG, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007; 39: 175-91.
22. Gautier PE, Hadzic A, Lecoq JP, Brichant JF, Kuroda MM, Vandepitte C. Distribution of injectate and sensory-motor blockade after adductor canal block. Anesth Analg 2016; 122: 279-82.
23. Jæger P, Jenstrup MT, Lund J, Siersma V, Brøndum V, Hilsted KL, et al. Optimal volume of local anaesthetic for adductor canal block: using the continual reassessment method to estimate ED95. Br J Anaesth 2015; 115: 920-6.
24. Yuan SC, Hanson NA, Auyong DB, Choi DS, Coy D, Strodtbeck WM. Fluoroscopic evaluation of contrast distribution within the adductor canal. Reg Anesth Pain Med 2015; 40: 154-7.

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Comparison of the ulnar nerve blockade between intertruncal and corner pocket approaches for supraclavicular block: a randomized controlled trial

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Background: The corner pocket (CP) approach for supraclavicular block (SCB) prevents ulnar nerve (UN) sparing due to needle proximity to the lower trunk. Improved ultrasound resolution has suggested that the intertruncal (IT) approach is a suitable alternative method. We compared efficiency of these two approaches on the UN blockade.
Methods: Sixty patients were randomized to undergo SCB using the ultrasound-guided CP or IT approach. For lower trunk blockade, 10 ml of local anesthetic agents (1 : 1 mixture of 0.75% ropivacaine and 1% lidocaine) were injected in the CP (CP approach) or between the lower and middle trunks (IT approach). Additional 15 ml was injected identically to block the middle and upper trunks in both groups. Sensory and motor blockade was evaluated after intervention.
Results: Complete sensory blockade (75.9% [22/29] vs. 43.3% [13/30], P = 0.023) and complete motor blockade (82.8% [24/29] vs. 50.0% [15/30], P = 0.017) of the UN at 15 min after SCB were significantly more frequent in the IT than in the CP group. Sensory block onset time of the UN was significantly shorter in the IT compared to the CP group (15.0 [10.0, 15.0] min vs. 20.0 [15.0, 20.0] min, P = 0.012).
Conclusions: The IT approach provided a more rapid onset of UN blockade than the CP approach. These results suggest that the IT approach is a suitable alternative to the CP approach and can provide faster surgical readiness.

Keywords: Brachial plexus block; Nerve block; Orthopedics; Subclavian artery; Ulnar nerve; Ultrasonography.

Introduction

The supraclavicular block (SCB) is widely used for intraoperative anesthesia and postoperative analgesia. The location of the lower trunk deep within the neural cluster, however, has raised concerns of ulnar nerve (UN) sparing when local anesthetic is not appropriately injected [1,2]. Incomplete blockade of the UN may be avoided by using the corner pocket (CP) approach during SCB [3]. The target for needle tip placement is between the lateral or inferolateral side of the subclavian artery and the first rib. This approach provides high rates of successful blockade, rapid sensory onset, as well as a relatively short performance time [4]. Unfortunately, even this approach cannot guarantee complete UN

blockade [4]. A previous study reported that injection into the perineural space through the sheath is required for a reliable block using the CP approach [3]. Technical difficulties also exist, such as the need for significant caudal tilting of the ultrasound probe [5]. This may cause difficultly of needle handling when using the in-plane technique, and anisotropy by angle of the insonating beam can result in poor image quality [6]. Moreover, there is concern of pneumothorax due to the proximity of the needle and pleura [7].

Recent improvements in ultrasound resolution have enhanced the ability to accurately identify and selectively block the three trunks of the brachial plexus [2,8], making the recently proposed intertruncal (IT) approach possible. This approach requires identification of the specific location of each individual trunk and the fine tissue planes between them [9]. In the IT approach, local anesthetic is injected into the adipose tissue planes between the upper/middle trunk and the middle/lower trunk.

Although both approaches have been found to avoid UN sparing during SCB, no studies to date have directly compared the efficiency of UN blockade by the IT and CP approaches. We hypothesized that the IT approach (injection between lower and middle trunks) would result in a more complete blockade rate of the UN compared to the CP approach (injection below the lower trunk) at 15 min after blockade. The present study therefore compared the ulnar block characteristics of these two approaches.

Materials and Methods

The protocol of this prospective, parallel-arm, double-blind, randomized controlled superiority study was approved by the Institutional Review Board of Chungnam National University Hospital (CNUH 2020-05-070-001) and the trial was registered at the Clinical Research Information Service, a clinical trial registry in Korea (KCT0005268). This clinical research was done following the ethical principles for medical research involving human subjects in accordance with the Helsinki Declaration 2013. This study enrolled patients aged 20–70 years with American Society of Anesthesiologists physical status classification I and II and scheduled for elective forearm or hand surgery at Chungnam National University Hospital (Daejeon, Korea). All patients provided written informed consent. Patients were excluded if they refused to participate, had a local infection at the nerve block site, were hypersensitive to amide local anesthetic, had ipsilateral arm neuropathy, or had a history of neck surgery.

Study data were collected and managed using Research Electronic Data Capture (REDCap) software, a secure, web-based platform designed to support capturing of data for research studies and hosted at Chungnam National University Hospital (redcap.cnuh.co.kr) [10]. This manuscript adheres to the applicable Consolidated Standards of Reporting Trials (CONSORT) guidelines [11].

All blocks were performed by a single anesthesiologist (Y.J.) with experience in ultrasound guided regional anesthesia and under the direct supervision of the principal investigator (B.H.). Patients were randomly assigned at a ratio of 1 : 1 to the IT or CP group. Block randomization at sizes of 2 and 4 was performed using a random sequence generator (www.randomization.com) [12]. To conceal the allocation, the sequence was uploaded onto REDCap, allowing access only to the researcher performing the assigned block. All other individuals who participated in the surgery, including attending anesthesiologists, surgeon, nurses, and outcome assessors, were blinded to the group assignment.

Immediately prior to the block, each patient was administered 1 mg intravenous midazolam for pre-medication. All blocks were performed under ultrasound guidance using an in-plane technique with a high-resolution ultrasound system (X-Porte, FUJIFILM SonoSite, Inc., USA), a high frequency linear probe (HFL50xp: 15–6 MHz, X-Porte), and a nerve stimulator (0.1 ms, 0.5 mA, 2 Hz, sentinel mode, MultiStim SENSOR, PAJUNK, Germany). Each patient was injected with a total of 25 ml of a 1 : 1 mixture of 0.75% ropivacaine and 1% lidocaine using a 22 gauge, 80 mm, echogenic needle (SonoPlex cannulas, PAJUNK, Germany).

Patients were maintained in a supine position with the head turned to the contralateral side and the ipsilateral shoulder slightly elevated with a pillow. The needle was inserted lateral to the brachial plexus through the prevertebral fascia. In the IT group, the hyperechoic outer boundaries (epineurium) of each trunk were distinguished by ultrasound scanning. The optimal image for patients in the IT group was defined as an image with well differentiated middle and lower trunks. Efforts were not required to obtain a perfect CP view. The gap between the lower and middle trunks was confirmed, first by carefully injecting 0.5 ml of local anesthetic agents to open up the adipose tissue layer (hydrodissection), and subsequently by securing a safe route for needle advancement in the IT plane. While confirming that the trunk of the brachial plexus was not swollen, 10 ml of local anesthetic agents was slowly injected between the lower and middle trunks, 7.5 ml was injected between the middle and upper trunks, and the remaining 7.5 ml was injected between the upper trunk and prevertebral fascia (Fig. 1A). In the CP group, the optimal image was obtained by placing the probe so that the entire subclavian artery was above the first rib. The needle tip was advanced between the

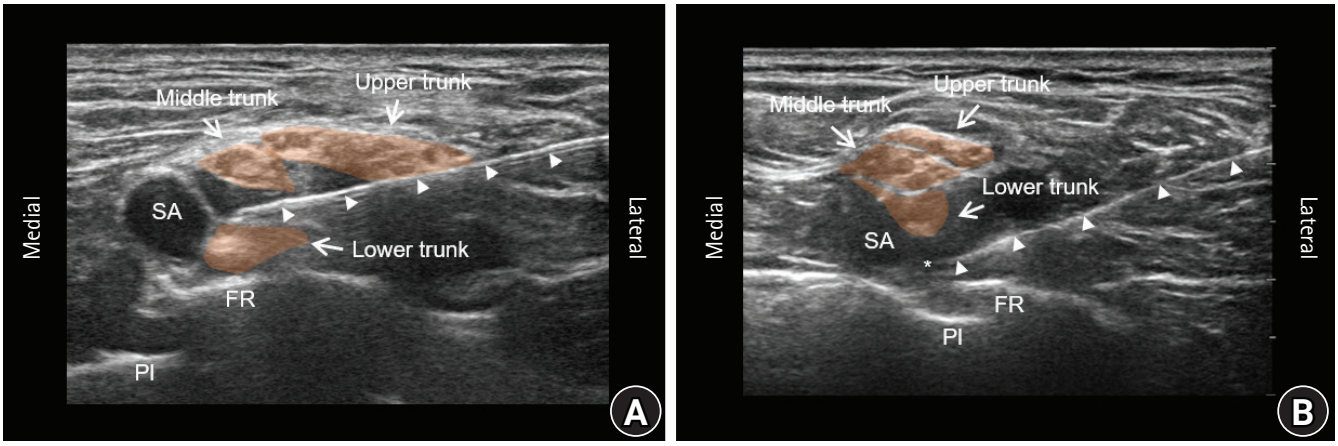

Fig. 1. (A) Ultrasonography image during the IT approach. Note the needle (white arrow head) has penetrated the brachial plexus sheath, and its tip is lying in the IT layer. The middle trunk appeared to be floating on the injected local anesthetic drug. (B) Ultrasonography image during the CP approach. Injection of local anesthetic agents in the CP. *CP: corner pocket, FR: first rib, IT: intertruncal, SA: subclavian artery, Pl: pleura.

lateral or inferolateral side of the subclavian artery and the first rib. While confirming negative blood aspiration, 10 ml of local anesthetic agents was slowly injected in the CP. The remaining 15 ml was injected in the planes identical to those in the IT group (Fig. 1B).

Sedation was induced using dexmedetomidine (loading dose 1 μg/kg for 10 min and maintenance dose of 0.2–0.5 μg/kg/h) and discontinued at the beginning of skin suture. Supplemental oxygen was administered prior to sedation at a rate of 5 L/min via a simple facial mask. Brachial plexus block (BPB) was considered successful when the surgery was completed without the need to inject additional local anesthetics into the surgical field, without the need to perform a rescue nerve block, and without conversion to general anesthesia. These decisions were completely at the discretion of the attending anesthesiologist. At the time of the BPB procedure, the procedure time, defined as the interval between needle insertion and removal, and the presence of the dorsal scapular artery (DSA) in the ultrasound scan images were recorded.

Immediately after the BPB procedure, the assigned, blinded outcome assessor, who was not present during the BPB procedure, measured patient satisfaction by asking the patients: How would you score your discomfort during the block on a scale of 0 to 10, where 0 indicates no discomfort and 10 indicates the worst discomfort imaginable. The same researcher assessed sensory block (pin-prick test) and motor block in the areas of the ulnar (UN), median (MN), musculocutaneous (MCN), and radial (RN) nerves every 5 min for at least 30 min until the blockade was complete. Sensory blockade was graded on a 10-point scale (normal = 10, absent = 0) relative to a pin-prick sensation in the contralateral arm. Sensory blockade of the UN, MN, MCN, and RN was assessed on the volar aspect of the fifth finger, the volar aspect of the thumb, the lateral aspect of the forearm, and the lateral aspect of the dorsum of the hand, respectively. Motor blockade was graded on a three-point scale (normal = 3, mildly reduced = 2, markedly reduced = 1, unable to move = 0). Motor blockade of the UN, MN, MCN, and RN was assessed by measuring thumb opposition with the little finger, thumb opposition with the index finger, elbow flexion, and wrist extension, respectively.

Sensory recovery in the UN territory was assessed every 30 min by the patients. The patients were instructed to repeatedly pinch the little finger of each hand and check the time of sensory normalization in the anesthetized hand by comparison with the opposite hand. The assessor visited the patient the following morning (within 24 h postoperatively) to ascertain the presence of residual blockade, neurologic deficits, and any other symptoms. Neurologic complications were evaluated again during an outpatient clinic visit 7 days after surgery. Postoperative chest radiography is a routine postoperative pathway of our institution and was used to identify accidental pneumothorax.

The primary outcome was the proportion of participants with complete sensory block of the UN 15 min after BPB. Complete sensory blockade of each nerve was defined as a pin-prick score of 0. Time to readiness for surgery was defined as the time required to achieve complete sensory block of the areas of all four nerves. Secondary outcomes included the proportion of patients with complete motor blockade, duration of the procedure, patient discomfort score during the procedure, incidence of noticing the DSA during the procedure, duration of sensory blockade of the UN, and sensory and motor scores as a function of time.

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Statistical analysis

The sample size was calculated based on the primary outcome according to the superiority hypothesis [13]. Based on our clinical experiences, about 40% of patients undergoing the CP approach had complete sensory blockade in the UN territory within 15 min after BPB. Based on the assumption that 80% of patients undergoing the IT approach would achieve complete anesthesia within 15 min, 27 subjects per group would have a power of 90% and a risk of 5% for type I errors. Based on a combined 10% rate of dropouts and data losses, 60 participants were enrolled.

All analyses were per protocol using R software version 4.0.0 (R Project for Statistical Computing, Austria). Normality of distribution of continuous variables was assessed using Shapiro–Wilk tests. Normally distributed continuous variables were reported as mean ± standard deviation (SD) and analyzed by independent sample t-tests, whereas non-normally distributed continuous variables were reported as median (interquartile range) and analyzed by Mann–Whitney *U* tests. Categorical variables were reported as number (%) and analyzed by χ^2 or, when expected count was < 5, Fisher's exact test. A two-tailed P value < 0.05 was considered statistically significant.

Results

Of 60 patients assessed for eligibility, 59 were enrolled and analyzed; one patient randomized to the IT group was excluded due to uncooperative outcome evaluation (Fig. 2). The baseline characteristics of the participants are described in Table 1. All patients successfully underwent ultrasound-guided SCB regardless of approach, and there were no complications directly related to the technique including pneumothorax or the use of local anesthetics.

The rates of complete sensory blockade (75.9% [22/29] vs. 43.3% [13/30], P = 0.023) and complete motor blockade (82.8% [24/29] vs. 50.0% [15/30], P = 0.017) of the UN after 15 min were significantly higher in the IT than in the CP group (Fig. 3). There were no between-group differences in rates of complete sensory and motor blockade in the four neural territories at each time point, with most patients achieving complete block within 20 min (Fig. 3). Time to onset of sensory block in the UN was significantly shorter in the IT than in the CP group (15.0 [10.0, 15.0] min vs. 20.0 [15.0, 20.0] min, P = 0.012), but there was no difference between the IT and CP groups in time to onset of complete sensory blockade of all nerves (15.0 [15.0, 20.0] min vs. 20.0 [15.0, 20.0] min, P = 0.189) (Fig. 4). The progression of sensory and motor blockade of the UN territory is shown in Supplementary Fig. 1.

Total procedure duration and patient discomfort scores were not significant in the IT and CP groups. However, the DSA was only seen in ultrasonographic images in the 7 patients of IT group. Unlike the onset time, which was faster in the IT group, the total duration of UN sensory block did not differ in the IT and CP groups (Table 2). None of the patients reported transient or persistent neurological signs or symptoms after 24 h or at the one-week follow-up after surgery.

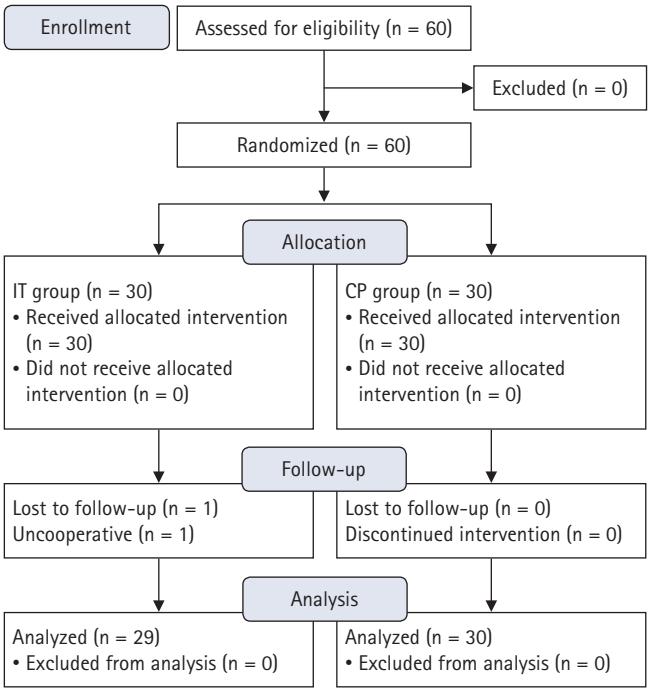

Fig. 2. CONSORT diagram showing the patients at every stage of the randomized controlled trial. IT: intertruncal, CP: corner pocket.

Table 1. Demographic and Clinical Characteristics

Variable	IT group (n = 29)	CP group (n = 30)
Age (yr)	52.0 (27.0, 59.0)	48.5 (26.0, 60.0)
Sex (M/F)	15/14	15/15
Height (cm)	167.0 (157.0, 176.0)	164.0 (154.0, 175.0)
Weight (kg)	65.0 (56.0, 80.0)	62.5 (55.0, 74.0)
Surgery time (min)	60.0 (52.0, 80.0)	64.0 (48.0, 82.0)
ASA PS (I/II)	9/20	9/21
Type of surgery (a/b/c/d)	2/17/6/4	3/10/4/13

Values are presented as median (Q1, Q3) or numbers. IT: intertruncal, CP: corner pocket, ASA PS: American Society Anesthesiologists physical status, Type of surgery; a: arthroscopic surgery, b: fracture or ulnar shortening, c: hardware removal, d: soft tissue, tendon, ligament repair surgery.

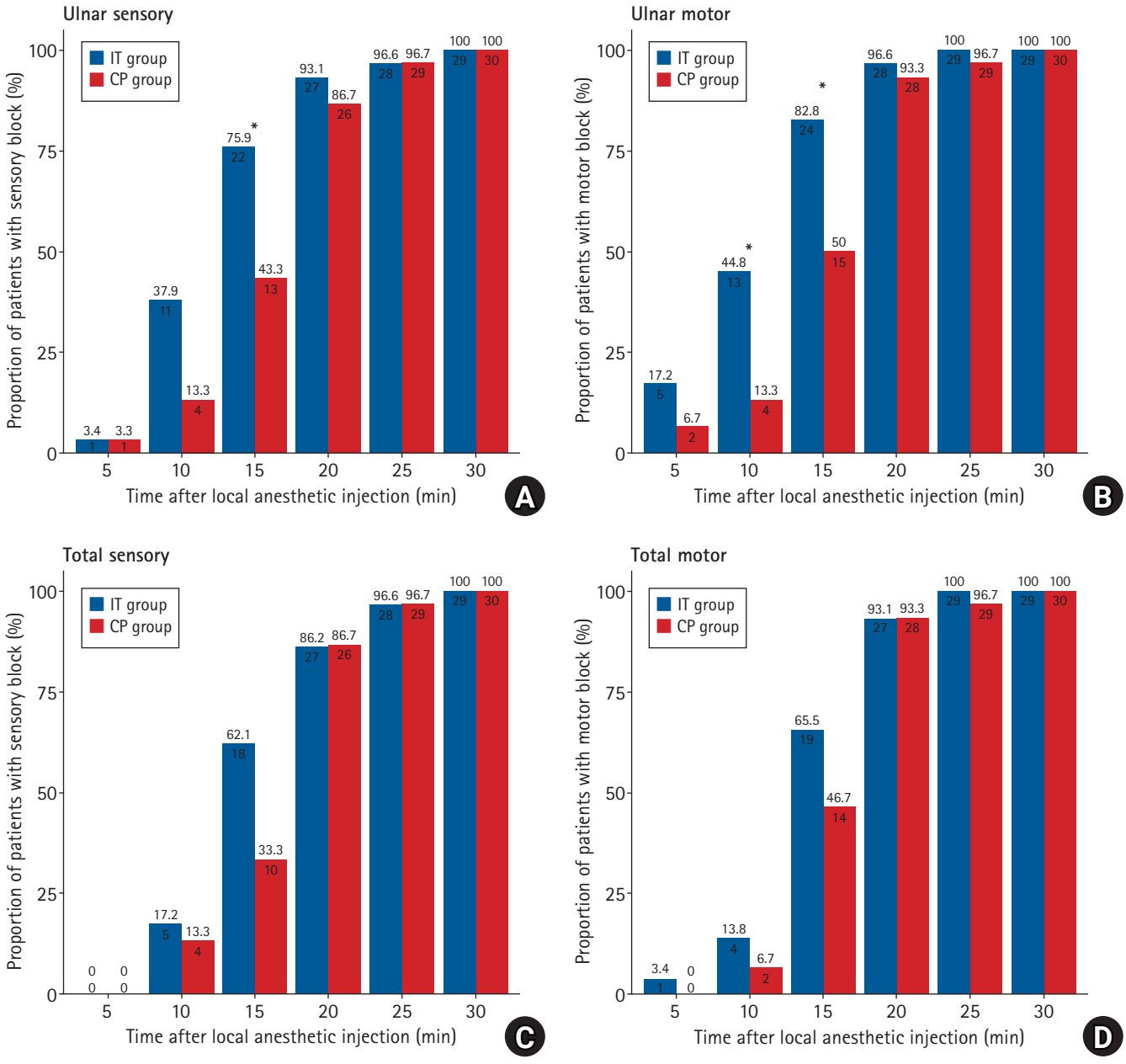

Fig. 3. Proportions of patients with complete sensory (A) and motor (B) block according to time in distributions of the ulnar nerve. Proportions of patients with complete sensory (C) and motor (D) block according to time in distributions of the all four nerves (total). IT: intertruncal, CP: corner pocket. *P < 0.05.

Discussion

UN sparing is a frequent limitation in the conventional approach to SCB when relying on blind techniques or nerve stimulated muscle contraction [14]. Although use of the CP approach under ultrasound guidance was thought to avoid UN sparing, studies suggest that UN sparing may still occur [4]. The present study found that, although both approaches were effective for UN block, the IT approach provided a faster onset of UN block.

Compared with extrafascial injection, subfascial injection was reported to induce a faster onset and prolonged duration of sensory and motor blockade without causing neurological complications [15]. The slower onset of UN block in the CP group may have been due to the extrafascial spread of local anesthetics. Moreover, the IT approach directly penetrates the sheath, whereas the CP approach does not. Additionally, injecting local anesthetic above the lower trunk may facilitate a circumferential pattern of spreading [16]. Our results suggest that the IT approach provides

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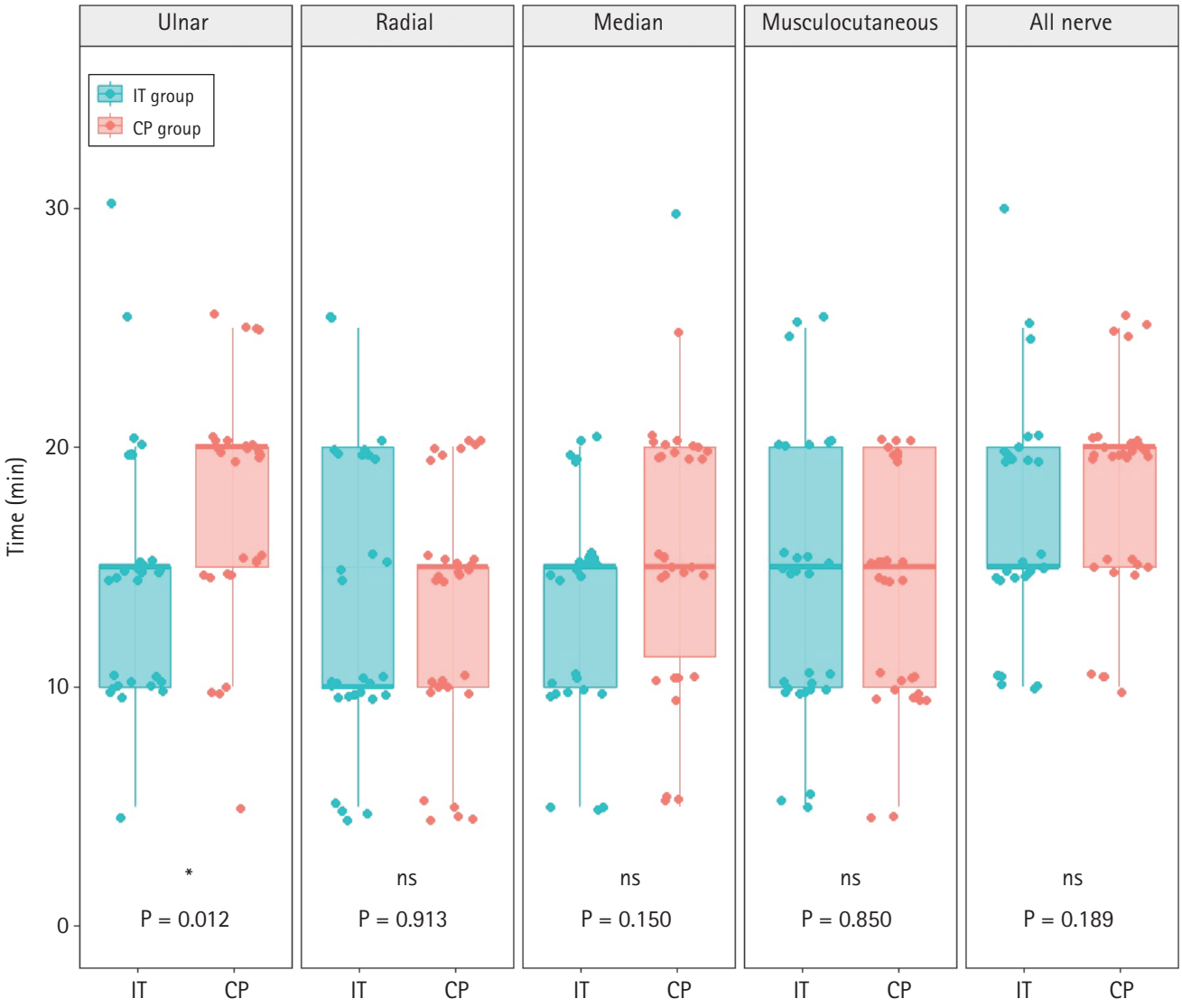

Fig. 4. Onset times of sensory block of each nerve and all four nerves in the IT and CP groups. IT: intertruncal, CP: corner pocket, ns: not significant. *P < 0.05.

Table 2. Effects of IT and CP Blockade on Patient Outcomes

Variable	IT group (n = 29)	CP group (n = 30)	P value
Procedure time (s)	250.0 (232.0, 277.0)	268.0 (213.0, 299.0)	0.834
Patient discomfort scale (0–10)	3.0 (2.0, 6.0)	5.0 (3.0, 6.0)	0.304
Visualization of DSA	7 (24.1)	0 (0)	0.014
Sensory block duration of UN (min)	548.5 (476.0, 698.0)	502.5 (433.5, 646.0)	0.313

Values are presented as median (Q1, Q3) or number (%). IT: intertruncal, CP: corner pocket, DSA: dorsal scapular artery, UN: ulnar nerve.

a faster onset of UN block than the CP approach. Also, the IT approach can be used as an alternative in cases where it is difficult to do the CP approach.

Early papers of ultrasound guidance described the brachial plexus as a 'cluster of hypoechoic nodules' or as a main and other satellite 'neural clusters' [14,17]. During targeted intracluster injection, the needle is advanced within the sheath containing one or more clusters of hypoechoic neurologic elements, and the local anesthetic is injected inside the clusters [18,19]. The nerve structures were approached as a group, without distinguishing the identity and location of each individual trunk due to relatively low qualities of ultrasound imaging. The only reported advantages of

intracluster injection are faster onset times and time to surgical readiness [9]. These advantages, however, may be offset by the risk of intraneural injection of local anesthetics, which may result in neuronal damage [18]. The performance of bilateral intracluster blocks on cadavers resulted in 25% of specimens having subperineural ink on histologic examination, with 90% of the latter being intrafascicular with evidence of axonal distortion or damage [20]. Intracluster injections may result in nerve injury due to unintended subperineural injection. The homogeneity of nerve elements, tightly compressed together in a small space, reduces generated echoes, such that the needle tip may not be clearly distinguishable within the cluster.

Recent advancements in sonographic resolution have led to the recognition that the original cluster was composed of individual trunks and/or divisions [2]. Higher resolution equipment has enabled the identification of the specific location of each individual trunk and the fine tissue planes between them. This has allowed the application of the IT approach using hydrodissection between fine adipose tissue planes and the outer boundary of the epineurium that surrounds the fascicle without accidental intraneural injection [9], which may overcome the disadvantages of the intracluster approach. In addition, concomitant use of a nerve stimulator further reduces the possibility of inadvertent neural complications, as the needle cannot come within too close a proximity to the nerve.

During proper injections, we observed the expansion of extraneural tissues and increases in the diameter of the entire complex under the fascia, while each trunk remained at its original size. For successful SCB, the block needle should penetrate the brachial plexus sheath and local anesthetic agents should be injected into the connective tissue matrix between the neural elements [21]. However, it remains unclear whether subfascially injected anesthetics spread intraneurally [22,23]. More than 50% of the brachial plexus in the supraclavicular region is thought to be composed of fat and connective tissue inside the sheath [16,22]. These findings suggest that subfascially injected local anesthetics are not necessarily deposited in the fascicles but in the connective tissue matrix, resulting in a mere injection into the adipose layer. We also found that none of our patients experienced permanent neurological complications or delayed recovery from nerve damage. Although the external boundaries of each trunk were identified and nerve integrity was preserved using the IT approach, additional clinical and histological studies are needed to evaluate the safety of this approach.

To obtain the optimal image of the CP and avoid pleural puncture, the probe had to be tilted more caudally until the subclavian artery and brachial plexus were above the first rib, particularly when the brachial plexus was located more medially with respect to the first rib. An important advantage of the IT approach is that caudal tilting of the probe and deep injection were not absolutely required during lower trunk block. Despite these advantages, however, the DSA was observed in about 24% of patients in the IT group. In such cases, it was inevitable to tilt the probe caudally as in the CP approach to avoid arterial puncture. The DSA was identified as a branch of the subclavian artery that passed through the brachial plexus. A study assessing the presence of the DSA at three ultrasound probe positions commonly used in SCB found that the DSA passed most frequently (23/106, 21.7%) through a probe position in which the brachial plexus was on the first rib or was partially on the pleura and lateral to the subclavian artery, which lay directly on the pleura [24]. This probe position is commonly used for the IT approach during SCB.

Another interesting point of our study is that unlike the previous study reporting UN sparing after the CP approach [4], all patients showed complete UN block. This may be due to differences in needle positioning. While we confirmed floating of the lower trunk as an optimal image during CP injection, the injection point in the previous study was an approximately 1 cm^2 area bounded medially by the subclavian artery. Although it is difficult to distinguish intra or extra sheath injection on ultrasound image during CP injection, the difference in proximity to the lower trunk may explain our excellent results regarding UN block.

This study had several limitations. First, the success of the block was evaluated at 15 min, suggesting the need for caution when generalizing our results. The time setting in this study was based on the work flow in our institution. Second, all nerve blocks were performed by experienced anesthesiologists. Because the IT approach requires the use of hydrodissection to construct a path between the trunks to avoid neural injury, there is a need for a learning curve. Third, the sensory block duration time was determined based on self-reporting by patients, suggesting that the quality of the data may be relatively low.

In conclusion, the IT approach provides a more rapid onset of UN blockade than the CP approach and can be a good alternative for SCB. However, additional studies are required to ascertain the safety of the IT approach, especially in terms of neural damage.

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Conflicts of Interest

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

Author Contributions

Yumin Jo (Conceptualization; Data curation; Methodology; Project administration; Writing – original draft)
Jiho Park (Investigation; Resources; Software; Writing – review & editing)
Chahyun Oh (Formal analysis; Software; Validation; Visualization)
Woosuk Chung (Validation; Visualization; Writing – review & editing)
Seunghyun Song (Conceptualization; Methodology; Software)
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Hansol Kang (Conceptualization; Methodology; Project administration; Validation)
Youngkwon Ko (Investigation; Supervision; Validation)
Yoon-Hee Kim (Investigation; Resources; Supervision)
Boohwi Hong (Conceptualization; Formal analysis; Funding acquisition; Supervision; Writing – review & editing)

Supplementary Materials

Supplementary Fig. 1. Progression of sensory and motor blockade of the UN territory in patients in the IT and CP groups. Sensory score (normal: 10, absent: 0), Motor grade (normal = 3, mildly reduced = 2, markedly reduced = 1, unable to move = 0). IT: intertruncal, CP: corner pocket.

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References

1. Kapral S, Krafft P, Eibenberger K, Fitzgerald R, Gosch M, Weinstabl C. Ultrasound-guided supraclavicular approach for regional anesthesia of the brachial plexus. Anesth Analg 1994; 78: 507-13.
2. Karmakar MK, Pakpirom J, Songthamwat B, Areeruk P. High definition ultrasound imaging of the individual elements of the brachial plexus above the clavicle. Reg Anesth Pain Med 2020; 45: 344-50.
3. Brull R, Chan VW. The corner pocket revisited. Reg Anesth Pain Med 2011; 36: 308.
4. Fredrickson MJ, Patel A, Young S, Chinchanwala S. Speed of onset of 'corner pocket supraclavicular' and infraclavicular ultrasound guided brachial plexus block: a randomised observer-blinded comparison. Anaesthesia 2009; 64: 738-44.
5. Feigl GC, Litz RJ, Marhofer P. Anatomy of the brachial plexus and its implications for daily clinical practice: regional anesthesia is applied anatomy. Reg Anesth Pain Med 2020; 45: 620-7.
6. Moorthy SS, Schmidt SI, Dierdorf SF, Rosenfeld SH, Anagnostou JM. A supraclavicular lateral paravascular approach for brachial plexus regional anesthesia. Anesth Analg 1991; 72: 241-4.
7. Bhatia A, Lai J, Chan VW, Brull R. Case report: pneumothorax as a complication of the ultrasound-guided supraclavicular approach for brachial plexus block. Anesth Analg 2010; 111: 817-9.
8. Karmakar MK, Areeruk P, Mok LY, Sivakumar RK. Ultrasound-guided selective trunk block to produce surgical anesthesia of the whole upper extremity: a case report. A A Pract 2020; 14: e01274.
9. Siddiqui U, Perlas A, Chin K, Reina MA, Sala-Blanch X, Niazi A, et al. Intertruncal approach to the supraclavicular brachial plexus, current controversies and technical update: a daring discourse. Reg Anesth Pain Med 2020; 45: 377-80.
10. Harris PA, Taylor R, Minor BL, Elliott V, Fernandez M, O'Neal L, et al. The REDCap consortium: Building an international community of software platform partners. J Biomed Inform 2019; 95: 103208.
11. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ 2010; 340: c332.
12. Lim CY, In J. Randomization in clinical studies. Korean J Anesthesiol 2019; 72: 221-32.
13. In J, Kang H, Kim JH, Kim TK, Ahn EJ, Lee DK, et al. Tips for troublesome sample-size calculation. Korean J Anesthesiol 2020; 73: 114-20.
14. Chan VW, Perlas A, Rawson R, Odukoya O. Ultrasound-guided supraclavicular brachial plexus block. Anesth Analg 2003; 97:

1514-7.
15. Sivashanmugam T, Ray S, Ravishankar M, Jaya V, Selvam E, Karmakar MK. Randomized comparison of extrafascial versus subfascial injection of local anesthetic during ultrasound-guided supraclavicular brachial plexus block. Reg Anesth Pain Med 2015; 40: 337-43.
16. Moayeri N, Bigeleisen PE, Groen GJ. Quantitative architecture of the brachial plexus and surrounding compartments, and their possible significance for plexus blocks. Anesthesiology 2008; 108: 299-304.
17. Techasuk W, González AP, Bernucci F, Cupido T, Finlayson RJ, Tran DQ. A randomized comparison between double-injection and targeted intracluster-injection ultrasound-guided supraclavicular brachial plexus block. Anesth Analg 2014; 118: 1363-9.
18. Retter S, Szerb J, Kwofie K, Colp P, Sandeski R, Uppal V. Incidence of sub-perineural injection using a targeted intracluster supraclavicular ultrasound-guided approach in cadavers. Br J Anaesth 2019; 122: 776-81.
19. Lee MG, Lee KC, Kim HS, Park SJ, Suh YJ, Shin HJ. Ultrasound-guided central cluster approach for the supraclavicular brachial plexus block: a case series. Korean J Anesthesiol 2015; 68: 603-7.
20. Gadsden J, Orebaugh S. Targeted intracluster supraclavicular brachial plexus block: too close for comfort. Br J Anaesth 2019; 122: 713-5.
21. Franco CD. Connective tissues associated with peripheral nerves. Reg Anesth Pain Med 2012; 37: 363-5.
22. Reina MA, Sala-Blanch X, Monzó E, Nin OC, Bigeleisen PE, Boezaart AP. Extrafasicular and intraperineural, but no endoneural, spread after deliberate intraneural injections in a cadaveric study. Anesthesiology 2019; 130: 1007-16.
23. Weller RS. Intraneural injection in regional anesthesia: what does the literature tell us? Curr Anesthesiol Rep 2013; 3: 236-41.
24. Murata H, Sakai A, Hadzic A, Sumikawa K. The presence of transverse cervical and dorsal scapular arteries at three ultrasound probe positions commonly used in supraclavicular brachial plexus blockade. Anesth Analg 2012; 115: 470-3.

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These findings were briefly presented at the ANESTHESIOLOGY 2012 Annual Meeting of The American Society of Anesthesiologists (ASA), October 2012, Walter E. Washington Convention Center, Washington, DC, USA.

Edaravone attenuates sustained pial arteriolar vasoconstriction independently of endothelial function after unclamping of the abdominal aorta in rabbits

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Background: Cerebral blood flow (CBF) has direct effects on neuronal function and neurocognitive disorders. Oxidative stress from abdominal aortic surgery is important in the pathophysiology of CBF impairment. We investigated the effect of edaravone on the pial arteriolar diameter changes induced by abdominal aortic surgery and the involvement of the endothelium in the changes.
Methods: The closed cranial window technique was used in rabbits to measure changes in pial arteriolar diameter after the unclamping of abdominal aortic cross-clamping with an intravenous free radical scavenger, edaravone (control group [n = 6], edaravone 10 μg/kg/min [n = 6], 100 μg/kg/min [n = 6]). Pial vasodilatory responses to topical application of acetylcholine (ACh) into the cranial window were investigated before abdominal aortic cross-clamping and after unclamping with intravenous administration of edaravone (control group [n = 6], edaravone 100 μg/kg/min [n = 6]).
Results: Aortic unclamping-induced vasoconstriction was significantly attenuated by continuous infusion of edaravone at 100 μg/kg/min. Topical ACh after unclamping did not produce any changes in pial arteriolar responses in comparison to before aortic cross-clamping in the control or edaravone groups. The changes in the response to topical ACh after unclamping in the saline and edaravone groups did not differ significantly.
Conclusions: Free radicals during abdominal aortic surgery might have contracted cerebral blood vessels independently of endothelial function in rabbits. Suppression of free radicals attenuated the sustained pial arteriolar vasoconstriction after aortic unclamping. Thus, the free radical scavenger might have some brain protective effect that maintains CBF independently of endothelial function.

Keywords: Cerebrovascular circulation; Edaravone; Endothelium; Free radical scavengers; Reperfusion injury; Vascular surgical procedures.

Introduction

Aortic cross-clamping during open aneurysmectomy elevates systemic blood pressure and decreases cardiac output [1].

Aortic unclamping decreases systemic blood pressure and cardiac output and increases pulmonary arterial pressure [1]. Such hemodynamic instability has the potential to affect cerebral circulation and induce neurological complications [2–5]. The incidence of delirium after elective abdominal aortic aneurysm (AAA) repair is reported as 30–54% [6–8]. Postoperative cognitive dysfunction (POCD) occurs in 0–62% of patients undergoing abdominal aortic surgery [7,9]. Advanced age [3,5,9–12], baseline neurocognitive function [3–6,9,10,12], smoking [4–6,9], and open aortic repair [3–5] have been identified as risk factors for both delirium and cognitive dysfunction after abdominal aortic surgery.

Acute delirium has been associated with a significant reduction in regional and global cerebral blood flow (CBF) [13]. Early POCD after major noncardiac surgery is secondarily associated with impaired intraoperative CBF autoregulation in the elderly [14]. Maintenance of adequate CBF and cerebral metabolism is vital for the preservation of cognitive function [2,15]. We previously reported that abdominal aortic unclamping induced transient dilation of pial arterioles followed by sustained constriction, as assessed using rabbits [16–18]. CBF changes induced by abdominal aortic unclamping may be involved in postoperative neurological complications.

In addition to changes in CBF, oxidative stress may also be involved in perioperative neurocognitive disorders [19]. Under ischemic conditions, the metabolism of adenosine triphosphate generates oxygen-derived free radicals [1,20]. Oxygen free radical production increases from the completion of proximal anastomosis, reaches a maximum at 5 min after reperfusion, then gradually decreases [21]. Free radicals mediate tissue injury following post-ischemic reperfusion [22]. Peripheral oxidative stress may provoke microcirculatory dysfunction and compromise cerebral perfusion via dysregulation of blood-brain barrier integrity and activation of the endothelium, ultimately leading to the development of POCD [23]. Localized oxidative stress and reactive oxygen species have a strong impact on endothelial dysfunction, which disturbs proper perfusion and CBF [24].

Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one), which is known to be a free radical scavenger, is used in the treatment of acute stroke [25]. Edaravone inhibits lipid peroxidation by scavenging free radicals and exerts neuroprotective effects by inhibiting oxidative damage to the cerebrovascular endothelium and brain cells [26,27]. Pretreatment with edaravone significantly reduces the incidence of cognitive impairment after carotid endarterectomy [28]. Edaravone may also decrease the expression of pro-inflammatory cytokines, alleviate surgery-induced neuroinflammation, and reduce disruption of the blood-brain barrier [29].

We hypothesized that free radical scavenging would improve CBF changes after the unclamping of aortic cross-clamping. The objective of the present study was to investigate, using rabbits fitted with a cranial window, the effects of edaravone on the pial arteriolar diameter changes induced by abdominal aortic clamping. We also investigated the involvement of the endothelium in the cerebral arteriolar response caused by abdominal aortic unclamping.

Materials and Methods

The experimental protocols were approved by the Institutional Committee for Animal Care of Gifu University Graduate School of Medicine (Protocol No. 20-84). The experiments were performed using 30 anesthetized rabbits weighing 2.0–2.2 kg. Each animal was initially anesthetized with pentobarbital sodium (25 mg/kg intravenously) and maintained by inhalation of 0.5% isoflurane. Mechanical ventilation was administered through a tracheotomy tube using oxygen-enriched room air to maintain an inspiratory oxygen concentration of approximately 50%. The tidal volume and respiratory rate were adjusted to maintain the end-tidal carbon dioxide tension ($P_{ET}CO_2$) at 35–40 mmHg, with $P_{ET}CO_2$ monitored throughout the experiment. Polyvinyl chloride catheters were placed in the femoral vein for the administration of fluid (lactated Ringer's solution: 5 ml/kg/h) and in the right axillary and left femoral arteries for the continuous monitoring of proximal and distal aortic pressures (PrAP and DiAP) and heart rate (HR), and for blood sampling (from the right axillary artery). The rectal temperature was maintained at 38.5–39.5°C with a heating blanket and a warming lamp. An incision was made in the skin of the lateral abdomen. The aorta was then taped just distal to the renal arteries for clamping.

A closed cranial window was used to observe the cerebral pial microcirculation. Each animal was placed in the sphinx posture, the scalp was retracted, and a 10-mm-diameter hole was created in the parietal bone. The dura and arachnoid membranes were opened carefully, and a ring with a glass coverslip was placed over the hole and secured using dental acrylic. The space under the window was filled with artificial cerebrospinal fluid (aCSF), the components of which were Na^+ 157 mEq/L, K^+ 3 mEq/L, Ca^{2+} 3 mEq/L, Mg^{2+} 1.3 mEq/L, Cl^- 139 mEq/L, HCO_3^- 25 mEq/L, urea 40 mg/dl, and glucose 67 mg/dl (pH was adjusted to 7.48). This solution was freshly prepared 4 h before use and bubbled with 5% CO_2 in air at 39.0°C for 15 min just before use. Four catheters were inserted into the ring. One was attached to a reservoir bottle containing aCSF to maintain a constant pressure of 5 mmHg in the window; the second was used to monitor the pressure in the window; the third was for the administration of

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experimental drugs and aCSF; and the fourth for draining the fluid. The temperature within the window was monitored using a thermometer (model 6510; Mallinckrodt Medical, USA) and was kept at 38.5–39.5°C.

Experiment 1

Rabbits (n = 18) were assigned to one of three groups as follows; systemic saline administration group (control group, n = 6) or systemic edaravone administration groups (E10 group, 10 μg/kg/min, n = 6; E100 group, 100 μg/kg/min, n = 6). All experiments were performed after at least 30 min of recovery from the surgical preparation. After each baseline pial arteriolar diameter measurement was made, each rabbit was administered saline (control group) or edaravone (E10 or E100 group) by intravenous infusion. All infusions continued throughout the experiment. The total doses of edaravone in the E10 and E100 groups were 2 mg and 20 mg, respectively. Fifteen minutes after the start of infusion, aortic clamping was performed for 20 min. The clamping and unclamping were performed gradually (each taking approximately 30 s) to minimize systemic hemodynamic changes. Measurements of two large (75–130 μm) and two small (40–75 μm) cerebral pial arteriolar diameters, hemodynamic variables (PrAP, DiAP, and HR), and various physiological variables (rectal temperature, intra-window temperature, arterial blood gas tensions, electrolytes, blood glucose, and blood pH) were performed at the following time points: immediately before the start of infusion, just before aortic clamping (pre-clamp), immediately after aortic clamping (after clamp), 20 min after clamping (before unclamping), and at 0, 2, 5, 15, 30, and 60 min after unclamping. The time point "0 min after unclamping" was actually 30 s after the start of unclamping, which took approximately 30 s to perform.

Experiment 2

Rabbits (n = 12) were assigned to one of two groups; systemic saline administration group (control group, n = 6) or systemic edaravone administration group (100 μg/kg/min, n = 6). After each baseline pial arteriolar diameter measurement was made, each rabbit was administered saline or edaravone by intravenous infusion. All infusions continued throughout the experiment. The total dose of edaravone was 33 mg. Fifteen minutes after the start of the infusion, 10^{-6} M acetylcholine (ACh) was infused under the window for 5 min at a rate of 0.5 ml/min. To reestablish the baseline vessel diameters, the window was continuously flushed with aCSF at 0.25 ml/min for 25 min. Then, 10^{-5} M ACh was topically administered into the window for 5 min at a rate of 0.5 ml/min, and the window was continuously flushed with aCSF at 0.25 ml/min for 25 min. Aortic clamping was performed for 20 min. Clamping and unclamping were performed gradually (each taking approximately 30 s to perform). At 60 min after unclamping, 10^{-5} M ACh was topically administered into the cranial window at 0.25 ml/min for 5 min. Measurements of two cerebral pial arteriolar (35–160 μm) diameters, hemodynamic variables (PrAP, DiAP, and HR), and physiological variables (rectal temperature, intra-window temperature, arterial blood gas tensions, electrolytes, blood glucose, and blood pH) were taken at the following time points: immediately before the start of topical administration, after the topical administration of ACh (10^{-6} or 10^{-5} M) for 5 min, at 60 min after unclamping, and at 5 min after the second administration of 10^{-5} M ACh.

The pial arterioles were measured in each cranial window using a videomicrometer (Model VM-20; Flovel, Japan) on a television monitor, which received pictures from a microscope (Model SHZ-10; Olympus, Japan). The data from the pial views were stored on videotape for subsequent playback and analysis. The percentage changes recorded for individual arteriolar segments were averaged for each type (large or small) of vessel in each rabbit, and this average value was used in the statistical analysis.

Statistical analysis

In experiment 1, all variables used to assess the time-dependent effects within groups were tested using one-way analysis of variance (ANOVA) for repeated measurements, followed by the Tukey-Kramer test for post hoc comparisons. The differences between groups were examined using two-way ANOVA followed by one-way ANOVA for factorial measurements and an unpaired t-test with Bonferroni correction. In experiment 2, all variables used to assess the dose-dependent effects of ACh and the effects of abdominal aortic clamping within groups were tested using one-way ANOVA for repeated measurements followed by the Tukey-Kramer test for post hoc comparisons. Differences between groups were examined using an unpaired t-test. Statistical significance was set at $P < 0.05$. All values are presented as the mean ± standard deviation (SD).

Results

The effect of edaravone on the pial arteriolar diameter changes induced by aortic clamping and unclamping

In experiment 1, there were no significant differences in base-

line hemodynamic or physiological variables between the three groups. Rectal and intra-window temperatures did not vary throughout the experiments in any group. PaO_2, Na^+, K^+, and blood glucose levels were stable at all stages of the experiment in all groups (data not shown). In all groups, PrAP decreased significantly at 0 min after unclamping, and the DiAP value after clamping was significantly decreased compared to the baseline value. Both PrAP and DiAP recovered after unclamping. However, HR did not show significant changes in any group during the experiment (Table 1). In all groups, the arterial pH decreased significantly at 0 and 2 min after unclamping, and $PaCO_2$ significantly increased at 0 and 2 min after unclamping (Table 2).

There were no significant differences between the groups in the baseline diameters of the large and small arterioles. For large pial arterioles, the diameters in all groups showed significant increases just after unclamping (control, 5.6% ± 2.8%, P = 0.041; E10, 6.7% ± 2.0%, P = 0.005; and E100, 6.4% ± 1.3%, P < 0.001). Diameters then decreased significantly, starting at 5 min after unclamping in the control group (P = 0.023), and at 15 min after unclamping in the E10 (P = 0.032) and E100 (P = 0.007) groups. The decreases in diameter remained significant (and, indeed, appeared to still be constricted) at 60 min after unclamping (control, –17.1% ± 4.3%, P < 0.001; E10, –13.2% ± 2.9%, P < 0.001; and E100, –7.9% ± 1.8%, P < 0.001). In the E100 group, but not in the E10 group, the decrease in diameter was significantly smaller than in the control group (15 min, P = 0.024; 30 min, P = 0.015; and 60 min, P < 0.001) (Fig. 1). For the small pial arterioles, the diameters in all groups showed significant increases at 0 and 2 min after unclamping (maximum increase: control, 10.0% ± 3.9%, P = 0.024; E10, 8.4% ± 3.7%, P= 0.001; and E100, 11.6% ± 1.7%, P < 0.001). Diameters then decreased significantly, starting at 15 min after unclamping in all groups (control, P < 0.001;

Table 1. Time Course of Hemodynamic Changes in Experiment 1

Variable	Baseline	Pre-clamp	After clamp	Pre-unclamp	Time after unclamp (min)					
					0	2	5	15	30	60
PrAP (mmHg)										
Control	95 ± 9	96 ± 11	98 ± 7	99 ± 12	83 ± 6*	93 ± 11	95 ± 9	95 ± 7	96 ± 8	95 ± 9
Edaravone-10	92 ± 10	91 ± 10	93 ± 10	93 ± 10	84 ± 6*	88 ± 8	92 ± 10	92 ± 11	91 ± 10	92 ± 9
Edaravone-100	92 ± 7	92 ± 6	93 ± 8	94 ± 5	82 ± 5*	87 ± 4	94 ± 6	95 ± 5	94 ± 7	95 ± 6
DiAP (mmHg)										
Control	94 ± 10	97 ± 11	19 ± 3*	19 ± 4*	83 ± 5*	91 ± 11	95 ± 10	95 ± 8	98 ± 8	97 ± 10
Edaravone-10	91 ± 10	90 ± 10	18 ± 2*	18 ± 2*	83 ± 6*	87 ± 8	91 ± 10	91 ± 11	91 ± 11	91 ± 9
Edaravone-100	92 ± 7	92 ± 7	18 ± 3*	18 ± 4*	82 ± 5*	87 ± 6	92 ± 8	94 ± 3	94 ± 6	94 ± 5
HR (beats/min)										
Control	256 ± 22	257 ± 22	253 ± 18	252 ± 17	261 ± 19	260 ± 19	259 ± 17	257 ± 17	259 ± 16	259 ± 14
Edaravone-10	247 ± 9	246 ± 12	250 ± 12	243 ± 8	256 ± 10	257 ± 17	259 ± 14	253 ± 13	250 ± 14	244 ± 11
Edaravone-100	250 ± 22	253 ± 20	253 ± 17	245 ± 18	257 ± 17	258 ± 25	254 ± 22	252 ± 19	250 ± 22	246 ± 26

Values are presented as mean ± SD. PrAP: mean proximal aortic pressure (mean arterial pressure obtained from the axillary artery), DiAP: mean distal aortic pressure (mean arterial pressure obtained from the femoral artery), HR: heart rate. *P < 0.05, versus baseline value in the same group.

Table 2. Time Course of Physiological Variables Changes in Experiment 1

Variable	Baseline	Pre-clamp	After clamp	Pre-unclamp	Time after unclamp (min)					
					0	2	5	15	30	60
pH										
Control	7.37 ± 0.02	7.38 ± 0.01	7.37 ± 0.02	7.38 ± 0.02	7.30 ± 0.02*	7.31 ± 0.01*	7.35 ± 0.02	7.37 ± 0.01	7.37 ± 0.01	7.38 ± 0.01
Edaravone-10	7.37 ± 0.02	7.37 ± 0.03	7.38 ± 0.02	7.37 ± 0.03	7.31 ± 0.03*	7.32 ± 0.02*	7.36 ± 0.01	7.37 ± 0.01	7.38 ± 0.01	7.38 ± 0.01
Edaravone-100	7.37 ± 0.01	7.37 ± 0.01	7.37 ± 0.01	7.37 ± 0.01	7.31 ± 0.01*	7.31 ± 0.01*	7.36 ± 0.01	7.37 ± 0.02	7.37 ± 0.02	7.37 ± 0.01
$PaCO_2$ (mmHg)										
Control	38.2 ± 1.3	37.9 ± 1.6	38.5 ± 0.4	37.0 ± 0.3	42.0 ± 1.4*	41.6 ± 1.1*	38.6 ± 0.9	38.7 ± 0.9	39.0 ± 0.8	39.2 ± 0.8
Edaravone-10	37.9 ± 0.9	38.7 ± 1.2	38.0 ± 0.3	37.3 ± 0.7	42.6 ± 1.9*	41.3 ± 1.0*	38.5 ± 1.3	38.5 ± 1.0	38.5 ± 0.8	38.5 ± 1.1
Edaravone-100	38.9 ± 0.6	38.5 ± 0.6	38.5 ± 0.4	37.6 ± 1.0	43.1 ± 0.7*	41.0 ± 1.1*	39.2 ± 0.5	38.3 ± 1.3	38.6 ± 1.5	38.7 ± 0.7

Values are presented as mean ± SD. $PaCO_2$: partial pressure of arterial carbon dioxide. *P < 0.05, versus baseline value in the same group.

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E10, P = 0.001; and E100, P = 0.041). The decreases in diameter remained significant (and, indeed, appeared to still be constricted) at 60 min after unclamping (control, –27.3% ± 6.8%, P < 0.001; E10, –20.9% ± 2.4%, P < 0.001; and E100, –10.0% ± 4.8%, P < 0.001). In the E100 group, but not in the E10 group, the decrease in diameter was significantly smaller than in the control group (15 min, P = 0.018; 30 min, P = 0.005; and 60 min, P < 0.001) (Fig. 2).

The effect of topical ACh administration on the edaravone-induced diameter changes in the pial arterioles

In the first experiment, edaravone suppressed the decreases in vessel diameter after unclamping in both the large and small arterioles. Next, we investigated whether vascular endothelial function was involved in the edaravone-induced attenuation of the decrease in pial arteriolar diameters after unclamping. In the second experiment, we investigated the average percentage change in the diameters of large and small pial arterioles. We initially examined the arteriolar response to ACh (an endothelium-dependent vasodilator) administered through the cranial window before aortic clamping. There were no significant differences in the hemodynamics at baseline or after the topical administration of ACh in either group (Table 3). As in the first experiment, the cerebral pial arterioles dilated transiently just after unclamping and then constricted gradually up to 60 min after unclamping. All percentages represent changes in diameter with respect to the diameter immediately before the topical administration of ACh. In the control group, the cerebral pial arteriolar diameters were not significantly changed by the topical administration of 10^{-6} M ACh (3.6% ± 2.1%, P = 0.056). However, the first topical administration of 10^{-5} M ACh before clamping and the second topical administration of 10^{-5} M ACh at 60 min after unclamping led to significant increases in vessel diameter in comparison to that immediately before each ACh administration (8.7% ± 4.3% and 6.2% ± 2.1%, respectively, P < 0.001) (Fig. 3). The changes observed after the topical administration of 10^{-5} M ACh before clamping and at 60 min after unclamping did not differ significantly. In the edaravone group, as in the control group, the topical administration of 10^{-5} M ACh before clamping and at 60 min after unclamping significantly increased the diameter of the pial arterioles immediately

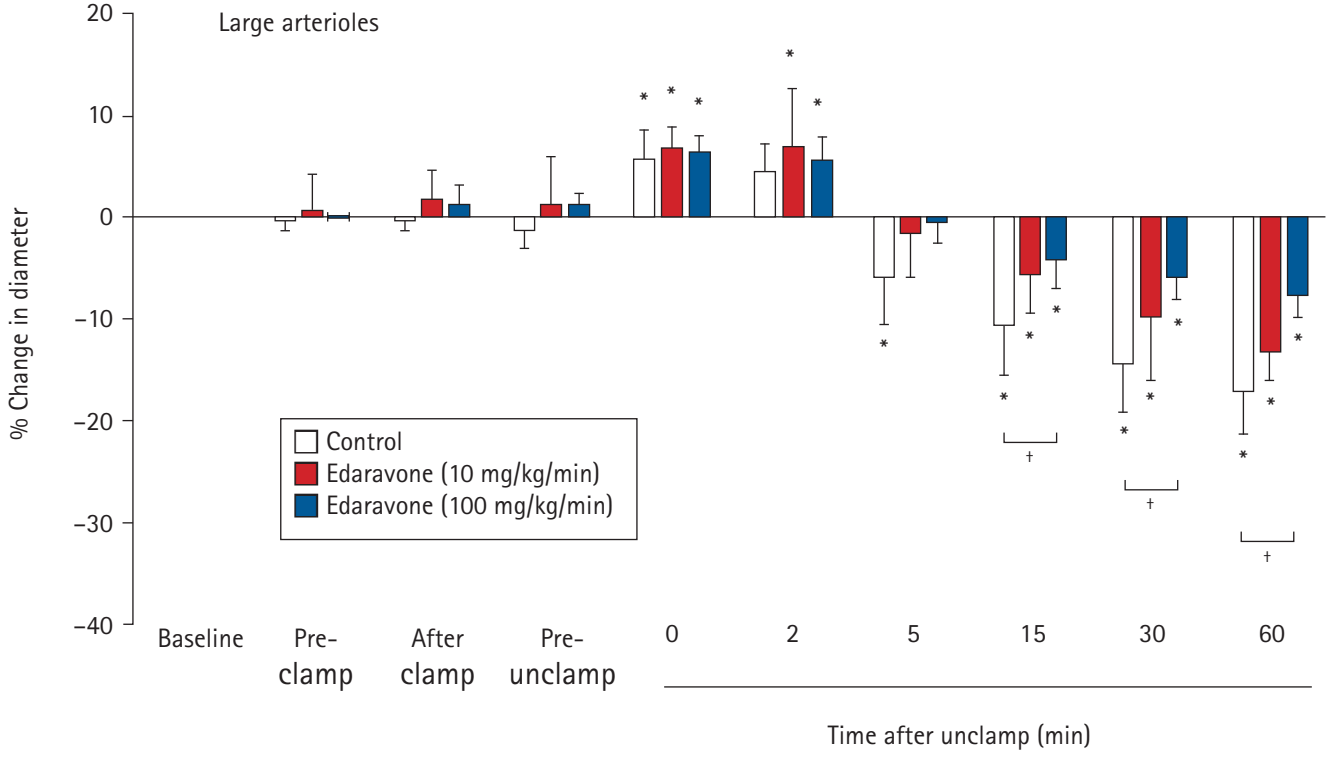

Fig. 1. Effects of the continuous intravenous infusion of edaravone on the diameter of large cerebral pial arterioles (≥ 75 μm) to aortic clamping and unclamping in 18 rabbits. Data are expressed as the percentage change from the baseline diameter measured just prior to the administration of saline or edaravone. Data are shown for pre-clamp (15 min after administration), after clamp (immediately after clamping), pre-unclamp (20 min after clamping), and at 0, 2, 5, 15, 30, and 60 min after unclamping. Values are presented as mean ± SD. *P < 0.05 in comparison to baseline in the same group. †P < 0.05 in the comparison of the indicated values.

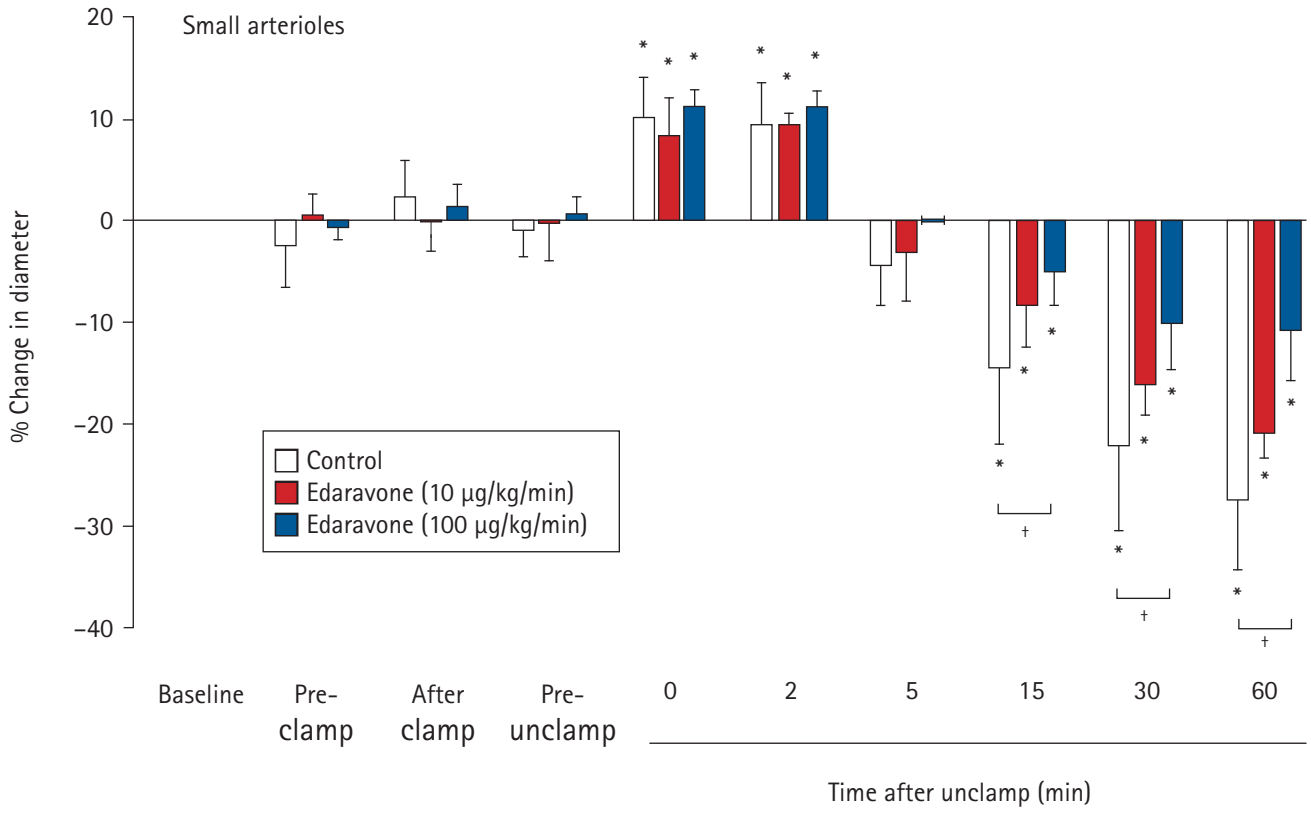

Fig. 2. Effects of the continuous intravenous infusion of edaravone on the diameter of small cerebral pial arterioles (< 75 μm) to aortic clamping and unclamping in 18 rabbits. Data are expressed as the percentage change from the baseline diameter measured just prior to administration of saline or edaravone. Data are shown for pre-clamp (15 min after administration), after clamp (immediately after clamping), pre-unclamp (20 min after clamping), and at 0, 2, 5, 15, 30, and 60 min after unclamping. Values are presented as mean ± SD. *P < 0.05 in comparison to baseline in the same group. †P < 0.05 in the comparison of the indicated values.

Table 3. Time Course of Hemodynamic Changes in Experiment 2

Variable	Pre-clamp			After unclamp
	Baseline	ACh 10^{-6} M	ACh 10^{-5} M	ACh 10^{-5} M
PrAP (mmHg)				
Control	87 ± 6	86 ± 4	94 ± 12	89 ± 14
Edaravone	89 ± 12	89 ± 13	93 ± 14	86 ± 16
DiAP (mmHg)				
Control	84 ± 7	87 ± 5	91 ± 7	86 ± 15
Edaravone	87 ± 17	88 ± 17	89 ± 15	90 ± 19
HR (beats/min)				
Control	278 ± 52	280 ± 67	264 ± 51	297 ± 46
Edaravone	273 ± 45	280 ± 48	287 ± 47	292 ± 34

Values are expressed as mean ± SD. ACh: acetylcholine, PrAP: mean proximal aortic pressure (mean arterial pressure obtained from the axillary artery), DiAP: mean distal aortic pressure (mean arterial pressure obtained from the femoral artery), HR: heart rate.

before each ACh administration (before clamping, 8.1% ± 5.7%, P = 0.001; 60 min after unclamping, 8.8% ± 4.7%, P = 0.003) (Fig. 3). The changes observed after the topical administration of 10^{-5} M ACh before clamping and at 60 min after unclamping did not differ significantly (control, P = 0.266; edaravone, P = 0.602). There were no significant differences between the control and edaravone groups in the changes in pial arteriolar diameters after the second administration of 10^{-5} M ACh at 60 min after un-

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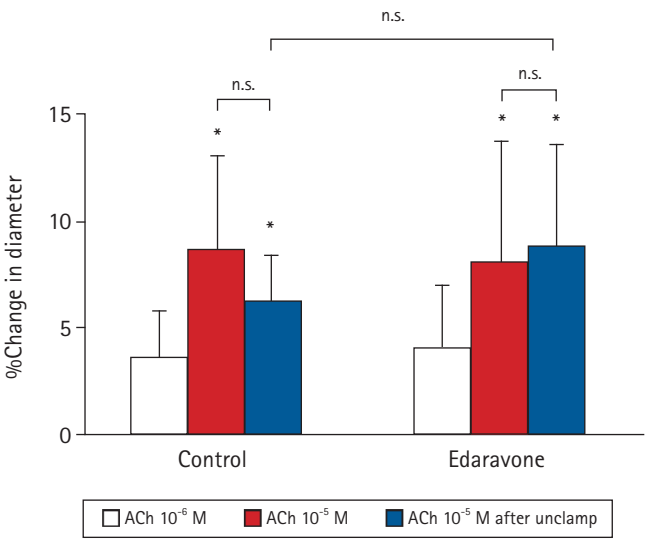

Fig. 3. Effects of topically applied acetylcholine (ACh) on the diameter of pial arterioles before and after abdominal aortic clamping in 12 rabbits. Data are expressed as the percentage change from the baseline diameter measured just prior to administration of ACh. Values are presented as mean ± SD. *P < 0.05 in comparison to the diameters before ACh administration. n.s.: not significant.

clamping (P = 0.227) (Fig. 3).

Discussion

The present study showed that edaravone, a free radical scavenger, attenuated the sustained pial arteriolar constriction observed after the unclamping of an abdominal aortic cross-clamp. This result suggests that the scavenging of free radicals attenuates the vasoconstriction of pial arterioles. However, the vascular reactivity to topical ACh did not show any changes before aortic clamping and after unclamping, and the intravenous administration of edaravone did not induce any significant changes in the cerebrovascular reactivity to ACh. The vascular endothelium may not be involved in the attenuation of vascular constriction by edaravone.

Open abdominal aortic surgery with aortic cross-clamping is a risk factor for brain dysfunction such as delirium, stroke, and POCD [3,6,7]. A previous study using xenon CT reported a significant reduction in regional and global CBF during acute delirium [13]. Early POCD after major noncardiac surgery in the elderly is secondarily associated with impaired intraoperative CBF autoregulation [14]. We previously showed that sustained pial arteriolar vasoconstriction is caused by unclamping after aortic cross-clamping in rabbits [16–18]. Pial arteriolar vasoconstriction after unclamping may be involved in functional brain disorders. In the present study, edaravone attenuated aortic unclamping-induced pial arteriolar constriction. Based on our findings, it is possible that scavenging free radicals improves functional brain disorders by inhibiting cerebral vasoconstriction.

Reperfusion after aortic unclamping generates free radicals, reactive oxygen species, and cytokines in the lower limbs and the gastrointestinal tract [1,20]. These mediators can cause high-grade systemic oxidative stress and increased inflammation during open repair of AAA [21,22,30,31]. At the vascular level, the alterations in intracellular signaling induced by oxygen free radicals lead to endothelial dysfunction, reduced vasodilation, increased vascular contraction, and structural remodeling, leading to increased peripheral resistance and elevated blood pressure [32,33].

ACh stimulates the release of nitric oxide from vascular endothelium, thereby relaxing vascular smooth muscle cells and causing vasodilation [34]. In the present study, we confirmed that topical administration of ACh dilated cerebral pial arterioles in a dose-dependent manner. Since there were no significant differences in the cerebral pial arteriolar response to ACh before abdominal aortic clamping and after unclamping, it is suggested that endothelial function does not play a major role in the vasoconstriction induced by unclamping. Thus, the suppression of free radicals on the vascular endothelium by edaravone is probably not responsible for the alteration in vascular response observed in the present study.

The mechanism by which edaravone attenuates vasoconstriction independent of endothelial function remains unclear. However, edaravone has been reported to show a clear and selective inhibitory effect against hydroxyl radical-induced endothelium-independent vascular contraction [35]. Our results are consistent with those findings. Aortic cross-clamping and unclamping produce compounds that include free radicals [20], thromboxane A2 [36,37], endothelin-1 [38,39], and tumor necrosis factor alpha [40,41], which are formed in ischemic tissues [1]. After unclamping, these humoral factors and mediators are washed out from the ischemic area to the systemic circulation, which can then damage the microcirculation in remote systems, including the central nervous system [42]. Several reports have demonstrated that free radical scavengers can inhibit the synthesis of these humoral factors [43–45]. Exogenous antioxidants, such as edaravone, might attenuate cerebral vasoconstriction by inhibiting the synthesis of humoral factors rather than through the protection of the vascular endothelium from free radicals. Further investigation is necessary to demonstrate the involvement of humoral factors.

Continuous edaravone infusion at 3–10 mg/kg/h (50–167 μg/kg/min) has been successfully used to obtain free radical scavenging in rodents [46–48]. Therefore, we investigated the effects of

two doses (10 and 100 μg/kg/min) of edaravone in the present study.

In conclusion, free radicals during abdominal aortic surgery might cause the contraction of cerebral blood vessels independent of endothelial function in rabbits. The suppression of free radicals attenuated sustained pial arteriolar vasoconstriction after aortic unclamping. Thus, free radical scavengers might have brain protective effects to maintain CBF independent of endothelial function.

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Conflicts of Interest

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

Author Contributions

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References

1. Gelman S. The pathophysiology of aortic cross-clamping and unclamping. Anesthesiology 1995; 82: 1026-60.
2. Ogoh S. Relationship between cognitive function and regulation of cerebral blood flow. J Physiol Sci 2017; 67: 345-51.
3. Marcantonio ER, Goldman L, Mangione CM, Ludwig LE, Muraca B, Haslauer CM, et al. A clinical prediction rule for delirium after elective noncardiac surgery. JAMA 1994; 271: 134-9.
4. Visser L, Prent A, van der Laan MJ, van Leeuwen BL, Izaks GJ, Zeebregts CJ, et al. Predicting postoperative delirium after vascular surgical procedures. J Vasc Surg 2015; 62: 183-9.
5. Raats JW, Steunenberg SL, de Lange DC, van der Laan L. Risk factors of post-operative delirium after elective vascular surgery in the elderly: a systematic review. Int J Surg 2016; 35: 1-6.
6. Benoit AG, Campbell BI, Tanner JR, Staley JD, Wallbridge HR, Biehl DR, et al. Risk factors and prevalence of perioperative cognitive dysfunction in abdominal aneurysm patients. J Vasc Surg 2005; 42: 884-90.
7. Bryson GL, Wyand A, Wozny D, Rees L, Taljaard M, Nathan H. A prospective cohort study evaluating associations among delirium, postoperative cognitive dysfunction, and apolipoprotein E genotype following open aortic repair. Can J Anaesth 2011; 58: 246-55.
8. Rudolph JL, Marcantonio ER. Review articles: postoperative delirium: acute change with long-term implications. Anesth Analg 2011; 112: 1202-11.
9. Benson RA, Ozdemir BA, Matthews D, Loftus IM. A systematic review of postoperative cognitive decline following open and endovascular aortic aneurysm surgery. Ann R Coll Surg Engl 2017; 99: 97-100.
10. Dasgupta M, Dumbrell AC. Preoperative risk assessment for delirium after noncardiac surgery: a systematic review. J Am Geriatr Soc 2006; 54: 1578-89.
11. Sugimoto M, Kodama A, Narita H, Banno H, Yamamoto K, Komori K. Pre- and Intraoperative Predictors of Delirium after Open Abdominal Aortic Aneurysm Repair. Ann Vasc Dis 2015; 8: 215-9.
12. Evered LA, Silbert BS. Postoperative cognitive dysfunction and noncardiac surgery. Anesth Analg 2018; 127: 496-505.
13. Yokota H, Ogawa S, Kurokawa A, Yamamoto Y. Regional cerebral blood flow in delirium patients. Psychiatry Clin Neurosci 2003; 57: 337-9.
14. Goettel N, Burkhart CS, Rossi A, Cabella BC, Berres M, Monsch AU, et al. Associations between impaired cerebral blood flow autoregulation, cerebral oxygenation, and biomarkers of brain injury and postoperative cognitive dysfunction in elderly patients after major noncardiac surgery. Anesth Analg 2017; 124: 934-42.
15. Toth P, Tarantini S, Csiszar A, Ungvari Z. Functional vascular contributions to cognitive impairment and dementia: mechanisms and consequences of cerebral autoregulatory dysfunction, endothelial impairment, and neurovascular uncoupling in aging. Am J Physiol Heart Circ Physiol 2017; 312: H1-20.

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16. Uchida M, Iida H, Iida M, Dohi S. Changes in cerebral microcirculation during and after abdominal aortic cross-clamping in rabbits: the role of thromboxane A2 receptor. Anesth Analg 2003; 96: 651-6.
17. Uchida M, Iida H, Iida M, Kumazawa M, Sumi K, Takenaka M, et al. Both milrinone and colforsin daropate attenuate the sustained pial arteriolar constriction seen after unclamping of an abdominal aortic cross-clamp in rabbits. Anesth Analg 2005; 101: 9-16.
18. Kumazawa M, Iida H, Uchida M, Iida M, Takenaka M, Dohi S. The comparative effects of intravenous nicardipine and prostaglandin E1 on the cerebral pial arteriolar constriction seen after unclamping of an aortic cross-clamp in rabbits. Anesth Analg 2007; 104: 659-65.
19. Lopez MG, Hughes CG, DeMatteo A, O'Neal JB, McNeil JB, Shotwell MS, et al. Intraoperative oxidative damage and delirium after cardiac surgery. Anesthesiology 2020; 132: 551-61.
20. Zammert M, Gelman S. The pathophysiology of aortic cross-clamping. Best Pract Res Clin Anaesthesiol 2016; 30: 257-69.
21. Thompson MM, Nasim A, Sayers RD, Thompson J, Smith G, Lunec J, et al. Oxygen free radical and cytokine generation during endovascular and conventional aneurysm repair. Eur J Vasc Endovasc Surg 1996; 12: 70-5.
22. Aivatidi C, Vourliotakis G, Georgopoulos S, Sigala F, Bastounis E, Papalambros E. Oxidative stress during abdominal aortic aneurysm repair--biomarkers and antioxidant's protective effect: a review. Eur Rev Med Pharmacol Sci 2011; 15: 245-52.
23. Skvarc DR, Berk M, Byrne LK, Dean OM, Dodd S, Lewis M, et al. Post-Operative Cognitive Dysfunction: an exploration of the inflammatory hypothesis and novel therapies. Neurosci Biobehav Rev 2018; 84: 116-33.
24. Grochowski C, Litak J, Kamieniak P, Maciejewski R. Oxidative stress in cerebral small vessel disease. Role of reactive species. Free Radic Res 2018; 52: 1-13.
25. Edaravone Acute Infarction Study Group. Effect of a novel free radical scavenger, edaravone (MCI-186), on acute brain infarction. Randomized, placebo-controlled, double-blind study at multicenters. Cerebrovasc Dis 2003; 15: 222-9.
26. Watanabe T, Morita I, Nishi H, Murota S. Preventive effect of MCI-186 on 15-HPETE induced vascular endothelial cell injury in vitro. Prostaglandins Leukot Essent Fatty Acids 1988; 33: 81-7.
27. Watanabe T, Yuki S, Egawa M, Nishi H. Protective effects of MCI-186 on cerebral ischemia: possible involvement of free radical scavenging and antioxidant actions. J Pharmacol Exp Ther 1994; 268: 1597-604.
28. Ogasawara K, Yamadate K, Kobayashi M, Endo H, Fukuda T, Yoshida K, et al. Effects of the free radical scavenger, edaravone, on the development of postoperative cognitive impairment in patients undergoing carotid endarterectomy. Surg Neurol 2005; 64: 309-13.
29. Zhou Y, Wu X, Ye L, Bai Y, Zhang H, Xuan Z, et al. Edaravone at high concentrations attenuates cognitive dysfunctions induced by abdominal surgery under general anesthesia in aged mice. Metab Brain Dis 2020; 35: 373-83.
30. Papalambros E, Sigala F, Georgopoulos S, Paraskevas KI, Andreadou I, Menenakos X, et al. Malondialdehyde as an indicator of oxidative stress during abdominal aortic aneurysm repair. Angiology 2007; 58: 477-82.
31. Gryszczyńska B, Budzyń M, Formanowicz D, Formanowicz P, Krasiński Z, Majewska N, et al. Advanced oxidation protein products and carbonylated proteins levels in endovascular and open repair of an abdominal aortic aneurysm: the effect of pre-, intra-, and postoperative treatment. Biomed Res Int 2019; 2019: 7976043.
32. Montezano AC, Touyz RM. Molecular mechanisms of hypertension--reactive oxygen species and antioxidants: a basic science update for the clinician. Can J Cardiol 2012; 28: 288-95.
33. Montezano AC, Touyz RM. Reactive oxygen species and endothelial function--role of nitric oxide synthase uncoupling and Nox family nicotinamide adenine dinucleotide phosphate oxidases. Basic Clin Pharmacol Toxicol 2012; 110: 87-94.
34. Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature 1980; 288: 373-6.
35. Tosaka M, Hashiba Y, Saito N, Imai H, Shimizu T, Sasaki T. Contractile responses to reactive oxygen species in the canine basilar artery in vitro: selective inhibitory effect of MCI-186, a new hydroxyl radical scavenger. Acta Neurochir (Wien) 2002; 144: 1305-10.
36. Mathieson MA, Dunham BM, Huval WV, Lelcuk S, Stemp LI, Valeri CR, et al. Ischemia of the limb stimulates thromboxane production and myocardial depression. Surg Gynecol Obstet 1983; 157: 500-4.
37. Paterson IS, Klausner JM, Pugatch R, Allen P, Mannick JA, Shepro D, et al. Noncardiogenic pulmonary edema after abdominal aortic aneurysm surgery. Ann Surg 1989; 209: 231-6.
38. Dovgan PS, Edwards JD, Rowley JM, Agrawal DK, Adrian TE. Effects of ischaemia and reperfusion on vasoactive neuropeptide levels in the canine infrarenal aortic revascularization model. Cardiovasc Surg 1996; 4: 470-5.
39. Fukuda S, Taga K, Tanaka T, Sakuma K, Fujiwara N, Shimoji K, et al. Relationship between tissue ischemia and venous endothe-

lin-1 during abdominal aortic aneurysm surgery. J Cardiothorac Vasc Anesth 1995; 9: 510-4.
40. Cabiè A, Farkas JC, Fitting C, Laurian C, Cormier JM, Carlet J, et al. High levels of portal TNF-alpha during abdominal aortic surgery in man. Cytokine 1993; 5: 448-53.
41. Vasdekis SN, Argentou M, Kakisis JD, Bossios A, Gourgiotis D, Karanikolas M, et al. A global assessment of the inflammatory response elicited upon open abdominal aortic aneurysm repair. Vasc Endovascular Surg 2008; 42: 47-53.
42. Katseni K, Chalkias A, Kotsis T, Dafnios N, Arapoglou V, Kaparos G, et al. the effect of perioperative ischemia and reperfusion on multiorgan dysfunction following abdominal aortic aneurysm repair. Biomed Res Int 2015; 2015: 598980.
43. Kamiya S, Shirahase H, Nakamura S, Kanda M, Matsui H, Yoshimi A, et al. A novel series of thromboxane A2 synthetase inhibitors with free radical scavenging and anti-peroxidative activities. Chem Pharm Bull (Tokyo) 2001; 49: 563-71.
44. Sedeek MH, Llinas MT, Drummond H, Fortepiani L, Abram SR, Alexander BT, et al. Role of reactive oxygen species in endothelin-induced hypertension. Hypertension 2003; 42: 806-10.
45. Onimaru S, Nakamura K, Kariyazono H, Ikeda R, Ueno T, Fukumoto Y, et al. Inhibitory effects of edaravone on the production of tumor necrosis factor-alpha in the isolated heart undergoing ischemia and reperfusion. Heart Vessels 2006; 21: 108-15.
46. Ishii H, Petrenko AB, Sasaki M, Satoh Y, Kamiya Y, Tobita T, et al. Free radical scavenger edaravone produces robust neuroprotection in a rat model of spinal cord injury. Brain Res 2018; 1682: 24-35.
47. Ohta S, Iwashita Y, Kakinoki R, Noguchi T, Nakamura T. Effects of continuous intravenous infusion of MCI-186 on functional recovery after spinal cord injury in rats. J Neurotrauma 2011; 28: 289-98.
48. Yamashita T, Shoge M, Oda E, Yamamoto Y, Giddings JC, Kashiwagi S, et al. The free-radical scavenger, edaravone, augments NO release from vascular cells and platelets after laser-induced, acute endothelial injury in vivo. Platelets 2006; 17: 201-6.

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Non-convulsive status epilepticus in the immediate postoperative period following spine surgery -a case report-

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Case Report

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Background: Non-convulsive status epilepticus (NCSE), in which continuous epileptiform discharges occur without seizure-like movement, is rare and unfamiliar to anesthesiologists, both of which make this condition overlooked in patients with decreased levels of consciousness following general anesthesia.
Case: We report on an elderly female patient who developed NCSE in the immediate postoperative period after the spine surgery. Initially, delayed emergence from anesthesia was suspected, but the electroencephalogram confirmed NCSE, and anticonvulsant therapy was initiated.
Conclusions: Delayed emergence is commonly attributed to cerebrovascular events or residual anesthetic effects, but NCSE must be included in the differential diagnosis, especially in elderly patients. Anticonvulsant therapy should be initiated as soon as possible for a better prognosis.

Keywords: Delayed emergence from anesthesia; Electroencephalography; Epilepsy; General anesthesia; Postoperative complications; Status epilepticus.

Non-convulsive status epilepticus (NCSE) can be defined as the condition of continuous or intermittent clinical epileptic activity without convulsion, lasting at least for 30 minutes with electroencephalogram (EEG) evidence of seizure [1]. The main clinical feature of NCSE is a change in behavior or consciousness such as mutism, mild amnesia to stupor, and agitation [1,2]. However, there is no universally accepted definition of NCSE.

A decreased level of consciousness after general anesthesia could be attributed to residual anesthetic effects, cerebrovascular events such as hemorrhage or ischemia, and other metabolic derangements. Therefore, it is not easy to distinguish NCSE among the many possible causes of decreased consciousness or lack of responsiveness. The occurrence of NCSE in the immediate postoperative period is too rare to estimate the prevalence. We found only two reported cases of NCSE in the immediate postoperative period after the brain surgery [3,4]. A single report from India documented two patients with NCSE after the extracranial surgery. However, the patients were thought to have NCSE based on circumstantial evidence, not EEG findings [5]. To our knowledge, the presentation of NCSE immediately after the non-cranial surgery has never been published.

The following case describes an elderly female patient who developed NCSE in the immediate postoperative period and presents a discussion that highlights the importance of NCSE in the differential diagnosis of decreased consciousness.

Case Report

The Institutional Review Board of Dongguk University Ilsan Hospital approved this case report (approval number: 2020-09-022). A 75-year-old woman with well-controlled hypertension and diabetes mellitus (height: 154.1 cm, weight: 52.8 kg) was scheduled to undergo a transforaminal lumbar interbody fusion of L3-S1. She had undergone uneventful surgery with general anesthesia for a laminectomy eight years earlier. She was taking oral hypoglycemic and antihypertensive agents with analgesics for back pain. She had no history of psychiatric illnesses or drug addiction. Her preoperative vital signs and biochemical parameters were unremarkable. General anesthesia was induced with propofol and maintained with air, oxygen, desflurane, remifentanil, and muscle relaxation with vecuronium. A mean arterial pressure (MAP) was maintained around 75 mmHg by an intermittent bolus injection of ephedrine, and her MAP was never below 55 mmHg at any point during the surgery. There was no episode of hypoxia, and the peripheral oxygen saturation was 100% throughout the surgery. The body temperature measured with an esophageal stethoscope was 36.1°C at the beginning of the surgery and gradually decreased even though an air warmer was applied, and at the end of the surgery, it was 35.1°C. Anesthesia lasted for 8 hours and 10 minutes, with the majority performed in the prone position. The estimated blood loss was 300 ml with a hemoglobin level of 10.2 g/dl without a transfusion. At the end of the anesthesia period, the residual neuromuscular block was reversed with 2.0 mg of neostigmine and 0.4 mg of glycopyrrolate and a train-of-four ratio of 1.0 was confirmed. The patient did not respond to verbal commands but breathed spontaneously with adequate tidal volume, and entropy was maintained over 95. Therefore, her condition was judged to be appropriate for extubation.

Upon arrival at the postanesthesia care unit (PACU), the patient still did not respond to verbal commands such as "open your eyes," "what is your name," and "squeeze my hand," exhibiting only painful moaning with firmly closed eyes and mouth. Her condition remained unchanged for the next 3 hours during her stay in the PACU, and we could only surmise from her facial expressions and moaning that she was in pain. A blanket and warmer were applied to treat hypothermia (35.1°C) throughout her stay in the PACU, and her temperature reached 36.1°C just before the transfer to the ward. Hypoglycemia and electrolyte abnormalities were ruled out (blood glucose concentration, 11.3 mmol/L; serum sodium, potassium, calcium, magnesium, and chloride, 140, 4.0, 4.4, 1.1, and 106 mmol/L, respectively). Her pupillary reflex could not be checked because her eyes were tightly closed, and a detailed neurological examination could not be performed due to her non-cooperation. However, there was no evidence of a cerebrovascular accident (CVA). She was hemodynamically stable, with a blood pressure of 140–170/60–90 mmHg and an SpO_2 of 97–98% on room air. The modified Aldrete's score was 8 due to unresponsiveness. We decided to transfer her to the general ward and obtain a neurology consultation for further evaluation.

The day after the surgery, the patient was transferred to the neurology service for evaluation and workup of her mental status change and the possible CVA occurrence. The neurological examination by a specialist showed no abnormal findings suggestive of a CVA. She voluntarily moved all four extremities upon occasion and responded to painful stimuli but remained mute and unresponsive to verbal commands. However, at most times, she seemed awake and possibly aware of her surroundings. At postoperative 18 hours, magnetic resonance imaging (MRI) and EEG were performed to differentiate between an ischemic stroke and NCSE in relation to speech impairment or unresponsiveness after anesthesia. The MRI findings were normal; the EEG showed a large number of generalized slow waves, and periodic lateralized epileptiform discharge-like patterns appeared occasionally over the right hemisphere (Fig. 1). After ruling out CVA and confirming the EEG pattern, she was given an intravenous loading dose of 200 mg of lacosamide and maintained on an oral dose of 50 mg of lacosamide twice a day starting on postoperative day 1. Over the next two days, she gradually became more alert and followed verbal commands and started ambulation on the third postoperative day. Thereafter, she was maintained on lacosamide, and no further episodes indicating NCSE were reported during her two-month follow-up period.

Discussion

Decreased responsiveness or alertness after general anesthesia poses many difficulties to anesthesiologists. Although there is no established definition of delayed emergence even after long periods of anesthesia, patients usually restore their response to stimuli and consciousness within 1 hour after discontinuing anesthetics.

Several factors are attributed to the delayed recovery from anesthesia in the immediate postoperative period. First, pharmacologic factors should be excluded. The residual effects from various anesthetics such as volatile anesthetics, opioids, and neuromuscular blocking agents could be responsible for delayed emergence or unresponsiveness. In our case, complete recovery from neuromuscular blocking agents was confirmed with a neuromuscular transmission monitor. The patient received a total of 3 mg of remifentanil and desflurane with an end-tidal concentration of 4% for the maintenance of anesthesia, which lasted for almost 8

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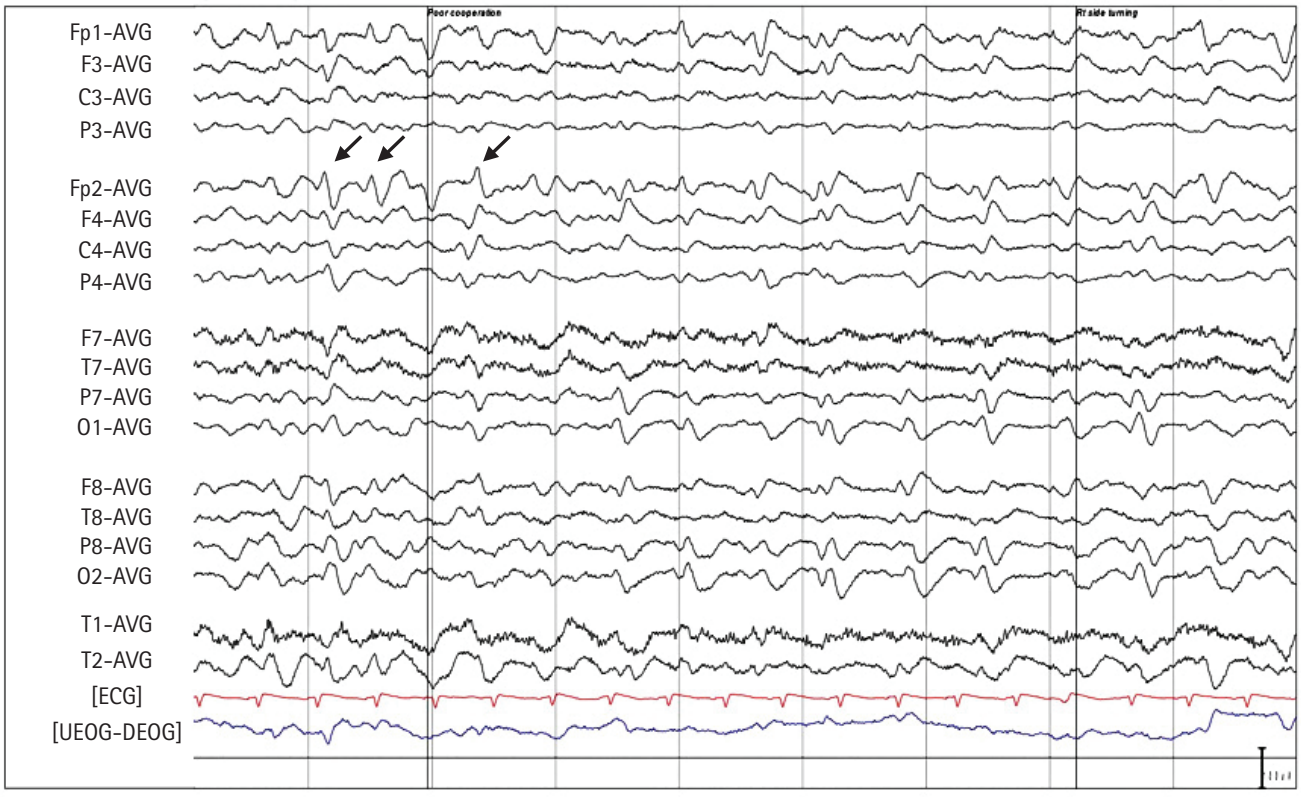

Fig. 1. Electroencephalogram (EEG) obtained during the patient's initial EEG recording on postoperative day 1 shows a large amount of generalized slow waves and periodic lateralized epileptiform discharge-like patterns (arrows) appeared occasionally over right hemisphere.

hours. Long anesthesia time could contribute to delayed emergence, but it was quite unusual that the residual anesthetic effects lasted so long, considering that remifentanil and desflurane are known for their short duration of action.

Next, metabolic causes, such as hypothermia, hypoglycemia, and electrolyte imbalance, should be considered for this circumstance. Upon arriving at the PACU, the patient's temperature was 35.1°C, which gradually rose to 36.1°C. However, her condition remained unchanged despite a rise in body temperature. Moreover, the patient's blood electrolyte concentrations were within the normal ranges, and hypoglycemia was not noted. After ruling out the usual causes of delayed emergence, neurologic events, which are relatively uncommon, but with serious sequelae, should also be considered as a possible etiology. The patient's non-cooperation made it impossible to complete a neurologic examination in the immediate postoperative period. There was no lateral sign implying CVA. However, the subsequent MRI study and a complete neurologic examination by the neurologist confirmed that. If the patient were suspected of having a stroke, we would have called for a neurologist immediately. A surgical emergency, however, was excluded based on the benign physical exam, and the patient's cardiovascular system was stable. Those non-specific findings made us hesitate to consult with the neurologist quickly.

NCSE is a condition with symptoms ranging from subtle muscle twitches to generalized coma and is difficult to diagnose unless an EEG shows the presence of seizure activity. The condition might be confused with delayed emergence or hypoactive delirium after anesthesia, especially in geriatric patients.

There is substantial variability in the reported incidence of NCSE, reflecting the lack of a universally accepted definition and the difficulty in diagnosis [6]. NCSE is likely to occur in any condition that causes brain tissue injury such as subarachnoid hemorrhage, traumatic brain injury, and intracranial surgery [7,8]. NCSE has been increasingly reported in other comatose patients in intensive care units [9]. The actual incidence would be supposed to be higher than reported, given that NCSE is easily missed. NCSE is particularly difficult to recognize in the postoperative period and often misinterpreted as residual anesthetic effects. NCSE is often a diagnosis of exclusion, and a high degree of suspicion is important. Jordan [10] suggested that NCSE should be suspected if consciousness is not restored for a long period after all types of surgery with a high risk of brain dysfunction. Old age and critical illness are known risk factors for NCSE development [11,12].

The prognosis of NCSE is highly related to an underlying disease, and when it is excluded, the prognosis may vary depending upon the presenting level of consciousness [13]. Newly developed status epilepticus in the elderly, a subtype of NCSE, is a morbid condition with mortality ranging up to 57% [1]. However, the prognosis in certain subsets of patients with *de novo* absence status is benign, such as in our patient who had no concomitant brain or systemic injury. But this does not mean that the treatment decision should be based solely on the expected outcome. Especially in postoperative patients, the risk of delayed ambulation and its associated potential complications, unnecessary diagnostic studies, and hospital costs should be considered. Although rare, delays in the diagnosis and initiation of treatment could have neurological sequelae [1,2].

With regard to treatment options, the response to initial treatment with benzodiazepines such as lorazepam is usually good but sometimes is delayed in elderly patients with *de novo* reactive status [2]. Devarajan et al. [3] reported that seizures slowly decreased 8 hours after initiating treatment and persisted for another 5 hours in the patient with newly developed NCSE in the immediate postoperative period. A follow-up EEG is not mandatory to confirm the therapeutic effect of anti-epilepsy medications, and the patient's symptoms gradually recovered over two days in our case.

The presence of seizure activity in the EEG is essential for the diagnosis and treatment of NCSE; but EEG is not one of the routine diagnostic tests for the presence of delayed emergence in the PACU, and obtaining an emergency EEG after regular working hours and during weekends is unavailable in some institutions. In this case, the patient stayed in the PACU for about 3 hours starting at 5 PM, and it was not until around 6 PM that the patient's condition raised our attention. Since we placed more possibility on hypoactive delirium and it was not regular working hours, the subsequent examination and referral were decided to be performed early the next day. However, as mentioned earlier, if circumstantial evidence highly suggestive of NCSE exists, a neurologic consultation should be sought as soon as possible for diagnosis and treatment.

Decreased consciousness can arise from serotonin syndrome and overlapping features with NCSE may lead to a misdiagnosis. Serotonin syndrome resulting from serotonin excess usually presents as a triad of neuromuscular hyperactivity, autonomic instability, and mental status changes, and the patient's history reveals current exposure to a serotonergic agent [14]. The patient reported here had been prescribed 75/650 mg of oral tramadol/acetaminophen twice daily, 5/2.5 mg of oral oxycodone/naloxone twice daily, and 100 mg celecoxib twice daily for back pain. Fentanyl was also administered for pain control in the PACU. Opioids including tramadol, oxycodone, and fentanyl have been considered serotonergic agents associated with serotonin syndrome [15]. Fentanyl in the setting of other serotonergic opioids might have caused the serotonin syndrome in our patient. This hypothesis, however, is not supported by the patient's symptoms as the patient did not show any autonomic instability including hyperthermia, hypertension, diaphoresis, or neuromuscular hyperactivity such as muscle rigidity, tremors, and bilateral Babinski signs. Initially, serotonin syndrome was ruled out based on the symptoms, and later NCSE was confirmed by EEG.

In conclusion, this case described *de novo* NCSE developments in an elderly woman after general anesthesia. This condition can be easily misdiagnosed, particularly in an unusual clinical setting such as the immediate postoperative period in the PACU and surgical locations other than the brain. The presence of NCSE after intracranial surgery or any other type of surgery should be considered in patients with an unexplained impairment of consciousness after anesthesia. Patients receiving an appropriate diagnostic approach and quick treatment are more likely to have a better prognosis.

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Conflicts of Interest

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

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References

1. Kaplan PW. The clinical features, diagnosis, and prognosis of nonconvulsive status epilepticus. Neurologist 2005; 11: 348-61.

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2. Meierkord H, Holtkamp M. Non-convulsive status epilepticus in adults: clinical forms and treatment. Lancet Neurol 2007; 6: 329-39.
3. Devarajan J, Siyam AM, Alexopoulos AV, Weil R, Farag E. Non-convulsive status epilepticus in the postanesthesia care unit following meningioma excision. Can J Anaesth 2011; 58: 68-73.
4. Burneo JG, Steven D, McLachlan RS. Nonconvulsive status epilepticus after temporal lobectomy. Epilepsia 2005; 46: 1325-7.
5. Sudha P, Koshy RC. Nonconvulsive status epilepticus: an unusual cause of postoperative unresponsiveness following general anaesthesia. Indian J Anaesth 2011; 55: 174-6.
6. Sutter R, Rüegg S, Kaplan PW. Epidemiology, diagnosis, and management of nonconvulsive status epilepticus: Opening Pandora's box. Neurol Clin Pract 2012; 2: 275-86.
7. Little AS, Kerrigan JF, McDougall CG, Zabramski JM, Albuquerque FC, Nakaji P, et al. Nonconvulsive status epilepticus in patients suffering spontaneous subarachnoid hemorrhage. J Neurosurg 2007; 106: 805-11.
8. Armon C, Radtke RA, Friedman AH. Inhibitory simple partial (non-convulsive) status epilepticus after intracranial surgery. J Neurol Neurosurg Psychiatry 2000; 69: 18-24.
9. Trevathan E, Ellen R. Grass Lecture: Rapid EEG analysis for intensive care decisions in status epilepticus. Am J Electroneurodiagnostic Technol 2006; 46: 4-17.
10. Jordan KG. Nonconvulsive status epilepticus in acute brain injury. J Clin Neurophysiol 1999; 16: 332-40.
11. Fernández-Torre JL, Díaz-Castroverde AG. Non-convulsive status epilepticus in elderly individuals: report of four representative cases. Age Ageing 2004; 33: 78-81.
12. Claassen J, Taccone FS, Horn P, Holtkamp M, Stocchetti N, Oddo M; Neurointensive Care Section of the European Society of Intensive Care Medicine. Recommendations on the use of EEG monitoring in critically ill patients: consensus statement from the neurointensive care section of the ESICM. Intensive Care Med 2013; 39: 1337-51.
13. Shneker BF, Fountain NB. Assessment of acute morbidity and mortality in nonconvulsive status epilepticus. Neurology 2003; 61: 1066-73.
14. Wilson L, Rooney T, Baugh RF, Millington B. Recognition and management of perioperative serotonin syndrome. Am J Otolaryngol 2012; 33: 319-21.
15. Rastogi R, Swarm RA, Patel TA. Case scenario: opioid association with serotonin syndrome: implications to the practitioners. Anesthesiology 2011; 115: 1291-8.

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Successful anesthetic management of a giant lower lip hemangioma patient using high flow nasal cannula -a case report-

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Case Report

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Background: Giant lip hemangioma is a rare disease that may cause difficulty in preoxygenation and ventilation when using face masks and intubation during general anesthesia induction.
Case: A laparoscopic cholecystectomy was planned for a 77-year-old woman. The patient had a giant lower lip hemangioma that was 12 × 5 × 5 cm, which made preoxygenation and ventilation through a face mask impossible and put her at risk of hemangioma rupture. We preoxygenated her through a high-flow nasal cannula (HFNC). Following propofol and succinylcholine administration, we intubated the patient with a video laryngoscope without desaturation, hemangioma rupture, or CO_2 retention.
Conclusions: HFNC is a useful tool when difficult intubation is expected in patients who have problems using conventional face masks.

Keywords: Airway management; Cannula; Continuous positive airway pressure; General anesthesia; Hemangioma; Mouth neoplasms.

Hemangioma is the most common benign tumor of vascular origin. Hemangiomas located around the airway can significantly increase the difficulty of endotracheal intubation as they occupy space and might rupture [1,2].

High-flow nasal cannula (HFNC) supplies a high flow of warm, humidified air or oxygen to the nasopharynx, reducing re-breathing and dead space, which in turn reduces CO_2 retention [3].

We report on a patient with giant lower lip hemangioma who was expected to have a difficult airway and who seemed to be impossible to preoxygenate and ventilate with a face mask. We successfully preoxygenated the patient through HFNC to induce anesthesia without desaturation.

Case Report

A 77-year-old female patient who was 153 cm tall and weighed 58 kg was admitted to hospital with chronic diarrhea. Abdominal and pelvis computed tomography showed that she had cholangitis due to gallbladder stones. The patient had a congenital giant hemangioma of the lower lip (Fig. 1). She had a history of hypertension and showed ele-

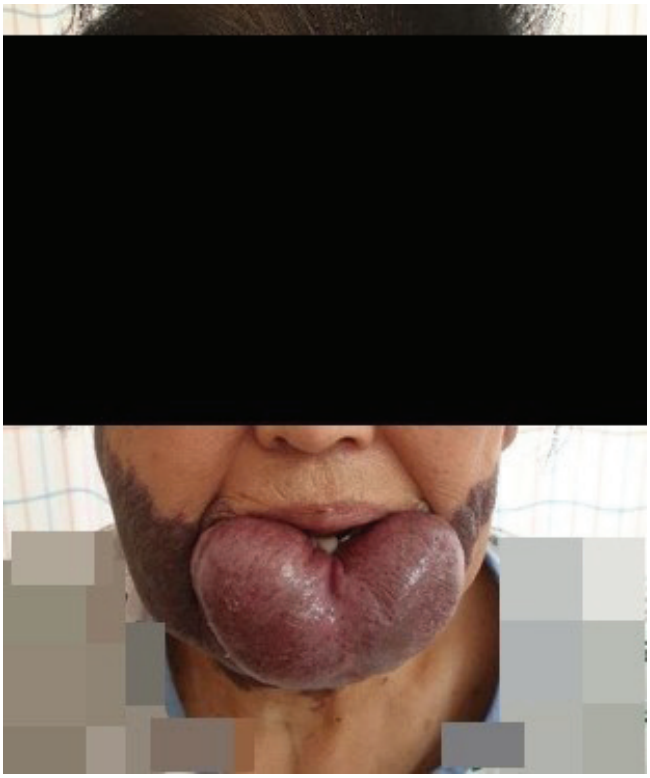

Fig. 1. The giant hemangioma of the lower lip, mixed type.

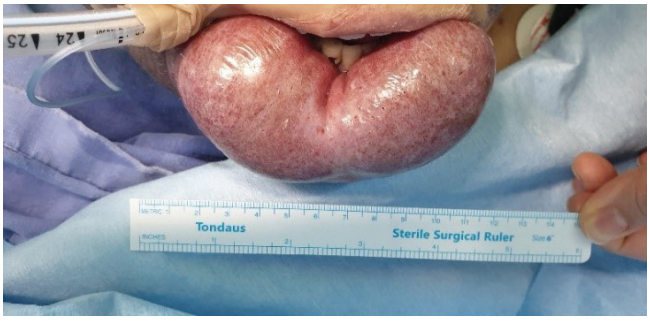

Fig. 2. Size measurement of lower lip giant hemangioma.

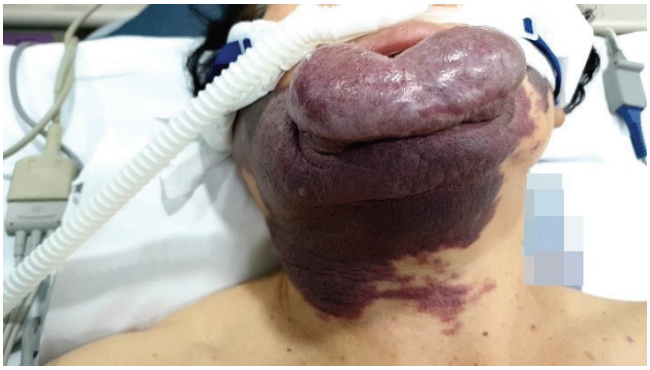

Fig. 3. Preoxygenation with HFNC in giant hemangioma patient. HFNC: high flow nasal cannula.

vated liver enzymes. Other preoperative laboratory results, including coagulation tests, were within the normal range.

Laparoscopic cholecystectomy was planned. Due to the giant hemangioma of the lower lip, airway management was expected to be difficult because it seemed like a mask would not fit. The hemangioma was 12 × 5 × 5 cm (Fig. 2). Its surface was dry with no visible bleeding, was soft when pressed, and did not occupy the oral cavity. Manual displacement to the caudad was possible and the lower gum was well exposed. The mouth opening was two fingers wide and we classified the patient as class 2 Mallampati. Neck range of motion, jaw translocation, and thyromental distance were normal. The day before surgery, we explained the pros and cons of various airway management methods and the possible need for invasive airway access and got written informed consent. The written informed consent of publication for the use of photos and case details in this report has been obtained. Initial vital signs checked in the operation theatre showed that her blood pressure was 156/77 mmHg, heart rate was 66 beats/min, and oxygen saturation was 97%. Intraoperative monitoring devices were a radial artery catheter to monitor arterial blood pressure, an electrocardiogram, pulse oximeter, a BIS A-2000TM bispectral index monitor (Aspect Medical System, USA), and a train of four scans (IDMED, France). An HFNC Optiflow THRIVE (Fisher & Paykel Healthcare, New Zealand) with an FiO_2 of 1.0 and a flow of 50 L/min was used for preoxygenation (Fig. 3). During 6 min of preoxygenation, we instructed the patient to breathe through her nose with her mouth closed. Arterial blood gas analysis after preoxygenation showed that her PaO_2 level was 462 mmHg and $PaCO_2$ level was 34 mmHg. To avoid bleeding due to the desiccation and friction, we covered the hemangioma with wet gauze to keep it moisturized. Difficult airway trolley, including emergency cricothyroidotomy kit and suction device were prepared. Anesthesia induction was performed using 1% propofol and succinylcholine. During airway manipulation, HFNC was maintained with an FiO_2 of 1.0 and a flow of 50 L/min. An assistant applied a backward-upward-rightward-pressure maneuver to assist in visualizing the glottis while also manually displacing the hemangioma caudad. A cuffed endotracheal tube with an internal diameter of 7.0 mm was intubated with a stylet using a video laryngoscope (KoMAC Co., Ltd., Korea). While advancing the blade of the laryngoscope, we avoided it coming into contact with the hemangioma. The vocal cord was well visualized and classified as Cormack-Lehane grade 1 even though the tip of the blade did not reach the epiglottis. Intubation was successful without desaturation or damaging the hemangioma. After connecting the ventilator, the first end-tidal CO_2 was 36 mmHg 118 s after propofol administration and analysis of arterial blood gas sampled right after

confirmation of proper endotracheal tube position showed that the patient's PaO_2 level was 375 mmHg and $PaCO_2$ level was 44 mmHg. Anesthesia was maintained with desflurane and remifentanil and 20 mg of rocuronium was administered at the start of surgery. At the end of the operation, HFNC was applied, all anesthetics were stopped, and muscle relaxation was reversed with sugammadex. The extubation and the recovery were uneventful. The patient was discharged at post-operation day 3.

Discussion

A hemangioma is a malformation of vascular structures that is at risk of rupture. Its incidence rate is higher in females, Caucasians, premature infants, twins, and infants born from elderly mothers. The most common site is the head and neck region (60%) and followed by the trunk (25%) and limbs (15%). Of these, hemangiomas occurring in the lip area are classified as either superficial, deep, or mixed according to their depth. The patient in this case had a mixed type, which accounts for 49% of hemangiomas. Among lip hemangiomas, 60% occur in the upper lip, 36% in the lower lip, and 6% were in commissure form [1].

In this case, we used HFNC to preoxygenate and avoid hypoxia and intubated the patient using a video laryngoscope. The lesion was on the lower lip and it was large, so a mask would not fit, limiting the use of airway maintenance devices, including oropharyngeal airways. Without an airway-securing device, patients are prone to be hypoxic during anesthesia induction. There were also high risks of bleeding and aspiration if the hemangioma was damaged during airway manipulation. Bleeding may have hindered the clear visualization of anatomical structures, making intubation even more challenging [2]. As a result, we decided that it was important to secure sufficient apnea time. Therefore, we needed to be sure that the patient was preoxygenated well. Thus, we needed a device capable of supplying high FiO_2 regardless of the patient's inspiratory flow. An airway assessment with modified LEMON(-Look externally, Evaluate 3-3-2 rule, Mallampati, Obstruction scores, Neck mobility) criteria indicated that intubation with a video laryngoscope seemed possible. We considered intubating the patient with a fiberoptic bronchoscope while she was awake. However, this procedure usually takes more time than intubation with a video laryngoscope. Moreover, sedation and analgesics used during fiberoptic bronchoscopy may cause hypoventilation leading to desaturation, which is grave when bag-mask ventilation is impossible. Furthermore, the chances of damaging the hemangioma would be higher when manipulating a fiberoptic bronchoscope, which we were less familiar with than a laryngoscope. If bleeding occurred, the fiberoptic bronchoscope would have been harder to use because the blood would severely limit visibility. Furthermore, the patient refused awake intubation because she was worried about the discomfort.

HFNC has many advantages over conventional oxygenation devices. HFNC supplies high oxygen flow and can warm and humidify it regardless of the high flow. Humidification enhances the washout of secretion and avoids mucosal injury. A high flow of oxygen reduces dead space because it decreases re-breathing and it generates positive end-expiratory pressure, which is higher with the mouth closed and is proportional to the flow. HFNC washes out CO_2 during apneic oxygenation [3]. There have been reports of various procedures being completed without CO_2 retention in a mean apnea time of 22.5 min using only HFNC with a FiO_2 of 1.0 and a flow of 40–70 L/min without endotracheal intubation [4]. HFNC also allowed us to maintain oxygenation while attempting orotracheal intubation because it does not occupy the oropharynx where the intubation occurs.

However, the use of HFNC is not well established in any difficult airway guidelines. Studies comparing HFNC with conventional devices are ongoing. It may be suitable for use for ventilation in a patient with severe hypoxemic respiratory failure, preoxygenation during general anesthesia, intubation support, post-extubation support, oxygenation during bronchoscopy in a patient with a high risk of respiratory decompensation, and ventilation in laryngologic surgery [3].

There is controversy about whether HFNC can be used as a preoxygenation and ventilation device as an alternative to conventional face masks to induce general anesthesia. Studies show that apneic oxygenation through HFNC has a longer apnea time than apneic oxygenation through a face mask [5]. Also, when HFNC was used for preoxygenation and apneic oxygenation was continued until the airway was secured, the median apnea time, which was the time until O_2 saturation falls below 90% after neuromuscular blockade was 14 min [6]. Furthermore, a study has shown that preoxygenation through HFNC increases operator convenience and reduces submandibular pain during induction [7]. Two studies are being conducted to determine whether HFNC can replace face masks during general anesthesia preoxygenation [8,9]. Taken together, this evidence shows that it may be possible to use HFNC in some patients instead of face masks for preoxygenation during general anesthesia induction.

We searched and reviewed cases in which face mask ventilation was not possible due to facial lesions and alternative methods were used. Full-text reviews were conducted for six articles [10–15] (Table 1). Our search strategy is presented in the Appendix. Of these articles, preoxygenation was performed using supraglottic airway device (SAD) in four cases [10–13], a Rendell-Bak-

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Table 1. Cases Using Alternative Preoxygenation Devices due to Difficult Face Masks Fitting

Authors	Age (yr)/ Sex	Type of lesion	Preoxygenation method	Intubation method	Mallampati/ Comack-Lehan	Size of lesion
Neeta et al. [10]	65/F	AVM of nose	SAD (i-gel)	Direct laryngoscopy	2/N/A	7 × 7 cm
Asai et al. [11]	53/F	Post gangrenous mass	SAD (Fastrach)	Awake FOI through SAD	N/A/N/A	5 × 5 cm
Nafiu and Coker [12]	17/M	Intraoral mass	SAD (N/A)	SAD in situ	N/A/N/A	N/A
Saini et al. [13]	1/M	Cystic hygroma	SAD (Proseal)	Direct laryngoscopy	N/A/N/A	12 × 10 cm
Saini and Bansal [14]	28/F	Neurofibroma	Rendell-Baker-Soucek	Direct laryngoscopy	N/A/N/A	N/A
Gusti et al. [15]	68/M	Rhinophyma	HFNC	Videolaryngosopy	2/1	12 × 7 cm

AVM: arteriovenous malformation, FOI: fiberoptic intubation, HFNC: high flow nasal cannula, N/A: not available, SAD: supraglottic airway device.

er-Soucek mask in one [14], and HFNC in one [15]. Regarding the use of SAD during preoxygenation after mild sedation while the patient is breathing on their own, inserting and removing an SAD for intubation might damage the hemangioma. Rendell-Baker-Soucek mask was not suitable for this patient due to the size of the hemangioma and might have pressed on the lesion, causing injury and bleeding.

In conclusion, we successfully managed a giant lower lip hemangioma patient for whom preoxygenation through a face mask seemed ineffective and bag-mask ventilation seemed difficult using HFNC. HFNC can be useful when difficult intubation is expected in patients who would have difficulty using a conventional face mask.

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References

1. George A, Mani V, Noufal A. Update on the classification of hemangioma. J Oral Maxillofac Pathol 2014; 18(Suppl 1): S117-20.
2. Murillo M, Zarza M, Gómez S, Chica J, Carrasquilla R, de la Vega J, et al. Anesthesia for emergency tracheostomy due to bleeding hemangioma of the tongue in a pregnant patient. Colomb J Anesthesiol 2012; 40: 313-7.
3. D'Cruz RF, Hart N, Kaltsakas G. High-flow therapy: physiological effects and clinical applications. Breathe (Sheff) 2020; 16: 200224.
4. Gustafsson IM, Lodenius Å, Tunelli J, Ullman J, Jonsson Fagerlund M. Apnoeic oxygenation in adults under general anaesthesia using Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE) - a physiological study. Br J Anaesth 2017; 118: 610-7.
5. Hua Z, Liu Z, Li Y, Zhang H, Yang M, Zuo M. Transnasal humidified rapid insufflation ventilatory exchange vs. facemask oxygenation in elderly patients undergoing general anaesthesia: a randomized controlled trial. Sci Rep 2020; 10: 5745.
6. Patel A, Nouraei SA. Transnasal Humidified Rapid-Insufflation Ventilatory Exchange (THRIVE): a physiological method of increasing apnoea time in patients with difficult airways. Anaes-

thesia 2015; 70: 323-9.
7. Tremey B, Squara P, De Labarre H, Ma S, Fischler M, Lawkoune JD, et al. Hands-free induction of general anesthesia: a randomised pilot study comparing usual care and high-flow nasal oxygen. Minerva Anestesiol 2020; 86: 1135-42.
8. Vourc'h M, Huard D, Feuillet F, Baud G, Guichoux A, Surbled M, et al. Preoxygenation in difficult airway management: high-flow oxygenation by nasal cannula versus face mask (the PREOPTIDAM study). Protocol for a single-centre randomised study. BMJ Open 2019; 9: e025909.
9. Jo JY, Kim WJ, Ku S, Choi SS. Comparison of preoxygenation with a high-flow nasal cannula and a simple mask before intubation during induction of general anesthesia in patients undergoing head and neck surgery: study protocol clinical trial (SPIRIT Compliant). Medicine (Baltimore) 2020; 99: e19525.
10. Neeta S, Rao R, Upadya M, Keerthi P. Arteriovenous malformation of face: a challenge to anesthesiologists. Anesth Essays Res 2017; 11: 784-6.
11. Asai T, Matsumoto H, Shingu K. Awake tracheal intubation through the intubating laryngeal mask. Can J Anaesth 1999; 46: 182-4.
12. Nafiu OO, Coker N. A rather unconventional use of the laryngeal mask airway. Paediatr Anaesth 2007; 17: 998-1000.
13. Saini S, Dayal M, Gupta A. Infantile cystic hygroma: an unusual perioperative course. Anesth Essays Res 2017; 11: 268-70.
14. Saini S, Bansal T. Anesthetic management of difficult airway in a patient with massive neurofibroma of face: Utility of Rendell Baker Soucek mask and left molar approach for ventilation and intubation. J Anaesthesiol Clin Pharmacol 2013; 29: 271-2.
15. Gusti V, Vaghadia H. Pre-oxygenation with Optiflow THRIVE™ (transnasal humidified rapid insufflation ventilatory exchange) in a patient with impossible bag mask ventilation due to large facial tumor. J Clin Anesth 2020; 64: 109847.

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Appendix

Search strategy

PUBMED, EMBASE

('difficult face mask' or 'difficult face mask' or 'difficult face mask' or 'difficult mask' or 'difficult airway' or 'impossible mask' or 'lip hemangioma' or 'face tumor' or 'face lesion' or 'perioral lesion' or 'perioral tumor' or 'face malformation' or 'circumoral tumor' or 'face deformity') and ('preoxygenation' or 'alternative airway' or 'laryngeal mask' or 'laryngeal airway' or 'HFNC' or 'High flow nasal cannula' or 'THRIVE' or 'transnasal humidified rapid insufflation ventilatory exchange' or 'rendell baker' or 'oxygen hood' or 'oxygen tent' or 'venturi mask' or 'non rebreather' or 'non rebreathing')

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Tube or not tube in COVID-19 positive patients: that is the question

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Managing a patient's airway is essential for adequate oxygenation and ventilation; failure to do so, even for a brief period of time, can be life threatening. In addition, medical literature indicates a significant association between obesity and the rate of difficult tracheal intubation, difficult laryngoscopy, Mallampati scores ≥ 3, and a risk of obstructive sleep apnea (OSA). Regional anesthesia is recommended by the American Society of Anesthesiologists for use in obese patients with OSA, when possible. It is ideal for such patients because it can avoid airway manipulation, the use of cardio-depressant inhaled anesthetics, and the use of respiratory depressant opioids [1]. However, even when regional anesthesia is used, anesthesiologists should always be prepared to obtain airway access in cases requiring conversion to general anesthesia [1].

The treatment of surgical patients with confirmed or suspected coronavirus disease (COVID-19) is a challenge for all anesthesiologists. General anesthesia requiring airway intervention may exacerbate COVID-19 pneumonia, and aerosol generation during airway intervention risks COVID-19 transmission to medical staff. However, regional anesthesia is not an aerosol-generating procedure [2].

Written informed consent was obtained from the patient and the patient described herein consented to the publication of this report.

At San Salvatore Academic Hospital in L'Aquila, Italy, a 65-year-old COVID-19 positive woman, without associated symptoms or evidence of pneumonia, underwent right superolateral quadrantectomy, with regional lymph node dissection, that was not deferrable according to the surgeon. Her height was 175 cm and weight was 140 kg (body mass index: 45 kg/m^2), and she had an American Society of Anesthesiologists physical status of 3. She had several comorbidities, including hypertension, OSA, respiratory insufficiency, diabetes mellitus type 2, dyslipidemia, peripheral neuropathy, and empty saddle syndrome. Arterial blood gas analysis showed a paO_2 of 63 mmHg and pCO_2 of 51 mmHg without oxygen supplementation. The patient fulfilled many criteria used to predict difficulty with intubation or ventilation: Mallampati = 3, STOP-Bang score = 7, El-Ganzouri score = 8, and neck circumference = 43 cm.

Two milligrams of midazolam was administered intravenously at the start. We elected to perform a pectoralis and serratus plane type 2 (PECS-2) block and a parasternal block under sedation and spontaneous breathing, with all equipment needed for difficult airway management at hand. The PECS-2 and parasternal blocks were performed in a block room using ultrasound guidance and a 50-mm needle. The patient was placed in a lateral position to direct any respiratory aerosol droplets away from the operator. In performing the PECS-2 block, the needle was advanced to below the pectoralis minor and above the serratus anterior, and a local anesthetic (20 ml of ropivacaine 0.75%) was deposited into this anatomical space (to cover the medial pectoral nerve and the lateral branches of the

intercostal nerves). In the parasternal block, ropivacaine 0.375% was injected between the pectoralis major and intercostal muscles. Subsequently, the patient underwent surgery wearing a surgical mask, in the operating room, with spontaneous breathing in all procedures. Monitoring included peripheral capillary oxygen saturation, non-invasive blood pressure, electrocardiogram, heart rate, and end-tidal CO_2. Under spontaneous breathing, propofol infusion was administered at 3–4 mg/kg/h, and oxygen was administered at 4 L/min per nasal cannula under the patient's mask.

No opioid or vasopressor medications were used. The surgery lasted approximately 1 h. The patient was then monitored for 30 min, and paracetamol at 1 g/8 h was scheduled. No rescue therapy was necessary, and no nausea, vomiting, or cardiac or respiratory complications were encountered postoperatively.

Regional anesthesia may have some advantages over general anesthesia in COVID-19 patients who have difficulty in airway [2].

The incidence of difficult intubation ranges from 1% to 8%, and the incidence of failed intubation ranges from 0.05% to 0.35% [1]. These findings highlight the importance of considering regional anesthesia techniques as alternatives to general anesthesia in COVID-19 patients who have difficulty in airway.

Moreover, regional anesthesia is associated with lesser postoperative complications such as deep vein thrombosis, pulmonary embolism, pneumonia, and cardiac events [3], as well as decreased overall hospital stay (and thus, economic cost). Obese patients who underwent regional anesthesia have similar pain scores (at rest), opioid requirements, incidence of postoperative nausea and vomiting, post-anesthesia care unit length of stay, and rate of unplanned hospital admission when compared to normal-weight patients [4]. Moreover, the use of regional anesthesia can reduce admission to the intensive care unit (ICU) after surgery; since the benefits of direct ICU admission after major elective noncardiac surgery remain unclear.

In a study conducted in our hospital center [5], ultrasound-guided pectoral nerve block type 2 provided anesthesia of the lateral thorax, from dermatomes T2 to T6, and ipsilateral parasternal block provided anesthesia of the medial area from T2 to T6. No supplemental opioids were used during the surgical procedure of quadrantectomy, and no perioperative complications were recorded.

The choice between general and loco-regional anesthesia, in obese patients with difficult airway and COVID-19 positive, remains a challenge for anesthesiologists. Literature suggests the use of regional anesthesia for surgery in patients with known or predicted difficult airway; however, data are insufficient regarding the use of fascial block in these patients. We propose this anesthesiologic approach in cases of anticipated airway management difficulty, especially in patients with COVID-19, recommending the use of a fascial block and trusting in future works that could validate our approach.

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References

1. Ye YA, Feng TR, Doyle DJ. Using regional anesthesia in difficult airway patients. Anesthesiology News 2018; 87-93. Avaliable from https://www.anesthesiologynews.com/download/Regional_ANAM18_WM.pdf
2. Hotta K. Regional anesthesia in the time of COVID-19: a minireview. J Anesth 2021; 35: 341-4.
3. Dhir S. Regional anesthesia for the high-risk patient. In: Anesthesia for the High-risk Patient. 2nd ed. Edited by McConachie I:

Cambridge, Cambridge University Press. 2009, pp 109-19.
4. Ingrande J, Brodsky JB, Lemmens HJ. Regional anesthesia and obesity. Curr Opin Anaesthesiol 2009; 22: 683-6.
5. Fusco P, Scimia P, Marinangeli F, Pozone T, Petrucci E. The association between the ultrasound-guided Serratus Plane Block and PECS I Block can represent a valid alternative to conventional anesthesia in breast surgery in a seriously ill patient. Minerva Anestesiol 2016; 82: 241-2.

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Meralgia paresthetica after pelvic fixation in a polytrauma patient

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Approximately half of the patients admitted to intensive care units (ICUs) experience moderate to severe pain during their stay [1]. Regional analgesia has been underused in ICUs despite the well-known importance of pain control in admitted patients and the available evidence on its efficacy and good safety profile. A review of regional analgesia techniques for pain management in patients admitted to the ICU has recently been published [2].

Critical trauma patients generally have several injuries that cause severe pain; some blocks have been studied in this subset of patients [3], but this is the first case report of ultrasound-guided infiltration of the lateral femoral cutaneous nerve (LFCN) in a critical care patient.

Meralgia paresthetica is an entrapment neuropathy of the LFCN, characterized by paresthesia and numbness on the anterolateral side of the thigh. It has also been described in an avulsion fracture of the anterior superior iliac spine [4] and recently in two prone-positioned patients to treat COVID-19-associated acute respiratory distress syndrome [5].

We present a 57-year-old male patient who was transferred to the emergency department of the University General Hospital of Valencia after suffering a crush while working, having been trapped by a truck. After a physical examination and computed tomography scan, a pelvic fracture, bladder injury, and perisplenic hematoma were observed, probably related to a contained subcapsular rupture of the spleen. Initially, an exploratory laparotomy was performed, 4 L of blood was evacuated, and splenectomy was performed. In addition, a tear of the sigmoid mesocolon was observed with bruising and active bleeding, and resection was performed. A massive transfusion of blood products was performed, and the patient was transferred to the ICU. In the second half of the next day, another intervention by the traumatology team was performed to treat the pelvic fracture (the left iliac fracture reaching the ipsilateral sacroiliac joint with a diastasis of the same, multiple sacral fractures with the involvement of the right sacroiliac joint, the comminuted fracture of the left ischiopubic and iliopubic branches that extend to the ipsilateral acetabulum). An Orthofix® (ORTHOFIX Srl, Italy) fixator was placed, and it was removed after the fracture had healed 56 days later. Admission to the ICU was prolonged, remaining sedated during the moments of greatest instability, and later, the patient was weaned from the ventilator, followed by progressive rehabilitation. During the last phase of admission, the patient reported severe pain with a numerical rating scale (NRS) of 8–9 that worsened with mobilization. The pain remained severe despite the treatment regimen with continuous infusion of oxycodone 8 mg/h, fentanyl 75 μg/h in patch, pregabalin 75 mg/12 h, and acetaminophen 1 g/8 h. On examination, the patient expressed localized pain on the outer face of the right thigh, from the iliac crest to the middle third of the thigh. The main suspicion was the lesion of the LFCN during the surgery for the placement and removal of the pelvic fixator (Fig. 1A). The radiograph shows the pelvic fixator

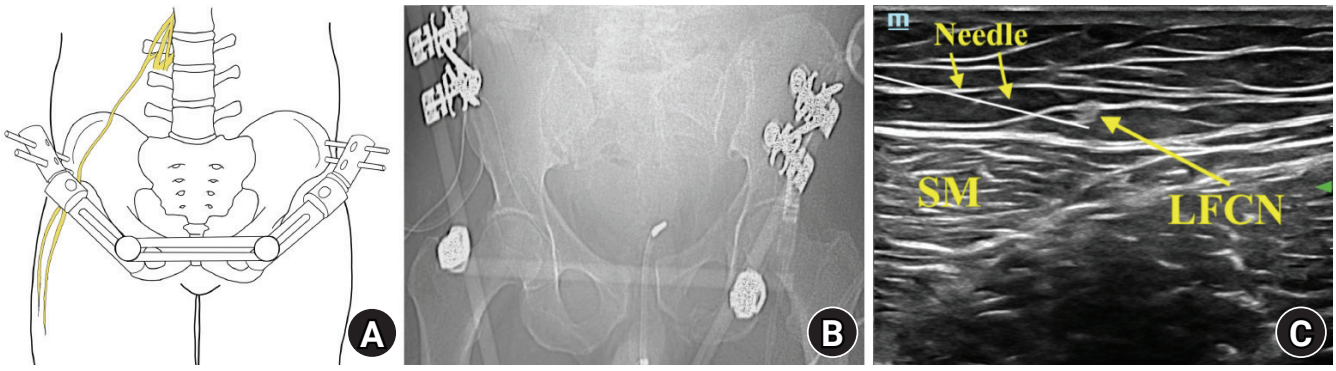

Fig. 1. (A) Representation of the lateral femoral cutaneous nerve (LFCN) in relation to the pelvic fixator. (B) X-ray with the pelvic fixator placed on the patient. (C) Ultrasound-guided infiltration of the LFCN. SM: sartorius muscle.

placed on the patient (Fig. 1B).

The ultrasound-guided infiltration of the right femoral cutaneous nerve was performed (Fig. 1C). Levo-bupivacaine 0.5% 10 mL and triamcinolone 40 mg were administered. One hour after the blockade, the patient presented an improvement of pain > 75%, shifting from NRS 9 to NRS 2. This improvement allowed the reduction of oxycodone from 8 to 6 mg/h at 1 h post-block, from 6 to 3 mg/h at 3 h post-block, from 3 to 1 mg/h at 6 h post-block, and then its final withdrawal 1 day later. The patient had stable pain relief, with an NRS score of 3 at 48 h after the LFCN block. The technique was repeated for four consecutive days. One week later, the patient's NRS score remained at 3. Pain control during the period between the blockade and discharge from the ICU kept the patient comfortable and helped to avoid the administration of high-dose opioids.

Ultrasound-guided regional analgesia techniques must be incorporated in the ICU care portfolio for the daily practice of anesthesiologists and intensive care physicians. They provide excellent pain control in several situations where high opioid doses are necessary, avoiding the side effects and dependence phenomena associated with opioids.

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References

1. Stanik-Hutt JA, Soeken KL, Belcher AE, Fontaine DK, Gift AG. Pain experiences of traumatically injured patients in a critical care setting. Am J Crit Care 2001; 10: 252-9.
2. Rubio-Haro R, Morales-Sarabia J, Ferrer-Gomez C, de Andres J. Regional analgesia techniques for pain management in patients admitted to the intensive care unit. Minerva Anestesiol 2019; 85: 1118-28.
3. Wiebalck A, Grau T. Ultrasound imaging techniques for regional blocks in intensive care patients. Crit Care Med 2007; 35(5 Suppl): S268-74.
4. Hayashi S, Nishiyama T, Fujishiro T, Kanzaki N, Kurosaka M. Avulsion-fracture of the anterior superior iliac spine with meralgia paresthetica: a case report. J Orthop Surg (Hong Kong) 2011; 19: 384-5.
5. Bellinghausen AL, LaBuzetta JN, Chu F, Novelli F, Rodelo AR, Owens RL. Lessons from an ICU recovery clinic: two cases of meralgia paresthetica after prone positioning to treat COVID-19 -associated ARDS and modification of unit practices. Crit Care 2020; 24: 580.

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Left-ventricular diastolic dysfunction in coronavirus disease: opening Pandora's box!

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Letter to the Editor

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As I read through the articles featured in a recent issue of the *Korean Journal of Anesthesiology* [1,2] that outlined the perioperative implications of coronavirus disease (COVID-19), I felt motivated to highlight the importance of COVID-19-related left-ventricular (LV) diastolic dysfunction (LVDD) in the management of this predisposed subset, particularly since the cardiovascular consequences of COVID-19 continue to be ardently discussed [3].

A systematic echocardiographic evaluation of 100 COVID-19 patients with a mean age of 66 years by Szekely et al. [4] revealed a 16% incidence rate of LVDD despite a preserved LV systolic function in as high as 90% of their patients. In addition to subclinical ventricular relaxation impairment given the advanced age of the patients and comorbidities such as systemic hypertension, the conglomeration of factors specific to COVID-19, such as systemic inflammatory milieu, endothelial dysfunction, microvascular thrombosis, arrhythmias, disturbed ventricular cross-talk (owing to the concomitant right ventricular dysfunction resulting from pulmonary hypertension), and myocardial oxygen supply-demand perturbations, can contribute significantly to LVDD, with a subsequent accentuated potential to culminate in heart failure with a preserved ejection fraction (HFpEF) [3,4].

Moreover, the use of high positive end-expiratory pressure (PEEP), which is quite commonly employed while ventilating hypoxemic COVID-19 patients, can result in an attenuated cardiac output in addition to the already impaired ventricular filling in HFpEF. This observation is supported by Chin et al. [5], who elaborated on progressive deterioration in LV lusitropy with the application of high PEEP in patients with pre-existing LV relaxation abnormalities. In addition, the underlying cardiopulmonary interactions present unique challenges in weaning mechanically ventilated patients with coexistent LVDD [3,5].

An improved comprehension of the likelihood of an altered diastology in COVID-19 patients is pivotal in staging a more well-directed management approach wherein targeted echocardiographic surveillance, cardiac biomarkers, and combined heart-lung ultrasound and inodilators can assist in the overall management of this critically ill cohort.

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Conflicts of Interest

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

References

1. Ong S, Lim WY, Ong J, Kam P. Anesthesia guidelines for COVID-19 patients: a narrative review and appraisal. Korean J Anesthesiol 2020; 73: 486-502.
2. Yek JL, Kiew SC, Ngu JC, Lim JG. Perioperative considerations for COVID-19 patients: lessons learned from the pandemic -a case series. Korean J Anesthesiol 2020; 73: 557-61.
3. Magoon R. COVID-19 and congenital heart disease: cardiopulmonary interactions for the worse! Paediatr Anaesth 2020; 30: 1160-1.
4. Szekely Y, Lichter Y, Taieb P, Banai A, Hochstadt A, Merdler I, et al. Spectrum of cardiac manifestations in covid-19: a systematic echocardiographic study. Circulation 2020; 142: 342-53.
5. Chin JH, Lee EH, Kim WJ, Choi DK, Hahm KD, Sim JY, et al. Positive end-expiratory pressure aggravates left ventricular diastolic relaxation further in patients with pre-existing relaxation abnormality. Br J Anaesth 2013; 111: 368-73.

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Long-lasting pain relief with interfascial plane blocks: key role of opening interfascial adhesions

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We read with great interest the correspondence by Piraccini and Byrne [1] in response to our report of a patient with myofascial pain syndrome (MPS), who underwent rhomboid intercostal block (RIB) at our clinic [2].

We thank the authors for their valuable comments and opinions. Their article might show a new way for both diagnosis and treatment of MPS due to fascial adhesion. We would like to share the details of long-term pain relief in our patient as additional information.

RIB is a novel interfascial block that has been used to treat MPS in recent times [2,3]. MPS is a chronic condition, and few cases might be refractory. MPS can be primary or secondary [1,2]. In secondary cases, such as in our patient, interfascial plane blocks might be a good alternative for treatment. However, it is not clear whether they provide short-term or long-term relief. To the best of our knowledge, previous case reports in the literature have described short-term pain relief on using fascial plane block for MPS [3–5]. Piraccini and Maitan [3] performed RIB in a female patient who had fascial adhesions and reported successful results; however, the long-term outcomes are unknown. Similarly, Piraccini et al. [4] performed an erector spinae plane block (ESPB) for MPS, but the authors emphasize that ESPB provides short-term relief and that fascial plane blocks should be combined with physical therapy.

In our case, we performed RIB using 20 ml of 0.25% bupivacaine with 8 mg of dexamethasone [2]. The patient was followed up for four weeks. For the first two weeks, we prescribed 25 mg oral dexketoprofen and 8 mg of thiocolchicoside. After four weeks of observation, the patient underwent follow-up once a month. He is still under follow-up. He had no recurrence of MPS in the last 6 months, required no analgesic drugs, and did not undergo physical therapy. He continues his work and daily activities. Our patient might have had fascial adhesions but experienced long-term relief with fascial hydro-dissection and bupivacaine with 8 mg of dexamethasone. Chronic pain is complicated, and interfascial adhesions might play a key role in this complex process. We aimed to treat several steps associated with the pain mechanism by using multimodal analgesia management with hydro-dissection.

The use of fascial plane blocks for MPS is a novel technique. There is a lack of information about long-term results in the literature. Further studies and larger case series are necessary to validate the results.

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References

1. Piraccini E, Byrne H. The efficacy of fascial plane blocks for myofascial pain syndrome: do they achieve long-term results? Korean J Anesthesiol 2020; 73: 566-7.
2. Ekinci M, Ciftci B, Alici HA, Ahiskalioglu A. Ultrasound-guided rhomboid intercostal block effectively manages myofascial pain. Korean J Anesthesiol 2020; 73: 564-5.
3. Piraccini E, Maitan S. Ultrasound guided rhomboid plane hydrodissection for fascial adhesion. J Clin Anesth 2020; 59: 13.
4. Piraccini E, Calli M, Taddei S, Byrne H, Rocchi M, Maitan S. Erector spinae plane block for myofascial pain syndrome: only a short-term relief? Minerva Anestesiol 2020; 86: 888-90.
5. Tulgar S, Thomas DT, Suslu H. Ultrasound guided erector spinae plane block relieves lower cervical and interscapular myofascial pain, a new indication. J Clin Anesth 2019; 53: 74.

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Unexpected visualization of the dorsal scapular artery during supraclavicular block

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Letter to the Editor

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The presence of the dorsal scapular artery (DSA) within the brachial plexus is a risk factor for complications when performing a supraclavicular block [1]. Vascular puncture-related cardiovascular and cerebrovascular complications can threaten the safety of the patient. Preoperative sonographic assessment, however, can significantly reduce the incidence of such complications.

This letter describes the unexpected visualization of the DSA during pre-operative sonographic assessment in a 60-year-old woman who was scheduled for surgery due to a fracture of the distal radius in January 2021. The DSA, a vessel branching from the subclavian artery, was identified beneath the inferior trunk while attempting to optimize imaging of the corner pocket (Fig. 1). Because the DSA was directly in the needle pathway, the corner pocket approach could not be utilized. Therefore, the intertruncal approach was used to inject between the trunks [2]. We first carefully injected a small amount of local anesthetics consisting of a 1 : 1 mixture of 1% lidocaine and 0.75% ropivacaine to open up to open up the adipose tissue layer between the inferior and middle trunk and subsequently by securing a safe route for needle advancement in the intertruncal plane [3].

The DSA often crosses the brachial plexus compartment, mostly between the inferior and middle trunk or between the middle and superior trunk [4]. Although this may increase the risk of vascular-related complications, the DSA has been rarely visualized on optimal sonographic images for the corner pocket approach [5]. If the DSA crosses beneath the first thoracic nerve root, as in the present patient, it lies directly in the path of the needle when performing the corner pocket approach. Moreover, the DSA has been reported to pass beneath the inferior trunk in 6.6% of cadavers [4]. Thus, although this condition is relatively uncommon, it is important to confirm the absence of the DSA during sonographic pre-assessment before utilizing the corner pocket approach. If the DSA is visible, an alternative technique should be used.

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Conflicts of Interest

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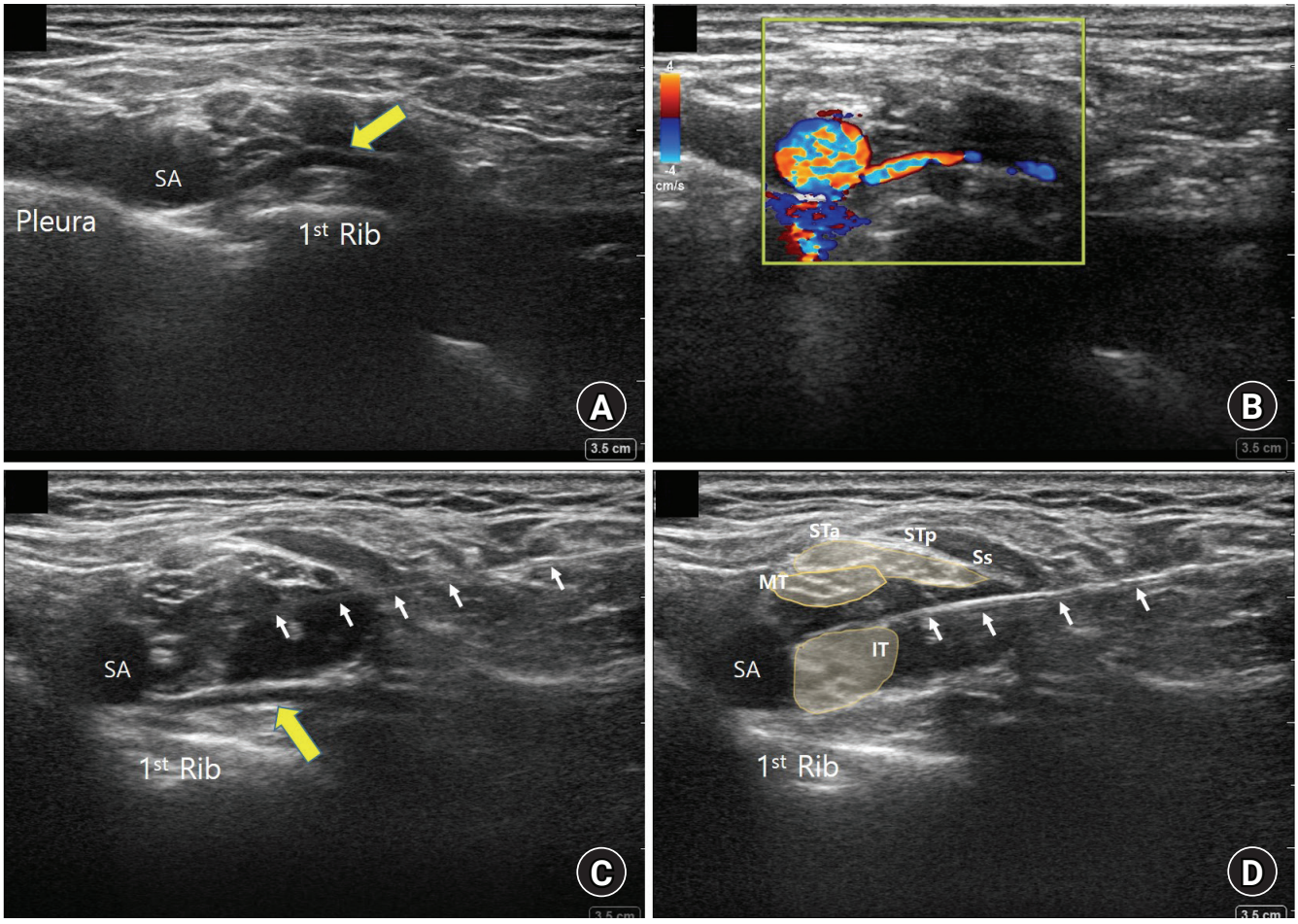

Fig. 1. Visualization of the dorsal scapular artery (DSA) while attempting to obtain the optimal sonographic image for the corner pocket block technique. (A) Image showing the DSA (yellow arrow) passing beneath the inferior trunk. (B) Color Doppler image showing that the DSA originated from the subclavian artery. (C) Image showing the needle (small arrows) aimed above the inferior trunk. (D) Image showing the injection of local anesthetics between the inferior and middle trunks. SA: subclavian artery, IT: inferior trunk, MT: middle trunk, Ss: suprascapular nerve, STp: posterior division of the superior trunk, STa: anterior division of the superior trunk.

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References

1. Nambyiah P, Umbarje K, Amir R, Parikh M, Oosthuysen SA. Sonographic assessment of arterial frequency and distribution within the brachial plexus: a comparison with the cadaveric record. Anaesthesia 2011; 66: 931-5.
2. Siddiqui U, Perlas A, Chin K, Reina MA, Sala-Blanch X, Niazi A, et al. Intertruncal approach to the supraclavicular brachial plexus, current controversies and technical update: a daring discourse. Reg Anesth Pain Med 2020; 45: 377-80.
3. Jo Y, Park J, Oh C, Chung W, Song S, Lee J, et al. Comparison of the ulnar nerve blockade between intertruncal and corner pocket approaches for supraclavicular block: a randomized controlled

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trial. Korean J Anesthesiol 2021; 74: 522-30.
4. Chaijaroonkhanarak W, Kunatippapong N, Ratanasuwan S, Amarttayakong P, Umka J, Prachaney P, et al. Origin of the dorsal scapular artery and its relation to the brachial plexus in Thais. Anat Sci Int 2014; 89: 65-70.
5. Murata H, Sakai A, Hadzic A, Sumikawa K. The presence of transverse cervical and dorsal scapular arteries at three ultrasound probe positions commonly used in supraclavicular brachial plexus blockade. Anesth Analg 2012; 115: 470-3.

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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.