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소아 전용 뇌파(electroencephalography, EEG) 모니터가 출시되고, 환자의 운동성이나 혈액학적 반응의 변화를 기반으로 한 기존의 투약 방법이 특이 과도한 마취로 인해 저혈압과 같은 부작용을 경험할 수 있다는 인식에 따라, 소아 마취 시 수술 중 뇌파 모니터링에 대한 관심이 높아지기 시작했다. 뇌파는 마취제가 의식 상실을 유도하는 표적 최종 기관인 뇌에 미치는 영향을 직접 측정한다. 지난 10년 동안 마취 및 컴퓨터 신경과학에 대한 연구를 통해 수술 중 소아 뇌파 모니터링에 대한 이해가 향상되고 임상에서 뇌파의 활용도가 확대되었다. 이제 우리는 발달 중인 소아 뇌의 신경 발달 변화, 기능적 연결성, 마취제 투여를 안내하기 위한 비독점적 EEG 파라미터의 사용, 마취 유도 중 간질성 EEG 변화, 황추/국소 마취로 인한 EEG 변화, EEG 불연속, 임상 결과 개선을 위한 EEG 사용에 대한 더 나은 통찰력을 얻게 되었다. 이 종설에서는 위에서 언급한 몇 가지 주제에 관한 최근 연구를 요약한다.

Keywords: Anesthesia; EEG; Electroencephalography; Electroencephalogram; Pediatric anesthesia; Pediatric.
Perioperative management of patients with cardiac implantable electronic devices

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Keywords: Artificial pacemaker; Cardiac arrhythmias; Cardiac resynchronization therapy devices; Cardiovascular diseases; Electromagnetic fields; General anesthesia; Implantable defibrillators; Operative surgical procedures.

 최근 몇 년 동안 심장 이식형 전자 장치(cardiac implantable electronic device, CIED)의 사용이 크게 증가하였다. 이에 따라 일생 동안 수술을 받는 CIED 환자가 늘어나면서 수술 전후 관리에 마취과 의사의 참여가 증가하고 있다. 기술의 지속적인 발전으로 영구 심박동기, 무선 심박동기, 이식형 제세동기, 심장 재동기화 치료-심박동기/제세동기, 이식형 사전기록기 등 다양한 유형의 CIED가 개발되었다. 전자기장에 노출된 CIED의 기능은 전자기 간섭의 영향을 받을 수 있으며, 그 잠재적 원인은 수술실에서 찾을 수 있다. 따라서 수술실에서 전자기 간섭으로 인한 잠재적인 부작용을 예방하기 위해 마취과 의사의 CIED에 대한 지식을 갖추고 각 유형을 식별할 수 있어야 한다. 본 종설은 CIED를 지닌 환자의 수술 전후 관리에 대해 기술한 것으로 기본 십협관 상태를 파악하기 위한 CIED 이식 적응증부터 수술 전 및 수술 중 CIED와 관련된 유의 사항, 자석 적용 및 장치 재프로그램밍을 비롯한 CIED의 수술 전후 관리, CIED 환자를 위한 수술 전후 추가적 조치까지 일련의 과정들을 포함한다. 전자 장치 및 제조 회사에 따라 프로그램링 기능과 자석 적용에 대한 반응이 다양하여 이를 이해하고 적용하는데 어려움이 있을 수 있기 때문에 본 종설은 CIED 환자의 안전한 수술 전후 관리를 위한 필수 정보를 제공한다.
Alternatives to the P value: connotations of significance

P값을 아우르는 통계적 유의성과 임상적 중요성의 어우러짐

Junyong In, Dong Kyu Lee

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연구 결과의 통계적 유의성은 귀무가설유의성검정을 기반으로 수학적으로 계산된 확률에 의해 결정된다. 통계적 유의성이 임상적 중요성을 보증하지는 않기 때문에, 통계적 유의성만으로 임상적인 의미를 부여하는 것은 적절하지 않다. 통계적 유의성만을 제시하는 결과보다는 임상적으로 의미를 가지는 차이를 내포하는 통계 결과를 제시하는 것이 바람직하다. 연구 설계의 초기 단계에서부터 임상적으로 의미 있는 최소화한 변화를 지칭하는 최소임상유의차이 (minimal clinically important difference, MCID)를 적용하는 연구 방법이 개발되었다. 이 글은 P값과 신뢰구간, 그리고 효과크기를 다루었던 지난 글에 이어서, 더 다양한 효과크기들과 MCID를 소개하고 예시와 함께 직접 계산하며, 임상적 중요성과 통계적 유의성이라는 용어 사용의 주의할 점을 다룬다.

Keywords: Clinical relevance; Clinical significance; Confidence intervals; Effect size; Minimal clinically important difference; Patient outcome assessment; P value; Statistical significance; Statistics.
Comparison of preemptive and preventive intravenous acetaminophen on opioid consumption in pediatrics undergoing posterior spinal fusion surgery: a randomized controlled trial

Yeon Ju Kim¹, Ha-Jung Kim¹, Sehee Kim², Hyungtae Kim¹, Choon Sung Lee³, Chang Ju Hwang³, Jae Hwan Cho³, Young-Jin Ro¹, Won Uk Koh¹

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Keywords: Acetaminophen; Opioid analgesics; Pain; Pediatrics; Prospective studies; Spinal fusion.

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Comparison of effects of telmisartan versus valsartan on post-induction hypotension during noncardiac surgery: a prospective observational study

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배경: 텔미사르탄(telmisartan)은 발사르탄(valsartan)보다 항고혈압 효과에 있어 더 우수한 효능을 보인다고 알려져 있다. 마취 유도 중 혈액학적 변화는 환자가 복용 중인 항고혈압(HTN) 약물에 의해 영향을 받을 수 있으므로, 본 연구에서는 비심장 수술에서 항고혈압 종류에 따른 마취 유도 후 저혈압 양상에 대해 관찰했다.

방법: 본 연구에서는 텔미살탄군과 발사르탄군의 두 군으로 나누어, 양 군에 균일하게 표준화된 마취유도를 시행하면서, 기관 내 삽관 전후 5분 이내와 수술적 절개 전후 10분 이내의 시간 동안 두 군의 마취 유도 후 혈액학적 변화와 좌심실 박출률을 담당한 좌심실 평가를 실시했다. 본 연구의 1차 평가변수는 텔미사르탄과 발사르탄 그룹에서 마취제 투여 후 평균 혈압의 감소였다. 또한, 다변량 로지스틱 회귀 분석을 사용하여 마취 유도 후 저혈압의 예측 인자를 확인했다.

결과: 비심장 수술을 받는 157명의 환자를 대상으로 관찰 연구를 진행한 결과, 복용 중인 항고혈압제 종류에 따라 마취 유도 후 평균 혈압이 유의하게 차이가 있었다. 마취 유도 후 혈액학적 변화와 좌심실 박출률은 양 군에서 유의한 차이를 보이지 않았다. 로지스틱 회귀분석 결과, 연령과 수술실에서의 수술 전 초기 평균 혈압이 마취 유도 후 저혈압의 독립적인 예측 인자로 밝혀졌다.

결론: 마취 유도 후 저혈압은 환자가 복용 중인 안지오텐신 수용체 차단제 유형에 의해 영향을 받지 않았다. 고령과 낮은 수술실 초기 혈압은 안지오텐신 수용체 차단제를 복용하는 환자에서 마취 유도 후 저혈압을 유발하는 인자이므로 유의해야 한다.

Keywords: Anesthesia; Angiotensin receptor antagonists; General surgery; Hypotension; Telmisartan; Valsartan.
Efficacy of intraoperative blood salvage and autotransfusion in living-donor liver transplantation: a retrospective cohort study

Jongchan Lee¹, Sujung Park², Jae Geun Lee³, Sungji Choo², Bon-Nyeo Koo²
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배경: 간 이식(LT)은 대량 출혈 및 동종 수혈의 필요성을 관련이 있을 수 있다. 수술 중 혈액 회수 자가 수혈(intraoperative blood salvage, IBSA)은 동종 수혈의 필요성을 줄일 수 있다. 이 연구는 LT에서 혈액 회수의 효과를 조사하는 것을 목표로 하였다.

방법: 2019년 1월 1일부터 2022년 12월 31일 사이에 선택적 생체 기증(LT)을 받은 355명의 성인 환자 중 진행성 간세포암종이 없는 59명의 이식대상자(CS 그룹)가 세이버(Cell Saver)를 사용하여 IBSA를 받았다. 성별, 나이, 말기 간 질환 모델(MELD) 점수, 수술 전 실험실 결과 및 기타 요인에 따라, IBSA를 받지 않은 296명의 이식대상자 중 118명을 성향 점수를 사용하여 매칭하였다(비-CS 그룹). 주요 결과는 수술 중 동종 적혈구(RBC) 수혈량이었다. 두 그룹 간에 수혈된 다른 혈액 성분의 양과 수술 후 실험실 소견을 비교하였다.

결과: CS 그룹의 수혈된 동종 RBC는 비-CS 그룹에 비해 유의하게 낮았다(1,506.0 vs. 1,957.5 ml, P = 0.026). 수혈된 신선 동결전혈장(FFP)은 두 그룹 간에 유의한 차이가 관찰되지 않았다. 수술 후 동종 적혈구 수혈량은 CS 그룹이 비-CS 그룹보다 유의하게 낮았다(1,500.0 vs. 2,100.0 ml, P = 0.039). 수술 후 1일째(POD1)에 퇴원 시에는 수술 후 실험실 소견에 유의한 차이가 관찰되지 않았다.

결론: LT 중에 IBSA를 사용하면 후속 응고 병증을 일으키지 않고 수술 전후 동종이계 수혈의 필요성을 효과적으로 감소시킬 수 있다.

Keywords: Autologous blood transfusion; Autotransfusion; Blood coagulation; Blood transfusion; Liver transplantation; Operative blood salvage; Postoperative complications.
Comparison of lung aeration loss in open abdominal oncologic surgeries after ventilation with electrical impedance tomography-guided PEEP versus conventional PEEP: a pilot feasibility study

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배경: 현재 수술 후 폐 합병증(postpulmonary complication, PPC)을 최소화하기 위한 이상적인 수술 중 호기말 양압(positive end-expiratory pressure, PEEP)에 관한 양질의 증거는 부족하다. 우리는 전기 임피던스 단층촬영(electrical impedance tomography, EIT)에서 도출된 개별화된 PEEP를 적용하면 수술 후 폐 합병증, 산소화 저하 및 PPC 발생을 줄일 수 있다는 가설을 세웠다.

방법: 개복 종양 수술을 받은 36명의 환자를 대상으로 예비 타당성 연구를 실시하였다. 환자들은 무작위로 배정되어 개별화된 PEEP 또는 일반 PEEP (4 cmH₂O)를 받았다. 수술 전 및 후 측정된 수정 폐 초음파 점수(modified lung ultrasound score, MLUS)를 이용하여 두 군간의 폐 합병증의 정도를 비교하였고, PaO₂/FIO₂ 비율과 PPC 발생률을 비교하였다.

결과: 개별화된 PEEP 그룹에서 수술 후 MLUS가 유의하게 증가 (12.0 ± 3.6 vs 7.9 ± 2.1, P < 0.001)하고 수술 전후 MLUS 값 사이에 유의한 차이(7.0 ± 3.3 vs 3.0 ± 1.6, P < 0.001)가 발견되어 폐 합병증의 증가를 보였으며, 수술 중 낮은 PaO₂/FIO₂ 비율을 보였다. 수술 후 PaO₂/FIO₂, 비율과 PPC 발생률은 두 그룹 간에 유의한 차이가 없었다. 사후 분석 결과 폐 합병증의 증가와 수술 중 산소화 저하는 개별화된 PEEP과 일반 PEEP과의 차이가 큰 환자에게 장점이 있다.

결론: 개별화된 PEEP은 폐 합병증과 수술 중 산소화 저하를 방지하는 것으로 보이며, 개별화된 PEEP과 일반 PEEP과의 차이가 큰 환자에게 장점이 있다.

Keywords: Electric impedance; Feasibility studies; General anesthesia; Laparotomy; Lung compliance; Positive-pressure respiration; Pulmonary atelectasis; Ultrasonography; Surgical oncology; Tomography.
The minimum effective concentration (MEC90) of bupivacaine for an ultrasound-guided suprainguinal fascia iliaca compartment block for analgesia in knee surgery: a dose-finding study

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배경: 최근 몇 년 동안 임상에서 장골 상부 근막 구획 차단술(suprainguinal fascia iliaca compartment block, SFICB)이 보편화되고 있다. 관절경 전방 십자인대 수복술을 받는 환자에서 1회 주사 SFICB를 위한 부피바카인(bupivacaine)의 최소 유효 농도(MEC90, MEC95)를 결정하기 위하여 평가자 맹검 용량 연구로 진행되었다.

방법: 3차 병원(수술 후 회복실 및 병동)에서 전향적 연구로 수행되었으며, SFICB는 척추마취 후 수술 후 진통을 위해 시행되었다. 70명의 환자가 편향된 동전 설계 상하 순차적 방법을 사용하여 할당되었으며, 부피바카인 농도를 달리하여 초음파 유도 SFICB를 시행하고 모든 환자에게 표준 복합 진통제를 투여하였다. 차단 성공은 수술 후 6시간 후 허벅지 중간 부위의 앞쪽과 옆쪽에서 실시한 단자 실험에서 통증이 없거나 촉각 감각만 남아 있는 경우로 정의하였다.

결과: 등장성 회귀 분석 및 브트스트랩 신뢰구간에 따르면, 성공적인 SFICB에 대한 부피바카인의 MEC90 값은 0.123% (95% CI [0.098, 0.191])였고 MEC95 값은 0.188% (95% CI [0.113, 0.223])였다.

결론: 본 연구에 따르면 수술 후 진통을 목적으로 SFICB를 통해 투여한 부피바카인의 MEC90 및 MEC95 값은 각각 0.123%와 0.188%였다. 저농도 부피바카인 사용의 장점은 수술 후 대퇴사두근 약화 감소와 관련이 있다는 것이다.

Keywords: Analgesia; Bupivacaine; Local anesthetics; Nerve block; Pain management; Regional anesthesia.
Comparison of analgesic effects between programmed intermittent epidural boluses and continuous epidural infusion after cesarean section: a randomized controlled study

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Keywords: Cesarean section; Continuous epidural infusion; Epidural analgesia; Obstetrical analgesia; Patient-controlled analgesia; Postoperative pain; Programmed intermittent epidural boluses; Ropivacaine.

Abbreviations: CS = Cesarean section, PIB = Programmed intermittent epidural boluses, CEI = Continuous epidural infusion, VAS = Visual Analog Scale, SMD = Standardized mean difference

*Yu Jeong Bang and Heejoon Jeong have contributed equally to this study as co-first authors.

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Neuroprotective effect of erythropoietin on anesthesia-induced neurotoxicity through the modulation of autophagy in Caenorhabditis elegans

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Keywords: Anesthesia-induced neurotoxicity; Autophagy; Caenorhabditis elegans; Erythropoietin; Isoflurane; Neuroprotection; Toxicity.
Programmed intermittent epidural bolus: a viable alternative to traditional methods?

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The demand for epidural analgesia, which has been widely used traditionally and particularly in thoracoabdominal surgery, has gradually declined owing to the development of minimally invasive surgery and the increasing number of red flags for anticoagulation in patients [1]. However, epidural analgesia remains one of the most reliable techniques for providing effective analgesia. Conventionally, continuous epidural infusion (CEI) and patient-controlled epidural analgesia (PCEA) have been widely used, with PCEA in particular allowing for the adjustment of the background infusion according to the situation or institution [2]. However, in recent years, interest in programmed intermittent epidural bolus (PIEB) as an alternative option has grown considerably.

PIEB involves the administration of boluses of a local anesthetic with narcotics at programmed intervals using an infusion pump. While extensive research has been conducted on PIEB in labor analgesia, to align with the trend of procedure-specific protocols, its application in postoperative pain management is also being explored. PIEB has been reported to reduce pain scores and breakthrough pain at various time points, increase patient satisfaction, and demonstrate equivalent or superior analgesic effects compared to CEI [3]. Additionally, PIEB reduces the incidence of motor blockade and reduces the total local anesthetic dose.

However, limited evidence persists for various clinical application challenges.

In this issue of the Korean Journal of Anesthesiology, Bang et al. [4] compared PIEB with CEI for postoperative pain control after cesarean section and showed that PIEB provided superior analgesia with less motor blockade. This study provides evidence for the effectiveness of PIEB as an analgesic and suggests its potential applicability in other surgical procedures.

However, further research and the clinical application of PIEB require addressing several issues, including determining the appropriate volume and concentration of boluses based on the minimal effective volume and concentration of the target nerve. Another critical consideration is the bolus interval, which differs significantly from CEI and can impact both analgesic and adverse effects [5]. Additionally, factors such as catheter design, pump device, maximal flow rate, volume, and resistance may vary, affecting the delivery of the prescribed bolus dose and infusion rate and thereby influencing epidural spread [6,7].

Furthermore, owing to the larger dose, volume, and longer interval of PIEB, unexpected complications such as intrathecal infusion or systemic delivery of local anesthetics may occur. Therefore, close monitoring of vital signs and sensorimotor functions is essential during bolus delivery.

With the accumulation of research results, I anticipate that PIEB will become a good
alternative option for postoperative analgesia.

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

**References**

Intraoperative pediatric electroencephalography monitoring: an updated review

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Intraoperative electroencephalography (EEG) monitoring under pediatric anesthesia has begun to attract increasing interest, driven by the availability of pediatric-specific EEG monitors and the realization that traditional dosing methods based on patient movement or changes in hemodynamic response often lead to imprecise dosing, especially in younger infants who may experience adverse events (e.g., hypotension) due to excess anesthesia. EEG directly measures the effects of anesthetics on the brain, which is the target end-organ responsible for inducing loss of consciousness. Over the past ten years, research on anesthetic and computational neuroscience has improved our understanding of intraoperative pediatric EEG monitoring and expanded the utility of EEG in clinical practice. We now have better insights into neurodevelopmental changes in the developing pediatric brain, functional connectivity, the use of non-proprietary EEG parameters to guide anesthetic dosing, epileptiform EEG changes during induction, EEG changes from spinal/regional anesthesia, EEG discontinuity, and the use of EEG to improve clinical outcomes. This review article summarizes the recent literature on EEG monitoring in perioperative pediatric anesthesia, highlighting several of the topics mentioned above.

Keywords: Anesthesia; EEG; Electroencephalography; Electroencephalogram; Pediatric anesthesia; Pediatric.

Introduction

Traditionally, pediatric anesthetics are administered according to patient movement (minimal alveolar concentration [MAC]) or changes in hemodynamic response (heart rate and arterial blood pressure). Inherent imprecisions in dosing occur when relying on population pharmacokinetics, spinal cord reflexes (MAC), or subcortical activity (hemodynamic responses). Therefore, the administration and dosing of anesthetics should be based on direct measurements of pharmacologic effects on the brain, the target end-organ responsible for inducing loss of consciousness.

Over the past 30 years, interest in using electroencephalography (EEG) to directly monitor the brain’s response to anesthetics has increased. EEG assesses neural oscillations (rhythms) within specific frequency bands that reflect local and large-scale network interactions [1,2]. EEG correlates of anesthetic effects can be found during critical periods of neurodevelopment in young children. As several national anesthesia societies have highlighted the importance of EEG-guided anesthesia, with recommendations such as “EEG monitoring should be considered as part of the vital organ monitors to guide anes-
anesthetic management” [3] and “anesthetists should be familiar with the principles, interpretation and limitations of EEG monitoring” [4].

Precise anesthetic dosing is especially important in pediatric patients and younger infants as they are at increased risk of adverse events (e.g., hypotension) from excessive anesthesia [5]. Research in anesthesia and computational neuroscience over the past ten years has improved intraoperative EEG monitoring in children and expanded the utility of EEG monitoring in clinical practice. We now have better insights into neurodevelopmental changes in the developing pediatric brain, functional connectivity, anesthetic dosing guided by non-proprietary EEG parameters, epileptiform EEG changes during induction, EEG changes from spinal anesthesia, EEG discontinuity, and the use of EEG to improve clinical outcomes. This review article summarizes recent literature on EEG monitoring in perioperative pediatric anesthesia, highlighting several of the topics mentioned above.

Search strategy

For this literature review, articles from NCBI PubMed published between 2013 and 2023 were retrieved. The following search terms returned 213 articles: “((pediatric anesthesia EEG) OR (pediatric anesthesia electroencephalography)) OR (paediatric anesthetia EEG).” The following articles were excluded: those not focusing on the intraoperative period; those focusing on epilepsy, autism, attention-deficit hyperactivity disorder, intensive care unit settings, and extracorporeal membrane oxygenation; and those from conference proceedings, editorials, reviews, case reports, protocols, and animal studies. Non-English language articles were also excluded. A total of 67 articles were selected for the final review.

EEG basics and changes in the anesthetized brain

EEG measures the summation of excitatory and inhibitory postsynaptic electrical discharges generated from pyramidal neuronal activity in the neocortex [6] and consists of waveforms that can be characterized by their amplitude (i.e., the magnitude of waveforms measured in microvolts [μV]) and frequency (i.e., the number of cycles per second [Hz]) [7]. Typical EEG amplitudes range from 10 to 100 μVs, which is 100 times lower than those of an electrocardiography. EEG activity is often described in terms of EEG power, which is the square of the EEG amplitude (μV2). EEG frequencies are grouped into different bands, conventionally called the slow (< 1 Hz), delta (1–4 Hz), theta (5–8 Hz), alpha (9–12 Hz), beta (13–25 Hz), and gamma (26–80 Hz) bands [2].

The relationship between EEG activity in different regions of the neocortex can be described using coherence and phase shift. Coherence measures the degree of correlation between two EEG signals in a specific frequency band; a coherence value of 1 represents two perfectly correlated synchronous signals, whereas a coherence value of 0 represents no correlation [8]. Typically, coherence is used to measure the synchronization between the left and right sides of the brain, and increased coherence is observed with deeper sedation or anesthesia. Phase shift or phase synchrony can be used to determine the temporal relationship (connectivity) between EEG signals in different regions of the brain [9].

Anesthetics alter the electrical activity of the brain and generate distinct age- and dose-dependent EEG patterns, followed by topographic distributions, suggesting that multiple neural circuits contribute to inducing loss of consciousness [2,10]. Gamma amino butyric acid (GABAergic) anesthetics (e.g., sevoflurane and propofol) increase EEG amplitude while decreasing EEG frequency. At surgical anesthesia levels, most EEG activity exists in the slow/delta and alpha bands. Alpha activity stems from the interaction between the cortical and thalamic pacemakers (corticothalamic network) [6], which can decrease with increased anesthetic doses and may not be present in younger infants, as discussed in the next section [8].

Intraoperative EEG changes with age

Infants undergo rapid changes in brain myelination and maturation, resulting in changes in EEG amplitude and frequency [8]. EEG in newborn children is dominated by slow oscillations that diminish in amplitude with age [6]. Markus et al. [11] measured frontal EEG in infants aged < 12 months under sevoflurane anesthesia and found that newborns had a much higher relative delta power (80%) than older infants aged 10–12 months (48%). Compared to older infants (4–6 months), newborns had lower relative alpha (4.6% vs. 14.4%) and beta (3.2% vs. 10.9%) power. De Heer et al. [12] found that in infants aged < 6 months under sevoflurane anesthesia, alpha coherence and beta coherence were absent, whereas theta and delta oscillations were present. In infants younger than 3 years under sevoflurane anesthesia, Cornelissen et al. [8] used multichannel EEG recordings to show that (1) slow/delta (0.1–4 Hz) oscillations were present in all ages, (2) theta (4–8 Hz) and alpha (8–12 Hz) oscillations emerged by 4 months, (3) alpha oscillations increased in power from 4 to 10 months, (4) frontal alpha-oscillation predominance emerged at 6 months, (5) frontal slow oscillations were coherent from birth until 6 months, and (6) frontal alpha oscillations became coherent at around 10 months, persisting into older ages. These EEG changes reflect de-
velceptment milestones in the maturation of the thalamocortical circuitry and "highlight the importance of developing age-dependent strategies to monitor the brain states of children receiving general anesthesia" [8].

In children under sevoflurane anesthesia, Akeju et al. [13] assessed changes in frontal EEG power spectra and coherence as a function of age and found that EEG power significantly increased from infancy through approximately 6 years, subsequently declining to a plateau at approximately 21 years. Alpha (8–13 Hz) coherence, an EEG feature associated with sevoflurane-induced unconsciousness in adults, was absent in patients aged < 1 year. In a study by the same group, Lee et al. [14] showed that under propofol anesthesia, the total EEG power (0.1–40 Hz) peaked at approximately 8 years and declined with increasing age. In children aged > 1 year, propofol-induced EEG was qualitatively similar regardless of age, featuring slow and coherent alpha oscillations. In infants aged < 1 year, frontal alpha oscillations were not coherent.

Intraoperative EEG changes with anesthetic dose

Changes in EEG due to variances in anesthetic levels have been evaluated in children. Rigouzzo et al. [15] described EEG properties in children aged 5–18 years over a wide range of anesthetic concentrations: (1) propofol using target-controlled infusion targets of 2–6 μg/ml in 1 μg/ml increments or (2) expired sevoflurane (eSevo) 1%–5% in 1% increments. Propofol induced dose-dependent EEG suppression of higher-frequency oscillations, whereas eSevo > 3% was associated with an increase in higher-frequency oscillations. Cornelissen et al. [16] used raw EEG data to report the relationship between sevoflurane concentrations and clinical signs of emergence in children aged 0–3 years. Frontal slow-delta (0.1–4 Hz) oscillations were present from 2% eSevo throughout emergence in all children. In children aged > 3 months, frontal alpha EEG oscillations were present at 2% eSevo and disappeared at 0.5%. The time from the disappearance of alpha oscillations and onset of body movement was 2.2 min (95% CI [0.6, 3.7]). In 99% of the patients, body movement occurred within 5 min of the loss of alpha oscillations. In children aged < 3 months with decreasing eSevo, frontal alpha power decreased with a simultaneous but transient increase in beta oscillations (13–30 Hz).

EEG functional connectivity

During changes in consciousness under general anesthesia, alterations in local EEG oscillations are accompanied by organized changes in the connectivity patterns between various brain regions, known as functional connectivity. Functional connectivity has been explored as an index of anesthetic state transitions and has been shown to discriminate between anesthetic-mediated changes in states of consciousness. This is important in children aged < 10 months as the power-frequency relationship-based EEG cannot always reliably distinguish between wakefulness and unconsciousness [17].

Puglia et al. [18] recorded a 16-channel EEG in children aged 8–16 years and observed changes in functional connectivity associated with anesthetic state transitions across multiple regions and frequency bands. The baseline period, prior to any sedation or anesthesia, was compared to the anesthetic maintenance period, approximately halfway between surgical incision and cessation of anesthesia, with an age-adjusted MAC value > 0.7 and a change of < 0.1%. Functional connectivity was estimated using a weighted phase lag index, which is a measure of the phase synchronization of two signals. If two EEG signals are completely synchronized (phase-locked), then the weighted phase-lag index is 1. Conversely, if the phase relationship between two EEG signals is random, the weighted phase-lag index would be lower. If there is no phase difference, the value is zero. From baseline to maintenance, an increase in connectivity between prefrontal–frontal regions was noted for the alpha frequency band: median (Q1, Q3) 0.07 (0.05, 0.10) vs. 0.47 (0.29, 0.61), P < 0.001 and theta frequency band: 0.04 (0.03, 0.05) vs. 0.40 (0.25, 0.49), P < 0.001 along with a decrease in parietal–occipital alpha connectivity: 0.17 (0.15, 0.24) vs. 0.09 (0.06, 0.13), P < 0.001. The authors concluded that general anesthesia in children correlates with changes in functional connectivity patterns. Unlike in adults, where functional connectivity can undergo structured transitions during the stable maintenance phase, even after controlling for surgical stimuli [19], functional connectivity in children did not exhibit the same transitions during the maintenance phase and was consistently dominated by theta and alpha prefrontal–frontal and alpha frontal–parietal connectivity.

In an exploration of functional connectivity and network topology in the developing brain, Desowska et al. [17] used a weighted phase lag index and found that sevoflurane-based anesthesia modulated functional connectivity in children aged 0–3 years. Functional connectivity was reduced in delta oscillations between anesthesia and wakefulness. Preserved alpha connectivity, notably in the frontal and frontoparietal connections, emerged at around 10 months. In the youngest infants (0–6 months) who lack robust alpha oscillations and exhibit little difference in power spectra between different anesthetic states, functional connectivity analysis could be used to identify differences between wakefulness and
unconsciousness. In another study by the same group that focused on young infants aged 0–4 months, Pappas et al. [20] showed that slow-wave connectivity decreased under sevoflurane administration, particularly between the frontal and parietal areas.

Phase-amplitude coupling (PAC), in which the phase of the slower wave modulates the amplitude of the higher-frequency wave, has been studied as another method for differentiating the depth of consciousness under anesthesia [21, 22]. Thalamocortical PAC is believed to be a process by which general anesthesia prevents information transmission across the brain by disrupting neuronal dynamics through coupled rhythmic oscillations [23]. Liang et al. [22] analyzed PAC as a function of age in children aged 0.6–18 years and in adults undergoing propofol induction and sevoflurane maintenance. In infants aged < 1 years, the PAC pattern between slow-alpha and delta-alpha oscillations was absent. In children aged > 1 years, the PAC modulation strength between delta-alpha oscillations increased with age. Zakaria et al. [21] reported similar delta-alpha PAC characteristics in children aged 10 months to 3 years under sevoflurane anesthesia. PAC was also absent in children aged < 1 years, presumably because of a lack of strong alpha oscillations.

**Non-proprietary EEG parameters**

**Limitations of proprietary processed EEG indices in children**

Commercial EEG monitors approved for intraoperative monitoring in children include the bispectral index (BIS) (Medtronic), SedLine (Masimo), Narcotrend (MonitorTechnik), and M-Entropy (GE Healthcare). These monitors were developed for adult patients using adult EEG data [24] and were adapted for children by reducing the size of the sensors. The processed EEG (pEEG) value is derived from the manufacturer’s proprietary algorithm, which is purported to summarize the depth of anesthesia. However, exactly how these pEEG numbers are computed for children or whether the algorithms are modified to account for age-related differences and changes with neurodevelopment [25], is not clear.

The rationale for creating a numeric proprietary index to indicate hypnotic depth is to simplify the technology and make it more accessible for anesthesiologists. However, this approach may lead to an overreliance on the pEEG index without a clear understanding of the EEG or the limitations of this index. Given age-related differences in intraoperative EEG, the fact that proprietary pEEG indices such as the BIS and patient state index (PSI) have been shown to be unreliable in young children [26, 27], particularly in neonates and infants aged < 6 months [28, 29], is not surprising. Although several studies have shown that BIS and PSI values generally correlate with increasing propofol and sevoflurane doses or sedation depth in children aged > 1 years [30, 31], this correlation is not always reliable.

In children aged 6 months to 12 years, the BIS decreases as expected in response to increasing sevoflurane from 1% to 3%; however, the BIS paradoxically increases when sevoflurane is increased from 3% to 5%, in association with the appearance of fast oscillations and epileptoid signs on EEG [15]. Children also have relatively greater power in the high-frequency bands; thus, children aged < 2 years may display higher pEEG than older children during similar sedative states [32, 33], which can lead to inaccurate or misleading pEEG data in children. Moreover, as in adults, pEEG indices do not reliably account for the effects of non-GABAergic agents, muscle tone, pain response, artifacts, and noise, which can lead to falsely high or low readings, further limiting their utility in assessing overall anesthetic depth.

Understanding the raw EEG waveform and non-proprietary EEG parameters can prevent an overreliance on pEEG numbers and prevent the misinterpretation of inaccurate or misleading pEEG values [25]. Most commercial EEG monitors display a pEEG index along with raw EEG waveforms and non-proprietary processed parameters, such as the density spectral array (DSA), spectral edge frequency (SEF95), and burst suppression ratio (BSR). These EEG parameters (Fig. 1), which will be discussed in the following sections, can be collectively used to guide anesthesia management.

**Density spectral array or spectrogram**

A DSA or spectrogram is a simplified quantitative method for analyzing EEG signals that provides information on the strength of different frequencies of synchronized neural activity over time [2]. Through Fourier transformation, at each point in time (x-axis), the power or energy at different frequencies (y-axis) is computed in decibels and represented by color, with red indicating high power and blue indicating low power. Anesthetic drugs with different mechanisms of action have varying effects on the EEG waveform and have different “signatures” on the DSA. For example, propofol and inhaled anesthetics are known to act in part through a GABAergic mechanism and thus have similar spectrogram signatures. Generally, the main markers of unresponsiveness under sevoflurane or propofol are high power in the alpha band and/or a slow-delta band (0.1–4 Hz) [15, 34]. At low doses, ketamine, an NMDA antagonist, acts primarily on inhibitory interneurons and causes downstream excitation, thereby inducing high-frequency gamma oscillations that are readily visible on DSA [35].
EEG parameters on a commercial EEG monitor. (A) EEG waveforms shows real-time 4-channel recordings from the left and right sides of the forehead, (B) percentage of EMG interference as number and graphic recordings, (C) PSI, a numeric proprietary index used by Masimo Inc., (D) percentage of BSR, (E) percentage of artifact, (F) SEF95 from left and right sides of the forehead, and (G) DSA showing left (top) and right (bottom) of the forehead (white line indicates the spectral edge frequency SEF95). This figure was adopted with permission [7]. EEG: electroencephalography, EMG: electromyography, PSI: patient state index, BSR: burst suppression ratio, SEF: spectral edge frequency, DSA: density spectral array.

**Spectral edge frequency (SEF95)**

The SEF95 is the frequency below which 95% of the EEG power is located. In general, when using GABAergic agents such as propofol or sevoflurane, a lower SEF95 represents a deeper state of hypnosis [36]. The SEF95 is often used together with the DSA to assess hypnotic depth. Whereas the DSA provides a graphical representation of EEG frequency and power over time, the SEF95 provides a numerical index of EEG frequency and power at any given time.

**Burst suppression**

Burst suppression reflects a profound state of brain inactivation and is frequently observed during deep anesthesia and hypothermia. The raw EEG waveform (Fig. 2) is recognized as cycles of short periods of high-amplitude activity (bursts) (B), switching back and forth every few seconds [37]. On DSA (Fig. 3), burst suppression appears as a pattern of alternating high- and low-power across many different frequencies, giving the spectrogram a striated appearance [38].

**Burst suppression ratio**

The BSR shows the percentage of time that the EEG is isoelectric. On the BIS monitor, the BSR represents the percentage of the previous 63 s epoch of EEG recognized as those periods longer than 0.5 s, during which the EEG voltage does not exceed approximately ± 5 μV (BIS VISTA Monitoring System [2008]). The BSR is 100% for an isoelectric EEG signal and 0 for an EEG signal without isoelectric periods [39].

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Fig. 1. EEG parameters on a commercial EEG monitor. (A) EEG waveforms shows real-time 4-channel recordings from the left and right sides of the forehead, (B) percentage of EMG interference as number and graphic recordings, (C) PSI, a numeric proprietary index used by Masimo Inc., (D) percentage of BSR, (E) percentage of artifact, (F) SEF95 from left and right sides of the forehead, and (G) DSA showing left (top) and right (bottom) of the forehead (white line indicates the spectral edge frequency SEF95). This figure was adopted with permission [7]). EEG: electroencephalography, EMG: electromyography, PSI: patient state index, BSR: burst suppression ratio, SEF: spectral edge frequency, DSA: density spectral array.

Fig. 2. Time domain trace (raw EEG waveform) on Sedline monitor showing burst suppression. Burst suppression is recognized on EEG as cycles of short periods of flat (isoelectric) activity (A) and short periods of high-amplitude activity (bursts) (B), switching back and forth every few seconds. Burst suppression reflects a profound state of brain inactivation during deep anesthesia and indicates a state of over-sedation. EEG: electroencephalography.

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Relative beta ratio

The relative beta ratio is the ratio of power in the theta versus beta frequency bands. A higher ratio indicates more power at slower frequencies and a deeper state of hypnosis. The relative beta ratio is used to compute the pEEG value but is not typically displayed on commercial monitors.

Non-EEG information on signal quality

The signal quality is indicated by various EEG monitors. The signal quality index of the BIS monitor predicts the reliability of the signal; the higher the signal quality index, the more reliable the BIS value. The electromyography (EMG) value indicates EMG activity, which reflects muscle stimulation caused by an increase in muscle tone or muscle movement. The higher the EMG value, the less reliable the pEEG number.

Combining non-proprietary EEG parameters to guide anesthetic dosing

The DSA can be monitored in conjunction with raw EEG waveforms and the SEF95 to guide anesthesia management in children [7,10,25,40]. DSA monitoring allows clinicians to directly and accurately visualize the effects of various anesthetic drugs on a patient’s EEG without relying on the pEEG number, enabling them to make better clinical inferences and titrate anesthesia doses more precisely to meet each patient’s requirements at any given time. This is particularly important in children with less predictable anesthetic requirements, such as those receiving total intravenous anesthesia (TIVA), neuromuscular blockers, or a combination of anesthetics with different mechanisms of action; those with atypical neurodevelopment or altered levels of consciousness prior to anesthesia; and those with hemodynamic instability as they need their anesthetic doses titrated more precisely to prevent over- or undersedation [25].

Children of all ages

In general, a shift in the SEF95 towards a lower frequency range during sevoflurane and propofol anesthesia (with a corresponding increase in slow/delta power on the DSA and decrease in alpha power) indicates increased hypnotic depth, while a shift in the SEF95 towards a higher frequency range indicates decreased hypnotic depth. For infants and children of all ages receiving propofol anesthesia, Xu et al. [41] suggested that SEF95 values of 15–20, 10–15, and 6–14 Hz should be targeted for sedation, surgical maintenance, and laryngoscopy/surgical incision, respectively. In infants aged > 3 months receiving sevoflurane anesthesia, Koch et al. [42] identified SEF95 cutoff values of < 7 Hz for deep anesthesia, < 13 Hz for surgical anesthesia, and > 20 Hz for sedation/consciousness, while Yuan et al. [10] proposed targeting SEF95 at 15–20 Hz for sedation, 10–15 Hz for surgical maintenance, and 6–14 Hz for laryngoscopy/surgical incision. These suggested values should be considered in the context of the patient’s raw EEG waveform, DSA, and other clinical parameters including heart rate, blood pressure, and movement to accurately assess the overall hypnotic state.

Infants aged 3 months to 1 year

Because proprietary pEEG indices are generally unreliable in infants aged < 1 years [26,27], the raw EEG waveform and DSA can be used to titrate both sevoflurane and propofol dosages. In infants aged > 6 months, alpha power is usually present [8], while in infants aged 4–5 months, intermittent (versus continuous) alpha power is often visualized using the DSA. Similar to that with older children, the EEG power shifts towards the slow/delta frequency range with increasing doses of propofol and sevoflurane. Thus, a shift in the SEF95 towards a lower range indicates increased hypnotic depth, while a shift in the SEF95 towards a higher range indicates decreased hypnotic depth.

Infants aged < 3 months

In infants aged < 3 months, frontal alpha coherence is absent. Alpha power is not visible on the DSA, and the overall power is low. Compared to that of older infants, neonatal EEG is characterized by a lower frequency and power. In preterm neonates at 28–34 weeks of gestational age, periods of isoelectric EEG are common, occurring during both wakefulness and sleep. Thus, a normal EEG in a non-anesthetized preterm neonate may appear similar to an EEG in an anesthetized child, potentially leading to confusion. The SEF95 and BSR do not reliably indicate changes in sevoflurane concentrations in infants aged < 3 months [43]. As such, the EEG waveform can be used to assess the level of hypnosis in neonates and infants and to identify periods of isoelectricity as an indicator of cortical inactivity and excess sevoflurane or propofol doses. When an infant demonstrates burst suppression or isoelectricity on the EEG waveform, with a correspondingly low SEF95, high BSR, and low EMG value (low likelihood of artifact), the sevoflurane or propofol dose should be decreased until activity returns on the EEG waveform. Correlations should be made with other clinical parameters, such as heart rate, blood pressure, and clinical signs of responsiveness.
EEG-guided anesthetic dosing examples

Figs. 3–5 illustrate examples of how to titrate anesthetic doses in response to oversedation, undersedation, and for young infants.

Case 1: Over-sedation

Fig. 3 shows a screenshot of the Sedline monitor of a 7-year-old, 23 kg male receiving sevoflurane anesthesia for right elbow fracture fixation. After sevoflurane inhalation induction, a laryngeal mask airway was inserted at Time A. The DSA showed high power in the slow/delta frequency range, and the SEF95 was between 6 and 8 Hz. As the eSevo was reduced from 5.1% (A) to 2.5% during the maintenance phase (B), the DSA showed an increase in alpha power, and the SEF95 (indicated by the blue arrow) increased from 8 to 14 Hz, indicating decreasing hypnotic depth. During positioning and surgical preparation, the patient developed laryngospasm in response to the change in stimulation (C). Sevoflurane was increased, and propofol (2 mg/kg) was administered to treat the laryngospasm. Less than a minute after the propofol bolus, the EEG showed burst suppression, as seen on the DSA by the appearance of striated black lines at 08:59. Burst suppression can be clearly visualized in the time-domain trace during this time (Fig. 2). The eSevo was temporarily decreased until the EEG no longer showed burst suppression, and the SEF95 gradually increased to approximately 10 Hz (D), after which sevoflurane was increased to 3.0% and surgery proceeded uneventfully.

This case illustrates how EEG monitoring of both the time-domain trace and DSA can help clinicians detect periods of oversedation and burst suppression (due to a propofol bolus), thus prompting a reduction in eSevo and avoiding further oversedation.

Case 2: Under-sedation

Fig. 4 illustrates a combination of three serial Sedline screen-shots of a 7-year-old, 19.1 kg female with cyanotic heart disease and pulmonary hypertension undergoing diagnostic cardiac catheterization. At Time A, the patient was hemodynamically stable, with an eSevo of 2.0%. During cannulation of the femoral vessels at Time B, the patient’s SEF95 increased from 14 to 18 Hz, with a corresponding decrease in slow/delta power, indicating a decrease in the hypnotic level. At Time C, the eSevo increased to 2.2%, SEF95 decreased to 15 Hz, and slow/delta power increased, indicating an increase in the hypnotic level. At Time D, the patient’s blood pressure started to decrease; hence, eSevo was reduced to 1.8%, which led to an increase in the SEF95 to 17 Hz and a decrease in the slow/delta power. At Time E, the patient suddenly developed transient severe hypotension (blood pressure, 40/20 mmHg) and bradycardia (heart rate, 48 beats/min). During this time, burst suppression was observed on EEG. Adrenaline 1 µg/kg was administered, cardiac output was rapidly restored, and EEG activity returned after approximately one minute. This was followed by a gradual increase in the SEF95 (24 Hz) with visible alpha power but minimal slow/delta power, indicating arousal. As the patient remained relatively hypotensive, eSevo was maintained at 1.6% until Time G, when the blood pressure stabilized in response to a vasopressor. This allowed the eSevo to increase to 1.8%, which led to a decrease in the SEF95 and return of slow/delta power.
This case illustrates how EEG can be used to detect undersedation during periods of hemodynamic instability. The DSA and SEF95 allow for accurate titration of sevoflurane concentrations within narrow therapeutic windows in hemodynamically unstable children.

**Case 3: Young infant**

Fig. 5 shows a combination of three Sedline screenshots from a 4-month-old, 6.6 kg male receiving sevoflurane anesthesia for laparoscopic inguinal hernia repair. The EEG and DSA showed low overall power, with a general absence of alpha power, as expected based on the child's age. After inhalation induction with sevoflurane, atracurium 0.5 mg/kg was administered and endotracheal intubation was performed at Time A. At this time, eSevo was 2.4%, the EEG waveform showed predominantly slow/delta oscillations, DSA showed high slow/delta power, and SEF95 was between 7 and 9 Hz. The eSevo was then increased to 2.7% and fentanyl 0.5 µg/kg and intravenous paracetamol were administered in anticipation of surgical incision at Time B. Following surgical incision, no increase in heart rate or blood pressure was observed; therefore, eSevo was reduced to 2.05%. Following the creation of pneumoperitoneum at Time C, the EEG waveform showed higher frequency oscillations, SEF95 increased to 16 Hz, and slow/delta power decreased on the DSA, indicating arousal. Minimal changes in the heart rate and blood pressure were noted. Fentanyl 0.5 µg/kg was administered and eSevo increased. At Time D, eSevo was 3%, the SEF95 had decreased to 10 Hz, and the DSA showed increased delta power, indicating an increased hypnotic level, albeit to a lesser extent than that at Time A. Surgery was completed uneventfully, and sevoflurane was discontinued at Time E. A progressive increase in SEF95 levels and a loss of delta power was observed as the patient returned to consciousness and extubation was performed within 10 min (Time F).

This case illustrates how the EEG waveform, DSA, and SEF95 can be used to titrate sevoflurane doses during anesthesia in a 4-month-old infant. EEG monitoring was useful for detecting periods of arousal and undersedation intraoperatively, even in the absence of hemodynamic changes.
Fig. 5. Combination of three serial Sedline screenshots of a 4-month-old infant. Combination of three serial screenshots of a 4-month-old receiving sevoflurane anesthesia. (A) eSevo 2.4%, EEG waveform shows predominantly slow/delta oscillations, DSA shows high slow/delta power, SEF95 is 7–9 Hz, (B) surgical incision, eSevo 2.7%, minimal change in EEG, heart rate, and blood pressure, (C) pneumoperitoneum, eSevo 2.05%, EEG waveform showing higher frequency oscillations, SEF95 increased to 16 Hz and slow/delta power decreased on the DSA, indicating arousal, (D) eSevo 3%, SEF95 decreased to 10 Hz, DSA shows increased delta power, indicating an increased hypnotic level, (E) sevoflurane stopped, progressive increase in SEF95 and loss of delta power, and (F) patient extubated awake. EEG: electroencephalography, SEF: spectral edge frequency, DSA: density spectral array.

**EEG-guided propofol anesthesia**

Whereas the dosing examples above were all for a sevoflurane-based anesthetic, propofol-based TIVA has gained popularity recently as an environmentally friendlier alternative to sevoflurane, with a lower associated incidence of laryngospasm, emergence agitation, and postoperative nausea and vomiting. Unlike eSevo concentration monitoring, the propofol concentration (Ce) in the brain cannot be easily monitored, making dosing less accurate and predictable. EEG has been suggested as a reliable dynamic surrogate for brain propofol Ce to guide propofol TIVA dosing [41]. However, EEG-guided TIVA is uncommon in pediatric patients, and EEG curricula are not commonly taught in anesthesia training programs [4]. To take advantage of the clinical benefits of propofol TIVA and improve the dosing accuracy with EEG, Yuan et al. [44] and Jones Oguh et al. [45] initiated a quality improvement project to train their division on using EEG to guide TIVA dosing. The group used a combination of intraoperative teaching, didactic lectures, and quality improvement metrics to develop a sustainable, effective, and scalable program. The group emphasized the use of a combination of raw EEG, SEF95, and DSA data to titrate propofol and provided algorithms for use during induction, maintenance (Fig. 6), and emergence. Over the 12-month period, 79% (62/79) of the clinicians completed the EEG training program, and their knowledge test scores improved from 38% before training to 59% after training (P < 0.001). Four Plan-Do-Study-Act (PDSA) cycles were initiated, and the prevalence of using EEG to guide TIVA cases increased from 5% to 75% [45]. The incidence of perioperative emergency activation did not change significantly, while the emergence time for EEG-guided TIVA cases was significantly longer, the difference was not clinically significant (18 vs. 16 min, P < 0.001).

**Epileptiform EEG changes**

Since the advent of sevoflurane for clinical use in pediatric anesthesia, reports have described involuntary behaviors suggestive of seizure-like movements [46]. Initial case reports and subsequent studies have described these movements, with some studies recording EEG to detect brain wave correlates [47]. EEG studies
have utilized nomenclature to describe patterns that have been defined in the neurology-epileptology literature but are unfamiliar to most anesthesiologists [47]. During induction, a prevalence of 30% (95% CI [27.2, 34.5]) has been reported for epileptiform changes [47], while other studies have reported estimates from 19% to 60% [48]. An important consideration to account for this wide range in prevalence is the use of heterogeneous EEG outcome classifications and variability in the number of channels recorded [47]. A standard definition, which is a simplified version of the International League Against Epilepsy (ILAE) and the American Clinical Neurophysiology Society (ACNS) classifications, has been proposed to help with future classifications. These classifications are presented verbatim below.

“(1) No interictal epileptiform discharges or electrographic seizures
(1a) Normal EEG
(1b) Focal or generalized slowing, including rhythmic delta activity
(2) Interictal epileptiform discharges, defined as spikes, polyspikes, sharp waves, or spike and wave complexes, reflecting possible areas of cortical irritability and potential epileptogenicity that are
(2a) Isolated/sporadic epileptiform discharges, meaning they occur singly without repetition or periodic recurrence.

Fig. 6. EEG-guided propofol TIVA dosing algorithm for anesthetic maintenance. This decision-making flowchart was provided to learners as a visual representation of the teaching points to help guide clinicians through EEG interpretation. The algorithm focuses on using raw EEG, SEF, and DSA to assess propofol Ce and titrate the propofol dose to the desired Ce to ensure an appropriate depth of hypnosis during the maintenance of general anesthesia (Adopted with permission [44]). EEG: electroencephalography, TIVA: total intravenous anesthesia, SEF: spectral edge frequency, DSA: density spectral array, propofol Ce: propofol concentration.
Discontinuity and isoelectric EEG in young children

Isoelectric EEG reflects electrical inactivity in the cortex and can be observed in states of brain pathology (e.g., hypothermia and coma). Intraoperative isoelectric EEG is concerning in both adults and children under anesthesia, as it is thought to represent an "over-anesthetized" brain. Isoelectric EEG is associated with worse long-term neurological outcomes in neonates undergoing cardiac surgery [54]. In adults, intraoperative low-voltage EEG has been associated with postoperative delirium [55]. In children aged < 3 years undergoing sevoflurane anesthesia, Cornelissen et al. [56] found that 51% experienced isoelectric/discontinuity EEG, which was mostly observed during the first 30 min of anesthesia and was associated with younger age. High induction doses of propofol were administered to children with discontinuity events. In a related study from the same group, Agrawal et al. [37] found that in children aged > 4 months, a decrease in high-frequency activity occurred tens of seconds before each discontinuous event and a decline in spectral edge frequency occurred in the seconds immediately following each discontinuity.

Yuan et al. [57] observed isoelectric EEG events in 63% of children aged 0–37 months undergoing sevoflurane or propofol anesthesia. In a follow-up 15-center international study, the observed occurrence of isoelectric EEG events was 32% in 648 children aged < 37 months, but varied significantly between sites (9%–88%), suggesting that variances in anesthesia practice could contribute to the occurrence of isoelectric EEG [58]. Isoelectric events were associated with younger age, endotracheal tube use, propofol bolus for airway placement, and higher eSevo, and were less likely to occur when muscle relaxants were used for intubation. Importantly, isoelectric events were associated with moderate and severe hypotension between induction and incision (odds ratio [OR]: 3.5–4.6) and during surgical maintenance (OR: 3.6–7.1). Infants aged 0–12 months who experienced isoelectric events had lower pediatric quality-of-life scores at baseline and postoperatively. The authors concluded that sicker infants were more prone to isoelectric EEG and relying on traditional MAC dosing may be "over-dosing" the infant brain.

To determine the sevoflurane concentration associated with the occurrence of isoelectric EEG in 50% of children (MACisoEEG), He et al. [59] enrolled children aged 3–8 years and allocated them to one of three groups: (1) sevoflurane in 100% O2, (2) sevoflurane in 50% N2O mixed with 50% O2, and (3) sevoflurane in 100% O2 with a fentanyl bolus (3 µg/kg). The MACisoEEG was determined using Dixon’s up-down method after a 15-min period of steady eSevo. The MACisoEEG in the 100% O2 group was (median [95% CI]): 5.30% (5.12, 5.48), 5.83% (5.67, 5.99) in the 50% N2O group, 299
and 5.37% (5.21, 5.53) in the fentanyl group. The authors concluded that the addition of 50% N₂O modestly increased the MACₜₐ₀EEG, whereas 3 µg/kg fentanyl had no effect on the MACₜₐ₀EEG.

**Alpha band associated with EEG discontinuity**

In older infants and children, propofol and sevoflurane generate an alpha frequency (8–12 Hz) oscillation that represents coordinated firing activity of neurons between the thalamus and cerebral cortex [60–62]. The degree of alpha oscillatory power during anesthesia decreases with age and is correlated with cognitive function, suggesting its capacity as a neurophysiological marker with potential clinical significance [63,64]. Plausibly, an association could be found between the alpha oscillatory power and low-voltage EEG patterns, such as discontinuous or isoelectric EEG, during anesthesia. Low alpha power in adults has been associated with the propensity for burst suppression and could be a neurophysiological phenotype for a “vulnerable brain” [65]. Similarly, in an observational cohort study of 54 infants, the degree of alpha oscillatory power induced by sevoflurane anesthesia was associated with the prevalence of EEG discontinuity, with every decibel increase in alpha power associated with a 49% reduction in the odds of developing low-voltage EEG (OR: 0.51, 95% CI [0.30, 0.89], P = 0.02), even after adjusting for chronological age and propofol administration [66]. No differences in alpha power in the baseline awake state were seen before anesthesia among the infants, and this effect could not be explained by differences in anesthetic dosing. These findings suggest hidden brain circuit properties could be unmasked under anesthesia. Anesthetic-induced alpha power is a putative marker of thalamocortical circuit development during the first year of life and can be useful in identifying young patients who have a greater chance of developing low-voltage patterns, with potential future applications in anesthesia management [66].

**EEG monitoring to improve clinical outcomes**

EEG monitoring provides insight into individual patients’ brain responses to anesthetic drugs, which are dependent on a variety of factors, including age, neurodevelopmental stage, disease state, concomitant medications, hemodynamic status, and surgical stimulation [10,25]. Multiple studies have demonstrated the utility of EEG monitoring in pediatric anesthesia [40,41,67,68], particularly during cardiac surgery, when cardiopulmonary bypass, induced hypothermia, and hemodynamic instability render the anesthetic requirements much less predictable [69,70]. EEG-guided anesthesia allows for accurate and timely visualization of brain responses and can complement routine monitoring in children to optimize anesthesia delivery and improve patient safety and experience. Recent studies have demonstrated that EEG monitoring may improve periprocedural outcomes in children undergoing anesthesia.

**Reducing anesthetic dosage**

Several randomized controlled trials (RCTs) have demonstrated that EEG-guided anesthesia can reduce intraoperative anesthetic dosage. In an RCT of 200 children aged 1–6 years undergoing minor surgery, Long et al. [71] showed that EEG-guided anesthesia resulted in lower sevoflurane requirements and a lower incidence of burst suppression than standard care. EEG guidance also enabled greater appreciation of the higher anesthetic requirements in younger children aged 1–2 years compared to children aged >2 years. Han et al. [72] studied 54 children aged 2–12 years undergoing urological surgery and demonstrated that EEG-guided anesthesia management reduced the intraoperative sevoflurane dose and incidence of emergence delirium (ED). Weber et al. [73] reported that in children aged 12–17 years undergoing deep sedation for gastrointestinal endoscopy, propofol dosing guided by the Narcotrend index led to faster recovery, lower propofol consumption, and fewer episodes of oversedation than propofol dosing according to clinical surrogate parameters of depth of hypnosis.

**Reducing perioperative adverse events**

EEG-guided anesthesia may be associated with a reduced incidence of periprocedural adverse events. In a retrospective study of 206 children aged 2–8 years undergoing deep sedation with propofol target-controlled infusion, those who underwent BIS monitoring had a lower incidence of periprocedural adverse events (including hypoxia, apnea, and recurrent cough) and a shorter time to discharge [74].

**EEG and emergence delirium**

ED is common following pediatric anesthesia and consists of an altered mental status following emergence from anesthesia, with hallmark features of behavioral agitation and disorientation that are generally self-limiting in duration [75]. Several observational studies have found that certain EEG characteristics can predict the occurrence of ED in the post-anesthesia care unit. In a study involving 62 children, Koch et al. [76] showed that epileptiform EEG discharges in the form of interictal spike events observed during anesthesia induction was correlated with ED occurrence. In a similar study of 97 children conducted by the same group, no association was observed between intraoperative burst suppression and the development of ED [77]. In another observational study of 155 children undergoing cardiac surgery, the incidence of ED was lower in children in whom EEG monitoring demonstrated EEG discharges in the form of interictal spike events compared to children who did not have interictal spike events [78].
Each patient’s needs at any given moment. EEG monitoring allows the current standard anesthesia monitoring and management principles in children, enabling anesthesia to be personalized to each patient’s needs at any given moment. EEG monitoring allows for the detection of periods of over- or under-sedation and avoidance of intraoperative burst suppression, a state of profound brain inactivation that is common in infants but unnecessary for routine surgical anesthesia [26,57,66]. At present, whether intraoperative burst suppression is associated with subsequent neurological sequelae is unknown [37,58]; however, prolonged intraoperative burst suppression is associated with postoperative delirium [55,82]. Future studies should investigate whether intraoperative burst suppression is associated with ED and long-term neurodevelopmental outcomes. Clearer EEG predictors (such as functional connectivity or PAC indices) need to be established for anesthetic state transitions and emergence, particularly in young children. Well-designed prospective studies with larger sample sizes are needed to demonstrate the value of intraoperative EEG monitoring in reducing adverse events and improving clinical outcomes.

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Conflicts of Interest
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Data Availability
Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Author Contributions
Ian Yuan (Conceptualization; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing) Choon L. Bong (Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing) Jerry Y. Chao (Conceptualization; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing)

Future Studies
EEG monitoring has been shown to be a useful complement to the current standard anesthesia monitoring and management principles in children, enabling anesthesia to be personalized to each patient’s needs at any given moment. EEG monitoring allows for the detection of periods of over- or under-sedation and avoidance of intraoperative burst suppression, a state of profound brain inactivation that is common in infants but unnecessary for routine surgical anesthesia [26,57,66]. At present, whether intraoperative burst suppression is associated with subsequent neurological sequelae is unknown [37,58]; however, prolonged intraoperative burst suppression is associated with postoperative delirium [55,82]. Future studies should investigate whether intraoperative burst suppression is associated with ED and long-term neurodevelopmental outcomes. Clearer EEG predictors (such as functional connectivity or PAC indices) need to be established for anesthetic state transitions and emergence, particularly in young children. Well-designed prospective studies with larger sample sizes are needed to demonstrate the value of intraoperative EEG monitoring in reducing adverse events and improving clinical outcomes.

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EEG monitoring has been shown to be a useful complement to the current standard anesthesia monitoring and management principles in children, enabling anesthesia to be personalized to each patient’s needs at any given moment. EEG monitoring allows for the detection of periods of over- or under-sedation and avoidance of intraoperative burst suppression, a state of profound brain inactivation that is common in infants but unnecessary for routine surgical anesthesia [26,57,66]. At present, whether intraoperative burst suppression is associated with subsequent neurological sequelae is unknown [37,58]; however, prolonged intraoperative burst suppression is associated with postoperative delirium [55,82]. Future studies should investigate whether intraoperative burst suppression is associated with ED and long-term neurodevelopmental outcomes. Clearer EEG predictors (such as functional connectivity or PAC indices) need to be established for anesthetic state transitions and emergence, particularly in young children. Well-designed prospective studies with larger sample sizes are needed to demonstrate the value of intraoperative EEG monitoring in reducing adverse events and improving clinical outcomes.

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Author Contributions
Ian Yuan (Conceptualization; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing) Choon L. Bong (Conceptualization; Investigation; Methodology; Writing – original draft; Writing – review & editing) Jerry Y. Chao (Conceptualization; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing)
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The use of cardiac implantable electronic devices (CIEDs) has increased significantly in recent years. Consequently, more patients with CIEDs will undergo surgery during their lifetime, and thus the involvement of anesthesiologists in the perioperative management of CIEDs is increasing. With ongoing advancements in technology, many types of CIEDs have been developed, including permanent pacemakers, leadless pacemakers, implantable cardioverter defibrillators, cardiac resynchronization therapy-pacemakers/defibrillators, and implantable loop recorders. The functioning of CIEDs exposed to an electromagnetic field can be affected by electromagnetic interference, potential sources of which can be found in the operating room. Thus, to prevent potential adverse events caused by electromagnetic interference in the operating room, anesthesiologists must have knowledge of CIEDs and be able to identify each type. This review focuses on the perioperative management of patients with CIEDs, including indications for CIED implantation to determine the baseline cardiovascular status of patients; concerns associated with CIEDs before and during surgery; perioperative management of CIEDs, including magnet application and device reprogramming; and additional perioperative provisions for patients with CIEDs. As issues such as variations in programming capabilities and responses to magnet application according to device can be challenging, this review provides essential information for the safe perioperative management of patients with CIEDs.

Keywords: Artificial pacemaker; Cardiac arrhythmias; Cardiac resynchronization therapy devices; Cardiovascular diseases; Electromagnetic fields; General anesthesia; Implantable defibrillators; Operative surgical procedures.

Introduction

The use of cardiac implantable electronic devices (CIEDs) has dramatically increased in recent years, resulting in substantially improved quality of life and increased survival of patients with cardiovascular disease. Consequently, more patients with CIEDs may be exposed to diseases requiring surgery or invasive procedures during their lifetime [1,2].

CIEDs utilized for rhythm management include the permanent pacemaker (PPM) for control of bradyarrhythmias, implantable cardioverter defibrillator (ICD) for treatment of life-threatening ventricular arrhythmias, cardiac resynchronization therapy-pacemaker/defibrillator (CRT-P/CRT-D) for treatment of heart failure with dyssynchronism, and implantable loop recorder (ILR) for monitoring cardiac arrhythmias.

The presence of these devices may present a problem during procedures that could expose the patient to electromagnetic interference (EMI), leading to inappropriate device
functioning. Thus, precautions should be followed prior to performing these types of procedures to ensure the safe management of patients with CIEDs.

This review provides an overview of the perioperative management of patients with CIEDs and a discussion of the various responses of CIEDs to the application of a magnet according to the device manufacturer, type, and programming.

**Indications for device implantation and nomenclature**

**Permanent pacemaker**

Indications for pacemaker insertion include symptomatic bradycardia caused by atrioventricular block (AVB) and sick sinus syndrome. AVB is classified according to the extent of the delay (first degree: PR interval prolongation > 200 ms) or interruption (second degree: intermittent interruption or third degree: complete interruption) of electrical conduction between the atria and ventricle. Several congenital or acquired etiological factors can cause deterioration of the atrioventricular conduction system, leading to AVB [3]. AVB occurs most commonly in the absence of significant cardiac disease and is generally attributed to idiopathic fibrosis of the conduction system [4]. Other causes of acquired AVB include iatrogenic, infectious, infiltrative, autoimmune, or ischemic processes [5–9]. Sinus node dysfunction with intermittent loss of P-waves or sinus arrest causing symptomatic episodes is known as sick sinus syndrome.

**Leadless pacemaker**

A leadless pacemaker, which is a novel alternative consisting of a capsule-like device containing a generator and an electrode system, is implanted into the right ventricle through the femoral vein. By eliminating the need for transvenous leads and a generator pocket, a leadless pacemaker can be placed in patients with subclavian venous stenotic disease and thus may help prevent lead- and pocket-related complications.

**Implantable cardioverter defibrillators**

The indications for ICD implantation can be divided into primary and secondary prevention. Primary prevention indicates prevention of sudden cardiac death in patients with symptomatic heart failure and left ventricular ejection fraction ≤ 35% after optimal medical therapy [10]. In most cases, ICDs are implanted for secondary prevention in patients who have survived a cardiac arrest or intolerable ventricular arrhythmias. Patients with heart failure or congenital heart disease or post-myocardial infarction are selected for ICD implantation. Patients with familial cardiac conditions, such as long QT syndrome, Brugada syndrome, or hypertrophic cardiomyopathy, are also at a high risk of sudden death due to ventricular arrhythmias. A small proportion of ICDs are subcutaneous ICDs, which are typically implanted in the left midaxillary region. Subcutaneous ICDs do not require leads located within the heart and offer no conventional pacing support [11,12].

**Cardiac resynchronization therapy-pacemaker/defibrillator**

Cardiac dyssynchronization is defined as a difference in the timing of electrical and mechanical activation of the ventricles, which can result in impaired cardiac efficiency. The purpose of CRT is to increase cardiac output by simultaneous biventricular pacing [13]. The function of these devices is to coordinate ventricular contraction; thus, they are programmed to ensure continuous pacing of the heart. For patients at risk of ventricular arrhythmias with indications for biventricular pacemakers, specialized ICDs that enable CRT are also available [14]. These devices, which are predominantly inserted for primary prevention, are known as CRT-D.

**Implantable loop recorder**

ILRs are small devices implanted or injected subcutaneously under local anesthesia in the left side of the chest. With an ILR, a patient’s electrocardiogram (ECG) is continuously recorded and deleted by the device’s retrospective memory and can be stored during syncope or significant arrhythmia [15]. ILRs can be useful for diagnosing arrhythmias in patients with potentially life-threatening symptoms, such as unexplained syncope.

**CIED nomenclature**

The nomenclature for pacemakers established by the North American Society of Pacing and Electrophysiology (NASPE) and the British Pacing and Electrophysiology Group (BPEG) is designated as the NBG code for pacing nomenclature [16]. The code consists of up to five letters (Table 1). Positions 1–3 refer to the chamber-paced, chamber-sensed, and response-to-sensing positions, respectively. The fourth position of the generic PPM code is rate-responsive pacing, whereby the paced heart rate can be altered by the CIED in response to motion or detection of physiological conditions. Importantly, all modern ICDs and CRTs also

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include pacemaker functions. Most commonly, activity during exertion is detected by an accelerometer, which increases the paced rate to optimize cardiac output. Other sensing mechanisms may detect an increase in physiological parameters, including minute ventilation or myocardial contractility, and adjust the heart rate accordingly. The fifth position is used to indicate the presence of multisite pacing.

<table>
<thead>
<tr>
<th>Chamber-paced</th>
<th>Chamber-sensed</th>
<th>Response-to-sensing</th>
<th>Rate modulation</th>
<th>Multisite pacing</th>
</tr>
</thead>
<tbody>
<tr>
<td>O = None</td>
<td>O = None</td>
<td>O = None</td>
<td>O = None</td>
<td>O = None</td>
</tr>
<tr>
<td>A = Atrium</td>
<td>A = Atrium</td>
<td>T = Triggered</td>
<td>R = Rate modulation</td>
<td>A = Atrium</td>
</tr>
<tr>
<td>V = Ventricle</td>
<td>V = Ventricle</td>
<td>I = Inhibited</td>
<td>V = Ventricle</td>
<td>D = Dual (A+V)</td>
</tr>
<tr>
<td>D = Dual (A+V)</td>
<td>D = Dual (A+V)</td>
<td>D = Dual (T+I)</td>
<td>D = Dual (A+V)</td>
<td></td>
</tr>
</tbody>
</table>

**Considerations for patients with CIEDs before surgical or invasive procedures**

**Electromagnetic interference**

The combination of the electric and magnetic fields is known as the electromagnetic field. Electric fields exist in the presence of electrical charges. The flow of electric current in a conductor with magnetic field lines perpendicular to the current flow produces a magnetic field. EMI can occur as a result of conducted or radiated electromagnetic energy. EMI can also occur when an electronic device is exposed to an electromagnetic field. Oversensing of EMI by the device may cause pacing inhibition in patients with PPMs and inappropriate shocks in patients with ICDs. Fig. 1 shows some examples of adverse responses to EMI in patients with CIEDs. Two patients with ICDs (intravenous and subcutaneous) received inappropriate shocks due to EMI oversensing during external electronic stimulation therapy (Figs. 1A and B). In a patient with a pacemaker (DDD mode), atrial oversensing of EMI caused failure of ventricular tracking following atrial contraction, and the pacing mode was ultimately changed from DDD to VVI (Fig. 1C).

Potential sources of EMI in surgical settings include intraoperative magnetic resonance imaging, monopolar electrocautery [17], bipolar electrocautery [18], nerve stimulators [19], transcatheter electrical nerve stimulation machines [20], argon plasma coagulation [21], and radiofrequency ablation devices [22].

**Preoperative evaluation of patients with CIEDs**

The preoperative evaluation of patients with CIEDs should include both a multidisciplinary and systematic approach. The manufacturer's identification card should be obtained from each
patient. The device identification card contains the date of implantation, type of CIED, and type of leads. A chest X-ray should be examined to confirm the device type and location of the generator and leads (Fig. 2). In general, the right ventricular lead of an ICD includes one or two thick radio-opaque sections representing high-voltage coils for the delivery of shock energy. A CRT device has two ventricular leads (one located in the right ventricle and the other that enters the coronary sinus and travels towards the lateral side of the left ventricle). A 12-lead ECG should be performed to determine baseline rhythm and pacing spikes. If pacemaker spikes are observed in front of all or most P-waves and/or QRS complexes, pacemaker dependency should be considered. Medical records should be reviewed for the device type, manufacturer, and indication for implantation. The CIED should be examined before surgery if this has not been performed electively during the preceding 12 months for PPM (6 months for ICD/CRT) or when battery longevity is unknown [14]. The patient should be informed about the potential risk of EMI during the procedure, and preventative measures should be taken in accordance with the needs and preferences of the patient. During the preoperative evaluation of a patient with a CIED, surgical information, including the type of procedure, location of the surgical site, patient position during the procedure, source of EMI, and anatomic location of EMI delivery, should be provided to the CIED team (defined as the physician, nurse, and technicians who care for the patient’s CIED).

Clinical status affecting risk of arrhythmia or device function

Most patients with CIEDs have underlying structural heart disease, significant intrinsic rhythm abnormalities, and risk of arrhythmias and thus are at an increased risk of developing fatal arrhythmias during the perioperative period. Additionally, depending on the type of procedure performed and the presence of significant fluid shifts, electrolyte and acid-base alterations, and hemodynamic deterioration of anesthetics, myocardial ischemia may occur and further increase the patient’s susceptibility to fatal

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Fig. 2. Typical examples of chest X-ray images in patients with cardiac implantable electronic devices. (A) Permanent pacemaker. (B) Implantable cardioverter defibrillator (ICD). (C) Cardiac resynchronization therapy-defibrillator. (D) Subcutaneous ICD. (E) Leadless pacemaker. (F) Implantable loop recorder (ILR). Black filled arrows show the shock coils of the ICD lead with a radio-opaque section. The black dotted arrow denotes the left ventricular lead for cardiac resynchronization. The black empty arrow shows the leadless pacemaker within the myocardium of the right ventricle. The white empty arrow shows the ILR within the left chest wall.

https://doi.org/10.4097/kja.23826
arrhythmias.

Several cases have suggested that the pacing threshold of CIEDs increase during surgery, resulting in pacing failure. This is associated with various pathological conditions, including myocardial ischemia, acid-base disturbances, electrolyte abnormalities, and elevated plasma concentrations of antiarrhythmic drugs as well as the local injection of sodium channel blockers (e.g., bupivacaine, lidocaine) [23–25].

Pacing dependence

In general, no intrinsic rhythm > 40 beats/min will be detected in patients with pacemaker dependency or the patient will have a hemodynamically unstable rhythm. However, pacemaker dependency is complex. Although no standard definition currently exists, pacemaker dependency can be described as the abrupt cessation of pacing resulting in the development of bradycardia-related symptoms or signs that lead to an emergent or urgent clinical situation [26]. Note that patients who are not usually pacemaker-dependent may become dependent intraoperatively (e.g., with sedation, direct or indirect vagal stimulation, certain high-potency opiates, other anesthetics, or other pharmacological agents) [26].

Intraoperative management of patients with CIEDs

General considerations

Patients with CIEDs are susceptible to both local and systemic infections. An association between CIED infections and increased mortality has been reported [27]; therefore, the use of ipsilateral central lines should be minimized. In cases of CIEDs placed less than three months prior, insertion and removal of the pulmonary artery catheter or central line should be performed under fluoroscopic guidance to prevent dislodgement of the lead. In addition, care should be taken to avoid advancement of the guidewire into the right ventricle, which could cause artifacts resulting in the delivery of an inappropriate ICD shock.

As most patients with ICDs typically exhibit impaired cardiac function and are potentially at risk of developing malignant arrhythmias, anesthetic management should be customized based on baseline left ventricular systolic function. In patients with heart failure, heart rate is considered a crucial factor affecting myocardial oxygen demand. An increased heart rate reduces the time spent in diastole, leading to premature cessation of diastole and decreased ventricular filling, causing a mismatch between supply and demand. This discrepancy can result in ischemia and malignant arrhythmia. It is essential to consider factors that may precipitate tachycardia, such as intubation, surgical stimuli, hypovolemia, anemia, hypoxia, hypercapnia, and postoperative pain.

Defibrillation patch

External defibrillation therapy should always be available in the preoperative setting. Defibrillator pads should be placed in an anterior–posterior electrode position at a distance ≥ 8 cm from the implanted device; never directly over the device itself. CIEDs rarely result in permanent damage by direct current cardioversion/defibrillation [28]. If cardioversion or defibrillation is performed, the device should be reprogrammed immediately after surgery.

Cardiac monitoring in the operating or procedure room

Intraoperative monitoring of patients with CIEDs is more complex than that of patients without CIEDs. The objective of intraoperative monitoring is to provide a safe environment for patients with a CIED undergoing a surgical or interventional procedure with expected EMI. Anesthesiologists should be aware of the potential limitations of ECG monitoring, such as heart rate overestimation due to double counting of the pacing spike and QRS complex. The use of intraoperative monitoring equipment can help prevent the misinterpretation of ECG artifacts as intrinsic QRS complexes. The monitoring process may include pulse palpation, auscultation of heart sounds, intra-arterial pressure curve monitoring, pulse plethysmography, and/or oximetry.

Diagnosing myocardial ischemia in patients who are unable to report chest pain due to general anesthesia is challenging. Diagnosing ischemic heart disease via ECG is particularly difficult in patients with CIEDs given the presence of ventricular paced rhythms [29].

Perioperative CIED management

CIED-related problems during surgery

Appropriate pacing may be inhibited by a pacemaker sensing EMI, as the device can incorrectly interpret EMI as an intrinsic cardiac rhythm. In patients with pacemaker dependency, EMI may lead to oversensing (interpreted as myocardial electrical activity) and inappropriate inhibition of pacing, with a risk of asystole. In addition, when a CIED uses a vibration sensor or minute ventilation sensor (impedance-based rate-responsive pacing function), manual ventilation for pre-oxygenation or manipulation of
the device can be sensed by the CIED, resulting in inappropriate high-rate pacing, although this is unlikely to cause any clinical harm. In patients with an ICD, EMI may induce inappropriate anti-tachycardia pacing (ATP) or shock therapy, causing the patient to move suddenly, possibly at a critical moment during surgery [30, 31]. Additionally, ventricular arrhythmia could occur with possible fatal outcomes in these patients [32].

PPM and ICD manufacturers either prohibit the use of surgical electrocautery or have issued strong warnings, particularly for the monopolar (most frequently used) mode of operation. Despite the minor risks associated with EMI, bipolar electrocautery should be considered (as opposed to monopolar electrocautery), wherever possible. If monopolar electrocautery is used at a site remote from the device, with the dispersive electrodes located away from the area of the device generator and leads, the current pathway does not pass through the device generator and leads. Thus, the risk of any effect on the device that may cause inappropriate functioning is low [33].

ILRs monitor cardiac signals but do not provide therapies. Patients with ILRs who undergo surgical procedures are not at risk. When using the device, EMI may be interpreted as a rapid heart rhythm and recorded as an episode of tachyarhythmia. However, this can be easily determined by examining the device. No additional precautions are required for patients with an ILR. However, elective examination of the device before the procedure and clearing of the diagnostic memory after the procedure may be useful if the memory is filled with episodes of detected EMI.

**Magnet application**

Magnets have been used during the perioperative period to convert PPMs into an asynchronous pacing mode at a rate of 80–100 beats/min (Table 2) and to turn off the tachycardia treatment of an ICD (Table 3). However, the magnetic response can vary depending on the CIED, manufacturer, and individual settings determined by the CIED team.

For PPMs, when applying the magnet, reprogramming is performed automatically in an asynchronous pacing mode (AOO, VOO, DOO). This means that the PPM is ‘neglecting’ impulses that are being sensed and paced. The rate at which PPM pacing occurs during magnet application depends on the manufacturer and the battery life of the generator. If the battery life is low, PPM pacing will occur at lower rates, which may not be adequate in the perioperative period. Higher pacing rates may be required for patients with PPMs who are undergoing major surgery than for those who typically require pacing in daily life. An increase in the heart rate is a normal response to decreased systemic vascular resistance and hypovolemia. However, the application of a magnet may place the patient in an asynchronous mode; therefore, the pacing rate may not meet the physiological demands of the patient.

This difference in function is critical when applying a magnet

*Table 2. Pacemakers’ Responses to Magnet Application according to the Manufacturer*

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Response to applying magnet*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biotronik</td>
<td>1) Asynchronous mode: AOO/VOO/DOO, frequency 90/min</td>
</tr>
<tr>
<td></td>
<td>2) Synchronous mode; magnet has no effect</td>
</tr>
<tr>
<td></td>
<td>3) Auto mode; asynchronous mode for 10 contractions, then return to synchronous mode with lower rate limit</td>
</tr>
<tr>
<td>Boston Scientific</td>
<td>Asynchronous mode; AOO/VOO/DOO, frequency 100/min</td>
</tr>
<tr>
<td>Medtronic</td>
<td>Asynchronous mode; AOO/VOO/DOO, frequency 85/min</td>
</tr>
<tr>
<td>Abbott (St. Jude Medical)</td>
<td>Asynchronous mode; AOO/VOO/DOO, frequency 100/min</td>
</tr>
<tr>
<td>Microport (Sorin)</td>
<td>Asynchronous mode; AOO/VOO/DOO, frequency 96/min</td>
</tr>
</tbody>
</table>

*All reactions occur when the battery capacity is sufficient; if the battery capacity reaches the elective replacement indicator or time, the pacing rate decreases.* See Table 1 for more information on these acronyms.

*Table 3. Implantable Cardioverter Defibrillators’ Responses to Magnet Application according to the Manufacturer*

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Anti-bradycardia function</th>
<th>Anti-tachycardia function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biotronik</td>
<td>None</td>
<td>Detection/therapy - OFF*</td>
</tr>
<tr>
<td>Boston Scientific</td>
<td>None</td>
<td>1) Inhibit therapy (nominal programming)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) Programmed off</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3) Store intracardiac electrogram</td>
</tr>
<tr>
<td>Medtronic</td>
<td>None</td>
<td>Detection/therapy - OFF</td>
</tr>
<tr>
<td>Abbott (St. Jude Medical)</td>
<td>None</td>
<td>Detection/therapy - OFF*</td>
</tr>
<tr>
<td>Microport (Sorin)</td>
<td>Asynchronous mode; AOO/VOO/DOO, frequency 96/min</td>
<td></td>
</tr>
</tbody>
</table>

*The programmed tachycardia therapy is reactivated after 8 h. †Response can be switched off.

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to an ICD versus a PPM. For ICDs, to prevent inappropriate treatment of tachycardia due to EMI oversensing, both ATP and defibrillation are deactivated by the application of a magnet. This has no effect on the pacing function of an ICD. Therefore, the application of a magnet to an ICD cannot cause the pacing function to shift into asynchronous mode. The effect of a magnet on an ICD can be programmed and can differ according to the manufacturer; thus, some ICDs do not exhibit typical behavior when a magnet is applied. Because this variation depends on the manufacturer and attending cardiologist, the effect of magnet application on each patient’s device should be determined prior to any operative procedure whenever possible. Patients should be continuously monitored for possible spontaneous or surgical stress-induced ventricular arrhythmias when deactivating ICDs using a magnet.

Magnets should be available in all operating rooms or units where surgical or invasive procedures are performed. In addition, all staff members should know the location of the magnet, situations requiring its use, and how to use it. Leadless pacemakers do not respond to magnets with asynchronous pacing; therefore, programming changes must be performed using the programmer for the specific device.

**CIED reprogramming**

EMI can cause CIED dysfunction, resulting in pacing failure in pacing-dependent patients with PPMs or CRT devices and inappropriate shocks in patients with ICDs. In general, determining whether to reprogram the CIED, place a magnet, or do nothing is the most important perioperative decision regarding a CIED. Although reprogramming the CIED is generally regarded as the most established method for managing patients with CIEDs, this can be a time- and resource-consuming process and may not be ideal in certain situations. In particular, hemodynamically unstable bradycardia due to EMI is rare in patients with PPMs without pacing dependence; thus, ECG monitoring during the procedure is sufficient. Pacing dependence is rare in patients with an ICD. However, for patients with pacing dependence who are exposed to EMI, the ICD must be deactivated and asynchronous pacing should be performed. The ICD cannot be programmed for asynchronous pacing when the ATP therapy is turned on.

Evidence indicates that CIED functioning is more likely to be affected by EMI when it is used near the generator or leads [34]. The greatest risk is associated with situations in which the current path crosses the CIED and/or leads. Therefore, the procedural site is the most important factor. During the perioperative period, reprogramming a CIED may not be necessary when EMI is not anticipated, bipolar electrocautery alone is used 15 cm away from the CIED [35], or when the procedural site is located below the umbilicus [36]. A postprocedural CIED check-up is usually not required in such cases. The suggested guidelines for reprogramming a CIED or applying a magnet in various clinical situations are listed in Table 4.

**Troubleshooting**

In cases of detectable inhibition of a PPM or evidence indicating that ICD shock therapy is being delivered, the surgeon should be informed immediately, and the use of equipment capable of producing EMI should be intermittent (breaks of 5 s between use) for short bursts (< 5 s) or discontinued [37]. The application of a magnet can also be considered. Therefore, it is important to establish a secondary method of pacing in the event of asystole. Alternative methods include transesophageal, transcutaneous, and transvenous pacing using a temporary cardiac pacing wire or a pacing pulmonary artery catheter. Regardless of the method chosen, all necessary equipment and support should be organized and available prior to starting the procedure.

| Table 4. Perioperative Management of Patients with Cardiac Implantable Electronic Devices |
|------------------------------------------|-------------------------------|-------------------------------|
| **Type of procedure** | **Permanent pacemaker (PPM)** | **Implantable cardioverter defibrillator (ICD)** |
| | Pacing-dependent | Not dependent | Pacing-dependent* | Not dependent |
| Surgery above umbilicus | Reprogramming with fixed-rate pacing | No reprogramming | Deactivation of ICD with reprogramming to fixed-rate pacing | Deactivation of ICD or magnet application |
| Ocular procedure [35] | No reprogramming | No reprogramming | No reprogramming | No reprogramming |
| Electroconvulsive therapy [35] | No reprogramming | No reprogramming | Deactivation of ICD or magnet application | Deactivation of ICD or magnet application |
| Transurethral resection of prostate/bladder [35] | Magnet application or short burst electrocautery | No reprogramming | Magnet application with short burst electrocautery | Magnet application or short burst electrocautery |
| Hysteroscopic ablation [35] | No reprogramming | No reprogramming | No reprogramming | No reprogramming |

*Magnet can be used as an alternative only when “short burst” electrocautery can be applied.*
Postoperative CIED management

Postoperative management of patients with CIEDs primarily involves the examination and restoration of device function. Ideally, patients with CIEDs should be managed in a postoperative recovery environment with continuous monitoring and the immediate availability of appropriate resuscitation equipment. The defibrillator function of an ICD and any rate modulator pacing function of a PPM that has been suspended should be reactivated by the CIED team as soon as possible after the surgical procedure. The device should be checked at the earliest opportunity if a magnet is used for intraoperative CIED deactivation or in the event of significant arrhythmic events. Device interrogation should be performed before the patient leaves the monitored environment. Precautions should be followed during the perioperative period even if the procedure does not cause EMI. The recommendations for pre-, intra-, and postoperative CIED management are summarized in Table 5.

Conclusion

The perioperative management of patients with CIEDs can be challenging because of the potential for EMI-induced device malfunction. To avoid CIED-related perioperative complications, the indication for device implantation should be assessed and clinicians should have a thorough understanding of perioperative management of CIEDs, including magnet application and device reprogramming. This review describes potential indications for device implantation, presurgical considerations, and the perioperative management of patients with CIEDs. We hope that this review will be helpful to anesthesiologists involved in the perioperative management of CIEDs.

Funding

None.

Conflicts of Interest

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

Data Availability

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Table 5. Basic Recommendations for Pre-, Intra-, and Postoperative CIED Management

<table>
<thead>
<tr>
<th>Perioperative period</th>
<th>Pre</th>
<th>Intra</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
<td>1) Check the device identification card to confirm CIED type and manufacturer (if not possible, check chest X-ray)</td>
<td>1) Caution is required when accessing central lines</td>
<td>The suspended functions of the CIED should be reactivated as soon as possible after the procedure</td>
</tr>
<tr>
<td></td>
<td>2) Check last interrogation date</td>
<td>2) Acid–base disturbances and electrolyte abnormalities should be avoided due to risk of precipitating arrhythmias and interfering with pacemaker capture</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3) Review the medical record to confirm indication for device</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>4) Check whether EMI will occur above the umbilicus</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pacemaker or CRT-P</strong></td>
<td>Check the ECG to see if pacing-dependent</td>
<td>1) Monitor the arterial pulse with pulse oximetry or intra-arterial pressure curve during episodes of ECG artifacts</td>
<td>No additional interrogation of the device beyond routine if no significant events</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) Check inappropriate inhibition of pacing (if this occurs, short burst electrocautery and/or magnet application should be considered; ensure the availability of temporary pacing)</td>
<td></td>
</tr>
<tr>
<td><strong>ICD or CRT-D</strong></td>
<td>Check magnet response of the ICD (note that magnet application could disable anti-tachycardia pacing and not convert to an asynchronous pacemaker function)</td>
<td>1) Defibrillator pads should be placed in anterior–posterior electrode position</td>
<td>After significant arrhythmic events, device interrogation should be performed before the patient leaves the monitored environment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2) Check for inappropriate shock therapy (if this occurs, short burst electrocautery and/or magnet application should be considered)</td>
<td></td>
</tr>
</tbody>
</table>

CIED: cardiac implantable electronic device, CRT-P/D: cardiac resynchronization therapy-pacemaker/defibrillator, ECG: electrocardiogram, EMI: electromagnetic interference, ICD: implantable cardioverter defibrillator.
**Author Contributions**

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**References**

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Introduction

When researchers review a paper, they expect to find scientific and clinically substantiated evidence for the effectiveness of the treatment of interest. To establish scientific evidence, employing a statistical approach encompassing sample size calculations is a common practice. The CONSORT statement includes statistical analysis-related content, such as sample size determination and appropriate statistical method selection, as well as research design components, such as randomization, blindness, and participant selection. Using the appropriate study design to acquire data becomes the foundation for statistical significance throughout statistical analysis. Because Pearson advocated for null hypothesis significance testing (NHST), a P value of 5% has become the threshold for determining statistical significance. Although the widely accepted significance level of 5% for the P value is an indicator of statistical significance, it does not constitute evidence of clinical relevance [1]. According to the International Committee of Medical Journal Editors (ICMJE) recommendations for medical journal standards [2], clinical relevance refers to an effect of an intervention or treatment that promotes healing from a certain disease or has another similar positive influence, reduces the complication rate and illness duration, or consequently improves the quality of life. The value of these positive effects is appreciated from various points of view, and the clinical relevance is determined based on the results. We have already introduced confidence intervals and effect sizes in a previous statistical round article on P values, confidence intervals, and effect sizes. In this article, we present hands-on examples of MCID and various effect sizes and discuss the terms statistical significance and clinical relevance, including cautions regarding their use.

Keywords: Clinical relevance; Clinical significance; Confidence intervals; Effect size; Minimal clinically important difference; Patient outcome assessment; P value; Statistical significance; Statistics.
round article entitled “Alternatives to P value: Confidence Interval and Effect size.” When presented with a P value, these indices are good indicators of statistical significance and clinical relevance [3].

In this article, we introduce various types of effect sizes that can be used to describe statistical results and other indices that indicate clinical relevance, such as the minimal clinically important difference (MCID). In addition, we discuss how to interpret and describe statistical results using these indices, which encompass both clinical relevance and statistical significance.

**Confidence intervals and effect sizes**

Statistical significance is determined according to the decision criteria of NHST. NHST is a statistical method based on validating the null hypothesis (H0: the compared groups do not differ) to determine that “the comparative groups are not different,” except with a type I error, which refers to the probability of accidentally observing a difference that is not there. This interpretation method does not indicate the direction or magnitude of the trial results; it simply indicates whether a statistical difference exists under the fixed significance level. In addition, the P value cannot be used to determine the magnitude of the difference because it is affected not only by the difference but also by the sample size and variability of the measured results [4]. A small absolute difference between central measures of groups can achieve statistical significance if the sample size is sufficiently large to create distinct or slightly overlapping distributions of observed data. Conversely, a large absolute difference between central measures of groups may not be statistically significant if the distributions substantially overlap due to a small sample size. Nonetheless, some researchers misinterpret the P value based on NHST as indicating something is “more significant” or “less significant.” These incorrect interpretations have frequently been presented, even though researchers should know that comparing P values cannot be used to interpret the strength of significance because the NHST implies a dichotomous decision (whether the null hypothesis is true or false) [5]. Confidence intervals and effect sizes can be used to rectify such errors to express the magnitude of the differences or ratios observed in clinical trial results, as discussed in a previous article [2].

**Confidence intervals**

The confidence interval can be calculated to determine the range estimation using statistical probability. The representative value (e.g., mean), the measure of statistical dispersion (e.g., standard deviation), and the sample size of the group are used to estimate the confidence interval. Although the real mean of the target population is unknown, we can presume, with a preset probability, that the expected mean of a future population in the same environment with the same intervention will be located within this confidence interval. This statistical process enables us to expect an effect from an intervention in a future sample regardless of the unknown real value of the target population. Beyond determining the statistical significance based on whether the confidence interval includes a null value, using a confidence interval allows us to presume the potential direction and magnitude of the effect that may be observed in future patients from the same population who receive the same intervention. The confidence interval provides a range that reflects the statistical uncertainty of sampling and the statistical test process, which enables us to speculate on the expected results in real clinical situations. The P value represents the probability of accepting or rejecting the hypothesis, and the confidence interval represents the range of the estimated representative value along with the uncertainty (margin of error), where the real value of the population would exist [6]. However, the confidence interval is not a property of the observed data but rather a characteristic of a sampling distribution, such as the standard error of the mean (SEM). The sampling distribution is an imaginary distribution composed of the means of data that are repeatedly sampled from the population using the same method as that of the observed data. For example, the means from the groups are the observed values, and the confidence interval of the mean difference is a range estimated by probability and statistics based on the hypothesis. Similarly, the standard deviation, which indicates the dispersion of data, is the observed value, while the upper and lower limits of the confidence interval are statistically estimated values. The confidence interval cannot be interpreted as the mean and the standard deviation explaining the observed data distribution. The confidence interval is interpreted such that if the experiment is repeated using the same hypothesis and a confidence interval is calculated from each experiment, we can expect that the true population mean would fall within the given range of those intervals with a certain probability (usually 95%).

Compared to the dichotomous nature of the P value, including the confidence interval in the statistical result has the advantages described above. However, determining quantitative differences between clinical trials is frequently complex except in cases of mean difference or ratio comparisons.

**Effect size**

The effect size is a statistic representing the observed effect’s standardized magnitude and direction. A detailed description of
<table>
<thead>
<tr>
<th>Statistical method</th>
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</table>
| Student's t-test        | Cohen's $d$                  | $d = \frac{\bar{X}_T - \bar{X}_C}{s_{pooled}}$                  | $\bar{X}_T, \bar{X}_C$: Means of treatment and control groups
|                         |                              | $\bar{X}_T, \bar{X}_C$: Means of treatment and control groups   | 0.2 to < 0.5: Small effect |
|                         |                              | $s_{pooled}$                                                     | $S_{pool}$: Pooled SD      | 0.5 to < 0.8: Medium effect |
|                         |                              | $n_T, n_C$: Sample size of treatment and control groups          | $n_T, n_C$: Sample size of treatment and control groups
| Mann-Whitney rank sum test (Mann-Whitney U test) | $r$                          | $r = \frac{|z|}{\sqrt{n}}$                                      | $z$: Test statistics
|                         |                              | $t$: Test statistics                                             | 0.1 to < 0.3: Small effect |
|                         |                              | $d$: Degrees of freedom                                          | 0.3 to < 0.5: Medium effect |
|                         |                              | $\delta$: Cohen's $d$                                            | $\geq 0.5$: Large effect   |
| Vargha and Delaney's A  |                              | $VDA = \frac{U}{n_1 \times n_2}$                               | $VDA$: Vargha and Delaney's A
|                         |                              | $U$: U statistics                                                | 0.56 to < 0.64: Small effect |
|                         |                              | $n_1, n_2$: Sample size of each group                            | $> 0.34$ to 0.44: Medium effect
| Cliff's delta*          |                              | $\delta = 2(VDA - 0.5)$                                         | $\geq 0.8$: Large effect   |
| Paired t-test           | Cohen's $d$                  | $d = \frac{\bar{X}_{after} - \bar{X}_{before}}{S_{after/before}}$| $\bar{X}_{after}, \bar{X}_{before}$: Mean of observations before and after
|                         |                              | $\bar{X}_{after}, \bar{X}_{before}$: Mean of observations before and after
|                         |                              | $S_{after/before}$: SD from differences in observations          | 0.2 to < 0.5: Small effect |
| Wilcoxon signed rank test (Wilcoxon Z test) | Matched-pairs rank biserial correlation coefficient | $r = 4\frac{|T - 0.5(R_r + R_s)|}{N(N+1)}$ | $r$: Biserial correlation coefficient
|                         |                              | $T$: Smaller value between $R_r$ and $R_s$                      | 0.1 to < 0.3: Small effect |
|                         |                              | $R_r, R_s$: Sum of ranks with a positive or a negative sign     | 0.3 to < 0.5: Medium effect
|                         |                              | $N$: Number of pairs                                            | $\geq 0.71$: Medium effect
|                         |                              | $z$: Test statistics                                             | 0.11 to < 0.28: Small effect
|                         |                              | $\geq 0.11$: Small effect                                        | $\geq 0.29$: Large effect   |
|                         |                              | $\geq 0.5$: Medium effect                                         | $\geq 0.29$: Large effect   |
|                         |                              | $\geq 0.71$: Medium effect                                        | $\geq 0.71$: Medium effect
| ANOVA                   | Coefficient $\eta^2$         | $\eta^2 = \frac{SS_g}{SS_S}$                                    | $SS_g$: Sum of squares for the effect
|                         |                              | $SS_S$: Total sum of squares                                     | 0.02 to < 0.13: Small effect
|                         |                              | $\eta^2_g$: Partial eta-squared                                   | 0.13 to < 0.26: Medium effect
|                         |                              | $SS_g$: Sum of squares for the effect                            | $\geq 0.26$: Large effect
|                         |                              | $SS_S$: Sum of squares error                                      | $\geq 0.26$: Large effect
|                         |                              | $\eta^2_g$: Partial eta-squared                                   | $\geq 0.26$: Large effect
|                         |                              | $\geq 0.26$: Large effect                                         | $\geq 0.26$: Large effect

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<table>
<thead>
<tr>
<th>Statistical method</th>
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<th>Calculation</th>
<th>Effect size interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coefficient $\omega^*$ (for</td>
<td>Small effect</td>
<td>$df_e \times \text{degrees of freedom for the effect}$</td>
<td>0.01 to &lt; 0.06 Small effect</td>
</tr>
<tr>
<td>between-subject designs, Unbiased estimate of $\eta^2$)</td>
<td>Medium effect</td>
<td>$df_e \times \text{degrees of freedom for the effect}$</td>
<td>0.06 to &lt; 0.14 Medium effect</td>
</tr>
<tr>
<td>Partial $\omega^*$</td>
<td>Large effect</td>
<td>$df_e \times \text{degrees of freedom for the effect}$</td>
<td>≥ 0.14 Large effect</td>
</tr>
<tr>
<td>$\eta^2 = \frac{df_e (MS_p - MS_e)}{SS + MS_e}$</td>
<td>Small effect</td>
<td>$\omega^2$: Partial $\omega^*$</td>
<td>0.01 to &lt; 0.06 Small effect</td>
</tr>
<tr>
<td>$\omega^2 = \frac{df_e (MS_p - MS_e)}{df_e MS_p + (n - df_e)MS_e}$</td>
<td>Medium effect</td>
<td>$\omega^2$: Partial $\omega^*$</td>
<td>0.06 to &lt; 0.14 Medium effect</td>
</tr>
<tr>
<td>$\omega^2 = \frac{df_e (MS_p - MS_e)}{df_e MS_p + (n - df_e)MS_e}$</td>
<td>Large effect</td>
<td>$\omega^2$: Partial $\omega^*$</td>
<td>≥ 0.14 Large effect</td>
</tr>
<tr>
<td>$n$: Sample size</td>
<td></td>
<td>$\eta^2$: Coefficient $\eta^2$ (Cohen's $f$ is interchangeable with $\eta^2$ as shown)</td>
<td>$\eta^2$: Coefficient $\eta^2$ (Cohen's $f$ is interchangeable with $\eta^2$ as shown)</td>
</tr>
<tr>
<td>Cohen's $f$</td>
<td></td>
<td>$f = \sqrt{\left(\frac{\sum_{j=1}^{p}(\mu_j - \mu)^2}{n}\right) / \sigma^2} = \sqrt{\frac{\eta^2}{1 - \eta^2}}$</td>
<td>0.10 to &lt; 0.25 Small effect</td>
</tr>
<tr>
<td>$p$: Number of groups</td>
<td></td>
<td>$\mu$: Mean of each group</td>
<td>0.25 to &lt; 0.40 Medium effect</td>
</tr>
<tr>
<td>$\mu$: Mean of whole sample</td>
<td></td>
<td>$\eta$: Standard deviation of the whole sample</td>
<td>≥ 0.40 Large effect</td>
</tr>
<tr>
<td>$\eta^2 = \frac{H - k + 1}{n - k}$</td>
<td></td>
<td>$\eta^2$: Partial eta-squared</td>
<td>0.02 to &lt; 0.13 Small effect</td>
</tr>
<tr>
<td>Kruskal-Wallis H</td>
<td></td>
<td>$\eta^2$: Partial eta-squared</td>
<td>0.02 to &lt; 0.13 Small effect</td>
</tr>
<tr>
<td>ANOVA on ranks</td>
<td></td>
<td>$\eta^2$: Partial eta-squared</td>
<td>0.02 to &lt; 0.13 Small effect</td>
</tr>
<tr>
<td>$\eta^2 = \frac{H - k + 1}{n - k}$</td>
<td></td>
<td>$\eta^2$: Partial eta-squared</td>
<td>0.02 to &lt; 0.13 Small effect</td>
</tr>
<tr>
<td>RM ANOVA</td>
<td></td>
<td>$\eta^2$: Partial eta-squared</td>
<td>0.02 to &lt; 0.13 Small effect</td>
</tr>
<tr>
<td>Partial $\eta^2$</td>
<td></td>
<td>$\eta^2 = \frac{SS}{SS + SS_{error}}$</td>
<td>0.13 to &lt; 0.26 Medium effect</td>
</tr>
<tr>
<td>Generalized $\eta^2$</td>
<td></td>
<td>$\eta^2 = \frac{SS}{SS + SS_{error}}$</td>
<td>0.13 to &lt; 0.26 Medium effect</td>
</tr>
<tr>
<td>$\delta$: 0 if the effect involves one or more measured factors; 1 if the effect involves only manipulated factors</td>
<td></td>
<td>0.13 to &lt; 0.26 Medium effect</td>
<td></td>
</tr>
<tr>
<td>$\eta^2$: Generalized $\eta^2$</td>
<td></td>
<td>$\eta^2$: Generalized $\eta^2$</td>
<td>≥ 0.26 Large effect</td>
</tr>
<tr>
<td>$\delta$: 0 if the effect involves one or more measured factors; 1 if the effect involves only manipulated factors</td>
<td></td>
<td>≥ 0.26 Large effect</td>
<td></td>
</tr>
<tr>
<td>$\eta^2$: Generalized $\eta^2$</td>
<td></td>
<td>$\eta^2$: Generalized $\eta^2$</td>
<td>≥ 0.26 Large effect</td>
</tr>
<tr>
<td>Partial $\omega^2$</td>
<td></td>
<td>$\omega^2$: Partial $\omega^2$</td>
<td>0.01 to &lt; 0.06 Small effect</td>
</tr>
<tr>
<td>$\omega^2 = \frac{df_e (MS_p - MS_e)}{df_e MS_p + (n - df_e)MS_e}$</td>
<td></td>
<td>$\omega^2$: Partial $\omega^2$</td>
<td>0.06 to &lt; 0.14 Medium effect</td>
</tr>
<tr>
<td>Friedman RM ANOVA on ranks</td>
<td></td>
<td>$\chi^2$: Friedman test statistic</td>
<td>0.1 to &lt; 0.3 Small effect</td>
</tr>
<tr>
<td>Kendall's W (coefficient of</td>
<td></td>
<td>$\chi^2$: Friedman test statistic</td>
<td>0.1 to &lt; 0.3 Small effect</td>
</tr>
<tr>
<td>concordance)</td>
<td></td>
<td>$\chi^2$: Friedman test statistic</td>
<td>0.1 to &lt; 0.3 Small effect</td>
</tr>
</tbody>
</table>
### Table 1. Continued

<table>
<thead>
<tr>
<th>Statistical method</th>
<th>Effect size</th>
<th>Calculation</th>
<th>Effect size interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chi-square test</td>
<td>Cramér’s V</td>
<td>$\phi_c = \frac{x^2}{n(k-1)}$</td>
<td>$\phi_c$: Cramér’s V (extended phi coefficient for 2 × 2 table) $k = 2$</td>
</tr>
<tr>
<td></td>
<td>(Cramér’s phi$^*$)</td>
<td>$\chi^2$: Chi-square statistic</td>
<td>0.1 to &lt; 0.3 Small effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$n$: Sample size</td>
<td>0.3 to &lt; 0.5 Medium effect</td>
</tr>
<tr>
<td>Fisher’s exact test</td>
<td>Phi coefficient$^{**}$</td>
<td>$\phi = \frac{x^2}{n}$</td>
<td>$\phi$: Sample size $\geq 0.5$ (see footnote) Large effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\chi^2$: Chi-square statistic</td>
<td>0.1 to &lt; 0.3 Small effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$n$: Sample size</td>
<td>0.3 to &lt; 0.5 Medium effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\geq 0.5$</td>
<td>Large effect</td>
</tr>
<tr>
<td>Two-proportions z-test</td>
<td>Cohen’s $h$</td>
<td>$h = \left[2 \arcsin \sqrt{P_1}-2 \arcsin \sqrt{P_2}\right]$</td>
<td>$P_1, P_2$: Two given probabilities or proportions $r_{arcsinh}$: Arcsine transformation $0.2$ to $&lt; 0.5$ Small effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$r_{arcsinh}$: Arcsine transformation</td>
<td>$0.5$ to $&lt; 0.8$ Medium effect</td>
</tr>
<tr>
<td>Correlation analysis</td>
<td>Pearson correlation coefficient $r$</td>
<td>$r = \frac{\sum(x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum(x_i - \bar{x})^2(y_i - \bar{y})^2}}$</td>
<td>$r$: Correlation coefficient $0.1$ to $&lt; 0.3$ Small effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\bar{x}, \bar{y}$: Means of x and y</td>
<td>$0.3$ to $&lt; 0.5$ Medium effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$x_i, y_i$: Samples of variable x and y</td>
<td>$\geq 0.5$ Large effect</td>
</tr>
<tr>
<td>Spearman’s $\rho$</td>
<td></td>
<td>$r_s = \frac{\text{cov}(R(X),R(Y))}{\sigma_{R(X)} \sigma_{R(Y)}}$</td>
<td>$r_s$: Spearman’s $\rho$ $0.1$ to $&lt; 0.3$ Small effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\text{cov}(R(X),R(Y))$: Covariance of the rank variables</td>
<td>$0.3$ to $&lt; 0.5$ Medium effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\sigma_{R(X)} \sigma_{R(Y)}$: Standard deviations of the rank variables</td>
<td>$\geq 0.5$ Large effect</td>
</tr>
</tbody>
</table>

The effect sizes listed in this table are not a complete list of all available effect sizes. The authors chose some effect sizes according to their preference and recommendation. BESD: binomial effect size display [3], SD: standard deviation, ANOVA: analysis of variance, RM: repeated measures. *The original definition of Cliff’s delta involves a pre-defined matrix and the following process [7]. Fortunately, Cliff’s delta is linearly related to Vargha and Delaney’s A [8]. Therefore, the interpretation of Cliff’s delta is converted from the recommendation of Vargha and Delaney’s A. “effect” indicates the within- and between-subject factors. †Generalized $\eta^2$ is different from $\eta^2$ and partial $\eta^2$. Generalized $\eta^2$ is an effect size considering the interaction and has various formulas according to the study design. For details, refer to the article by Bakeman [9]. ‡Kendall’s W uses Cohen’s interpretation guidelines. Kendall’s W is a test statistic of agreement between groups where $W = 1$ indicates that all groups have identical rank by the intervention, a complete agreement. That is, high Kendall’s W represents concordant changes by the intervention (a repeated measures factor). ‡As mentioned above, Kendall’s W is a statistic related to Friedman’s ANOVA and represents the general effect of the overall ANOVA test. The effect size $r$ from each multiple comparison (such as Bonferroni corrected Wilcoxon signed-rank tests) would be informative. *Guideline based on Cohen’s suggestion. Alternatively, refer to the Table 4 of the previously published article [3].

<table>
<thead>
<tr>
<th>Small effect</th>
<th>Medium effect</th>
<th>Large effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k = 2$</td>
<td>0.100 to &lt; 0.300</td>
<td>0.300 to &lt; 0.500</td>
</tr>
<tr>
<td>$k = 3$</td>
<td>0.071 to &lt; 0.212</td>
<td>0.212 to &lt; 0.354</td>
</tr>
<tr>
<td>$k = 4$</td>
<td>0.058 to &lt; 0.173</td>
<td>0.173 to &lt; 0.289</td>
</tr>
<tr>
<td>$k = 5$</td>
<td>0.050 to &lt; 0.150</td>
<td>0.150 to &lt; 0.250</td>
</tr>
<tr>
<td>$k = 6$</td>
<td>0.045 to &lt; 0.134</td>
<td>0.134 to &lt; 0.224</td>
</tr>
</tbody>
</table>

$^*$Using the phi coefficient for the Fisher’s exact test is controversial because it comes from the chi-square statistic. Using the odds ratio instead of the phi coefficient has been recommended. However, some articles still report using the phi coefficient or Cramér’s V for the Fisher’s exact test results. One problem with using the phi coefficient, Cramér’s V, and Cohens’ w is that they require uniformly distributed marginals for a 2 × 2 table.
the basic concept of effect size is provided in a previous article [3]. Table 1 summarizes the effect sizes corresponding to the different statistical analysis methods. Including the effect size in the statistical analysis results overcomes the limitations of the P value and enables descriptions of the quantitative and qualitative magnitude of the treatment effect, making it possible to compare the effects between groups or between trials and, thus, is the main statistic used in systematic reviews. The effect size is a point-estimated value, such as a mean, and a standardized value of an effect of a clinical trial intervention. In this respect, the advantage of the effect size is that it is more intuitive than the confidence interval and easy to interpret its meaning. Considering these advantages, an increasing number of studies have presented statistical results using effect sizes [10–13].

The effect size also has its own confidence interval based on the significance level, and there are often situations where interpretation of effect size using confidence intervals is necessary. Presenting the confidence intervals with the odds ratio (OR), relative risk, and area under the receiver operating characteristic curve is common practice. Various effect sizes can be calculated using R (R Core Team). The supplementary document presents the methods for calculating various effect sizes and the corresponding confidence intervals (Supplementary Materials 1 and 2).

Besides the effect size from a specific statistic, the number needed to treat (NNT; also, the number needed to treat for an additional beneficial outcome [NNTB]) is useful to describe the number of changes between comparison groups. The NNT describes the required number of patients to include in the treatment group to observe a beneficial effect in one patient from the treatment in a clinical trial. The NNT is an epidemiological measurement that is usually used to discuss the treatment effect of a certain medication. In clinical trials, the NNT is considered an index of effect, even though it is not a statistic like the effect size. A large NNT suggests that the experimental treatment is less effective because a large number of patients are required to obtain an effect from the treatment.

The NNT is the inversed value of the absolute risk reduction:

\[
\text{NNT} = \frac{1}{(I_c - I_t)}
\]

where \(I_c\) is the incidence of the control group and \(I_t\) is the incidence of the treatment group.

An example is as follows: a randomized controlled trial is conducted to investigate the preventative effect of Drug A on postoperative nausea and vomiting. The observed postoperative nausea and vomiting rates are 40% and 30% in the control and treatment groups, respectively. The absolute risk reduction is thus 10% (40%–30%) and the NNT is 10. This means that the preventive effect can be observed when 10 patients are treated with Drug A. Similar to the NNT, the number needed to harm (NNH) is an index of a hazardous effect and can also be useful for comparing effects.

**Minimal clinically important difference (MCID)**

In the early 20th century, MCID was introduced to measure clinical improvement in patients [14]. At the beginning of the 21st century, magnitude-based inference (MBI) was introduced in the field of sports medicine. MBI assesses the observed effects based on three criteria: harmful, trivial (small changes), and beneficial [15]. However, some scholarly journals no longer accept MBI as a valid statistical approach because it lacks a clear mathematical foundation and is associated with an increased risk of type I errors [16,17]. On the contrary, MCID is a statistical method of approaching the difference in the effects perceived by the patient in clinical settings rather than the numerical difference based on statistical significance. This measure is becoming increasingly common in statistical and medical research areas [18,19]. MCID is a representative method for determining clinical relevance that involves setting a specific value of the measured outcome as the threshold for meaningful effects.\(^2\) This threshold indicates the minimal amount for important or meaningful changes in the measured outcome to be observed in patients or participants, and changes in the outcome that are larger than this threshold are considered clinically relevant. However, no method is generally accepted as the standard for determining the threshold for clinically relevant changes. Several articles on determining MCID for outcomes in various situations have recently been published in various medical fields [20–24].

MCID is useful for assessing the clinical relevance of the outcome variable in participants. Particularly in pain research, patient-reported outcomes (PROs), such as the visual analog scale (VAS) or numerical rating scale (NRS), are commonly used, along with opioid consumption. The statistical analysis of these results contributes to the clinical values of the findings. However, statistically significant differences in these variables do not constitute an evaluation of the treatment effect as perceived by patients. MCID was thus introduced to define the treatment effect as perceived by the patients. In a study assessing the effect of pain management after surgery, for instance, different minimum thresholds for the clinical importance of pain relief may need to be set for patient

\(^2\)Besides MCID, several terms have been proposed, such as the minimal clinical difference (MCD), minimal clinically important improvement (MCII), and robust clinically important difference (RCID).
groups undergoing different types of surgery, such as abdominal or foot surgeries. Additionally, within the same study, the minimum threshold for judging the side effects of pain medications may vary depending on the severity of pain, as patients may tolerate side effects differently based on pain intensity. Therefore, interpreting differences in opioid consumption in the context of pain relief also differs based on clinical considerations and patient perceptions.

Interpreting MCID often involves testing the statistically significant proportion of patients who achieve a change equal to or greater than MCID in both the control and treatment groups using NHST. Alternatively, researchers may divide the study population into groups based on whether they exhibit a change equal to or greater than MCID and then statistically analyze the factors associated with the observed differences. This approach demonstrates how meaningful effects are observed in an actual patient population beyond simply presenting the differences in treatment effects between the two groups.

A standard method for calculating MCID has not been fully established. Some representative calculation methods include a distribution-based method based on the distribution of observed values and an anchor-based method that involves comparing generally accepted measurements as the standard (anchor) against an evaluation method that is widely used in clinics or more specific evaluation methods. As these methods have various limitations, a new method of comparing and coordinating the results of these methods to determine MCID, known as the triangulating method, has recently been attracting attention. In addition, the Delphi method, which involves a panel of experts and patients reaching a consensus on the criteria through multiple rounds and determining MCID through a literature review, is another method. Unfortunately, none of these methods have been accepted as standard because each has advantages and disadvantages.

The distribution-based method follows a process similar to that used to determine the measurement error or effect size. For this method, factors such as the standard error of measurement (SEa = SD × \sqrt{1 - \text{Cronbach’s } \alpha}) and the standard deviation, or the factors involved in these measurements are utilized. Commonly recommended distribution-based indicators include the SEa, standard deviation of baseline (pretreatment) observations, 0.5 standard deviations, and the associated 1.96 SEa, which is related to the reliable change index (RCI). RCI can be calculated as the standard error of the difference in scores between two measurement methods, represented as \((x_1 - x_2)\sqrt{2 \times SE_a^2}\), where \(x_1\) and \(x_2\) are scores from the respective measurement methods. If the calculated value is > 1.96, it is considered significant at the 5% level, indicating that the change in measurement is "not likely due to a measurement error. Some researchers have also added additional criteria that they considered important regarding the characteristics of experimental design and data. Furthermore, based on the general interpretation of effect sizes, an effect size of 0.2, corresponding to a small effect, is sometimes set as MCID. With distribution-based methods, making a case for clinical significance is challenging because no clinical anchor is available to provide meaning to the criteria.

The anchor-based method involves using a reference assessment technique, such as the global assessment scale (GAS) or the global impression of changes (GIC), as an "anchor." For this method, values measured by individuals or researchers to estimate MCID are used (Fig. 1) [25]. This method involves comparing the mean change in response based on the assessment method under study (e.g., the VAS or NRS, which are PROs) with individual improvement effects based on a comprehensive assessment scale (anchor). This can also be determined using a receiver operating characteristic (ROC) curve analysis. This method begins with the assumption that the measurement method used is significantly associated with a reference evaluation method (anchor) chosen from among various assessment methods. Therefore, a relatively strong correlation is desirable (correlation coefficient ≥ 0.7). If a meaningful correlation is not observed, having strong confidence in the changes observed using the measurement values applied in a study is challenging. Furthermore, if a comprehensive assessment scale is evaluated retrospectively, relying on patients’ memory may lead to recall bias. Therefore, re-validating the results using additional measurable criteria (anchors), such as analgesic consumption, to mitigate potential bias is advised [26].

Given that multiple methods are available to determine MCID, a variety of MCID values can be calculated for the same patients in the same situation. Although comparing and reconciling the outcomes of various methods using the triangulating method is advised, a comprehensive systematic approach for this purpose has not yet been established. The process typically begins with a distribution-based analysis, followed by a supplementary evaluation using a comprehensive assessment scale. Subsequently, among MCID values identified using these two methods, researchers often employ ROC analyses to determine the most appropriate choice, or they may opt for the average of these values as the final MCID [27,28]. Given the lack of established statistical methods for these procedures, the recommended approach for establishing the robustness of the selected MCID value involves

\[^{1}\text{The triangulating method is a measurement technique that utilizes the properties of triangles for measurement, known as triangulation. Here, it is used to determine a more accurate and reliable MCID through deciding between two different MCID values.}\]
conducting a sensitivity analysis. This analysis assesses the impact of assumptions on outcomes, examines how changes in these assumptions affect results, and identifies uncertainties in research design and data collection processes. By evaluating their impact on final outcomes, researchers can verify the consistency of research findings under different conditions and enhance the reliability of their results. In the supplementary document, the overall process for calculating MCID along with an example of conducting the sensitivity analysis is presented.

Additional considerations must also be taken into account. First, the fundamental notion of “minimal” must be adequately considered. Determining whether the measurement tool used (e.g., the VAS or NRS) adequately captures the minimum amount of change is essential. If the instrument does not reflect the minimum change reported by the patient, this can lead to increased errors due to inaccurate measurements. Furthermore, the minimum change reported by patients is influenced by their perception thresholds; thus, measurement tools that can capture this should be employed. Research in the field of psychophysiology indicates that the minimum change based on patient reports is approximately 0.5 standard deviations (SD) of the effect size. This value is often used in anchor-based methods that rely on reference-assessment techniques. Second, even for results obtained using the same measurement tool, various factors influence MCID value, such as the study setting, participants, and the method of calculation. Therefore, applying an established MCID from one specific study to a clinical trial is challenging. To use a previously reported MCID, researchers must assess and consider the differences between the circumstances of the research conducted to determine MCID and the current one being conducted.

Clinical relevance vs. statistical significance

As discussed previously, the presence of statistical significance in the data analysis does not imply clinical relevance. Conversely, the absence of statistical significance does not necessarily mean a lack of clinical relevance. The latter scenario often arises when a study is conducted with an inadequate sample size or when the method of measuring the outcome variable exhibits significant variability. For instance, if the severity of postoperative nausea is recorded by the patients themselves using an NRS, patients’ subjectivity cannot be entirely eliminated. Depending on the circumstances, similar levels of nausea symptoms could be measured differently. Consequently, even if an antiemetic with a potentially meaningful effect is administered, statistical significance may not be attainable. The concept of clinical relevance lacks an agreed-upon definition, and traditionally, many studies have assessed clinical relevance based on statistical significance.

The clinical effects reflected by the effect size estimate the average effect observed in the experimental group due to the intervention, allowing for the interpretation of the magnitude of the effect. However, the effect size does not provide a specific indication of how much an individual can expect to benefit; rather, it captures the overall effect, encompassing the entire group. Furthermore, the effect size is a dimensionless comparative measure, which means interpreting it directly at an individual level is challenging. One benefit of MCID is that it employs the same units of measurement as the actual variable, enabling assessment of clinical relevance for specific patients. It can serve as a reference for deciding whether to continue the current treatment or consider alternative approaches in individual patients within a clinical context. Essentially, it enables assessment at the individual level. Furthermore, integrating MCID in research facilitates its application in the evaluation of novel treatment methods.

However, MCID also has several limitations. In addition to the issues of bias and lack of established calculation methods mentioned earlier, the assessment of treatment effects through MCID can vary depending on the patient’s circumstances or past experiences. For example, required MCID may be higher if a patient experienced higher pain levels before treatment. Similarly, if a patient has repeatedly encountered similar types of pain in previous experiences, a greater effect might be required to achieve a state of comfort. Additionally, because MCID represents the smallest
meaningful effect, it may not be suitable as a criterion for judging meaningful outcomes of a particular clinical intervention that aims to achieve substantial treatment efficacy [29]. The limitations of MCID continue to be evident. Anchor-based methods are often difficult to conduct given the lack of appropriate anchor measurements for a wide range of cases. Distribution-based methods frequently result in findings that lack clinical meaning for the chosen criteria and variable MCID values owing to changing criteria with every sample extraction, even when the same study is repeated.

**Conclusion**

Researchers and medical practitioners have developed new treatments and medications based on accumulated evidence from clinical trials, aiming to offer patients the best possible care. Research outcomes that demonstrate statistically significant differences are the strongest evidence provided that they are sufficiently clinically relevant. The statistical significance of a research outcome is determined through a binary decision-making process that involves a mathematical calculation based on the null hypothesis, which states that no difference or effect is present. However, clinical decision making requires constructive information on the expected effect of the treatment or medication, beyond the presence or absence of an effect. The effect size is a standardized statistic (value) of the magnitude and direction of change observed in a study, and MCID is a robust threshold for determining clinical relevance.

By combining metrics of clinical relevance, such as the effect size and MCID, with the conventional application of statistical significance and presenting outcomes derived from robust research designs, it becomes imperative that we can establish a foundation that holds both scientific and clinical significance. This approach has the potential to enhance our understanding not only from a scientific standpoint but also in terms of the practical clinical implications.

**Funding**

None.

**Conflicts of Interest**

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

**Data Availability**

The datasets generated during and analyzed during the current article are available as supplementary material 2.

**Author Contributions**

Junyong In (Writing – original draft; Writing – review & editing) Dong Kyu Lee (Conceptualization; Data curation; Formal analysis; Methodology; Software; Validation; Writing – original draft; Writing – review & editing)

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**Supplementary Materials**

Supplementary Material 1. Examples of the effect size and MCID calculation.
Supplementary Material 2. Sample data.

**References**

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Comparison of preemptive and preventive intravenous acetaminophen on opioid consumption in pediatrics undergoing posterior spinal fusion surgery: a randomized controlled trial

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Background: Posterior spinal fusion (PSF), commonly used for adolescent idiopathic scoliosis (AIS), causes severe postoperative pain. Intravenous (IV) administration of acetaminophen has shown promise for opioid-sparing analgesia; however, its analgesic effect and optimal timing for its standard use remain unclear. Our study aimed to evaluate the analgesic effect and optimal timing of IV acetaminophen administration in pediatric and adolescent patients undergoing PSF and requiring adequate pain control.

Methods: This prospective, randomized, triple-blind trial was conducted in patients aged 11–20 undergoing PSF. Participants were randomized into three groups: the preemptive group (received IV acetaminophen 15 mg/kg after anesthetic induction/before surgical incision), the preventive group (received IV acetaminophen 15 mg/kg at the end of surgery/before skin closure), and the placebo group. The primary outcome was cumulative opioid consumption during the first 24 h postoperatively.

Results: Among the 99 enrolled patients, the mean ± standard deviation (SD) amount of opioid consumption during the postoperative 24 h was 60.66 ± 23.84, 52.23 ± 22.43, and 66.70 ± 23.01 mg in the preemptive, preventive, and placebo groups, respectively (overall P = 0.043). A post hoc analysis revealed that the preventive group had significantly lower opioid consumption than the placebo group (P = 0.013). However, no significant differences between the groups were observed for the secondary outcomes.

Conclusions: The preventive administration of scheduled IV acetaminophen reduces cumulative opioid consumption without increasing the incidence of drug-induced adverse events in pediatric and adolescent patients undergoing PSF.

Keywords: Acetaminophen; Opioid analgesics; Pain; Pediatrics; Prospective studies; Spinal fusion.

Introduction

Posterior spinal fusion (PSF), a common surgical technique for correcting adolescent idiopathic scoliosis, causes severe postoperative pain due to extensive dissection, inflammation, and nerve sensitization. Managing pain in pediatric and adolescent surgical patients is challenging due to difficulties in pain assessment, concerns regarding oversedation, and worries regarding the side effects of opioids [1–3].
Acetaminophen, a widely used non-opioid drug, has a well-established safety profile and good tolerance in adolescent and pediatric patients [4]. Intravenous (IV) administration of acetaminophen offers rapid and predictable analgesic effects, particularly beneficial for all groups of patients in nil per os (NPO) status during the perioperative period [5]. However, few trials have examined the effects of IV acetaminophen in patients with PSF, and their conclusions are under debate [6,7].

Moreover, the optimal timing of IV acetaminophen administration for painful procedures in pediatric patients is not well defined. The role of acetaminophen as a preemptive analgesic, administered before surgical incision to prevent central sensitization, remains unclear [8]. Clinical trials investigating the timing of acetaminophen administration have yielded conflicting results [9,10]. Therefore, a well-designed randomized controlled study is needed to compare preemptive and preventive IV acetaminophen administration in painful procedures [11]. Our study aims to identify the optimal timing of IV acetaminophen to reduce opioid consumption in pediatric and adolescent patients undergoing PSF and requiring adequate pain control.

Materials and Methods

Ethics approval

This prospective, randomized, triple-blind trial received approval from the Institutional Review Board (IRB) of Asan Medical Center (Seoul, Republic of Korea) on March 19, 2021 (IRB#: 2021-0411), before patient enrollment. Written informed consent was obtained from all patients and their legal guardians after providing a sufficient explanation of the study protocol and rationale. The trial was registered at ClinicalTrial.gov (NCT04959591, Principal investigator: Won Uk Koh) and conducted following the original protocol and the Consolidated Standards of Reporting Trials (CONSORT) guidelines. We conducted this study in accordance with the Declaration of Helsinki, 2013, and followed the Consolidated Standards of Reporting Trials guidelines for study reporting.

Patient population

We enrolled adolescent and pediatric patients aged 11 to 20, classified as American Society of Anesthesiologists physical status I–III, scheduled for PSF. Trial eligibility screening was performed by one researcher, and another researcher approached the patient in the general ward for data collection. The operations were conducted by two orthopedic spine surgeons (C.S.L. and C.J.H.). Patients unable to participate due to mental impairment, developmental delay, allergies to acetaminophen or its additives, existing liver disease, dysfunction, or being deemed ineligible by the medical staff were excluded.

Participant allocation and blinding

Participants were randomized in a 1:1:1 ratio using computer-generated simple randomization in blocks of six, concealed in sealed envelopes. Each participant was assigned to one of the three groups: IV acetaminophen after anesthetic induction/before incision (preemptive group), at the end of surgery/before skin closure (preventive group), or placebo group. The principal investigator (W.U.K.), the only person with knowledge of the group allocation, performed the randomization and assigned the study drugs for each treatment arm but was not involved in pain assessment or determining the necessity of rescue analgesics. Another investigator (H.J.K.) prepared the study drugs for each patient but was blinded to the group allocations and not involved further in the study process, including clinical management, outcome assessment, and data analysis. After randomization, the subjects and their group assignments were recorded in a master log. To ensure blinding, the study drugs were concealed from all medical staff involved in the patient’s care, including anesthesiologists, orthopedic surgeons, nurses in the post-anesthesia care unit (PACU) and ward, the patients, and their guardians. Investigators and statisticians assessing outcomes were completely blind to randomization. The study drugs (acetaminophen and placebo normal saline) were prepared by the same manufacturer with identical volumes (100 ml) and bag shapes, including the port. To maintain blinding during infusion in the operating room and the ward, the drug bags were masked with non-transparent white tape and covered with a green-colored opaque envelope (Supplementary Fig. 1).

Anesthesia and analgesic protocol

The anesthetic technique was standardized, with no preoperative analgesics or sedatives administered. All patients received standard monitoring, including an arterial catheter in a radial artery and a central venous catheter in the right internal jugular vein. General anesthesia was induced with lidocaine (1 mg/kg), propofol (2–3 mg/kg), rocuronium (0.6–0.8 mg/kg), and endotracheal intubation was performed. Anesthesia was maintained with remifentanil and propofol target-controlled infusions, titrated to surgery requirements, and the depth of anesthesia was maintained at the anesthesiologist’s discretion. Depth was evaluated using a SEDLine® monitor (Masimo). Mechanical ventilation continued...
with a 40% O₂-air mixture and end-tidal CO₂ maintained at 35–40 mmHg. During the operation, somatosensory and motor-evoked potentials were monitored by a neurologist and a neurophysiologic technician. IV tramadol (1 mg/kg, maximum 50 mg) was administered before skin closure for immediate postoperative analgesia. Standardized postoperative administration of rescue analgesics was implemented. Patients were initiated on IV patient-controlled analgesia (PCA) devices (AutoMed™3200, Ace Medical) with fentanyl infusions up to a maximum of 1–1.5 μg/kg/h on demand, without a basal rate. The attending orthopedic surgeon was informed of the study drug administration that was recorded in the electronic medical record. In the PACU, if a patient’s numeric rating scale (NRS) score was four or higher, 1 μg/kg IV fentanyl was administered based on body weight.

In the general ward, patients with an NRS score ≥ 4 received tramadol (1 mg/kg or 50 mg intravenously) for breakthrough pain. For NRS scores ≥ 7, hydromorphone was administered at a dose of 0.02 mg/kg or 1 mg intravenously. Starting on the day after surgery, oral acetaminophen was routinely administered at 10 mg/kg or a maximum of 500 mg per dose, three times a day.

**Study drug administration protocol**

Participants in the preemptive group received 15 mg/kg (maximum 1 g) of IV acetaminophen (acetphen premix®, HK inno.N Corp.) after anesthetic induction/before surgical incision. The same dose was given postoperatively at 8-h intervals for 24 h. A single dose of placebo (0.9% Normal Saline Inj., HK inno.N Corp.) in an identical volume was given at the end of surgery before skin closure to conceal the allocation of study drugs. In the preventive group, participants received 15 mg/kg (maximum 1 g) IV acetaminophen at the end of surgery before skin closure and at 8-h intervals postoperatively for 24 h. A single dose of placebo in an identical volume was administered after anesthetic induction and before the surgical incision. The placebo group received 1.5 ml/kg of placebo (maximum 100 ml of normal saline) before surgical incision and skin closure and the same volume of normal saline at 8-h intervals postoperatively for 24 h.

**Primary and secondary endpoints**

The primary outcome was postoperative cumulative opioid consumption during the first 24 h after surgery, measured in IV morphine milligram equivalents (MME). Opioid consumption was recorded and converted into IV MME based on a previously published method [12].

Secondary outcomes included postoperative cumulative opioid consumption at 48 h and pain scores in the PACU at 4, 8, 24, and 48 h after surgery. The severity of postoperative pain was evaluated using an 11-point NRS (0 = no pain, 10 = worst imaginable pain). To collect NRS pain scores, patients were asked to indicate their pain levels at rest, during coughing, and at their worst. Worst and resting pain levels were defined as the most severe breakthrough pain since the last evaluation and the average resting pain, respectively. Pain during the cough was measured at the time point of the visit by requesting the patient to make a forceful cough. Additionally, the incidence of adverse drug events (such as respiratory depression, postoperative nausea and vomiting, pruritus, and constipation) was recorded. Following surgery, the length of hospital stays (from the end of surgery to discharge) and the time it took patients to ambulate, resume oral intake, and have a bowel movement were monitored and documented postoperatively. Patient satisfaction for recovery was assessed using the Korean version of the Quality of Recovery-15 (QoR-15K) questionnaire (QoR-15K: 0, very poor recovery; 150, excellent recovery) between 3 and 5 days after surgery [13]. In addition, laboratory parameters, including renal and hepatic function (creatinine, aspartate transaminase [AST], and alanine transferase [ALT]), and inflammatory markers, including C-reactive protein, were assayed preoperatively and on the day of surgery, the first, second, and fifth postoperative days.

**Sample size calculation**

The sample size calculation was based on the primary outcome. A retrospective review of 32 patients at our institution (15 patients in the acetaminophen group and 17 patients in the placebo group) showed that acetaminophen-treated patients had a 24-h opioid consumption of 1.84 mg/kg, while the placebo group had a consumption of 2.49 mg/kg with a standard deviation (SD) of 0.9. With 80% power and an α-level of 0.05, the required sample size was determined to be 31 patients per group using analysis of variance (ANOVA). A final sample size of 102, with 34 patients per group, was selected to facilitate a dropout rate of 10%.

**Statistical analysis**

All analyses were performed using R statistical software version 3.6.3® (R Foundation for Statistical Computing). A univariate statistical analysis was conducted to analyze baseline characteristics. Categorical variables were represented as numbers and percentages. Continuous variables are represented as mean ± SD or median and interquartile range, as appropriate.

For the primary outcome analysis, outcomes were compared...
using a one-way ANOVA for continuous data. Pairwise group comparisons for sensitivity analysis were performed using a two-sample t-test. Pairwise group comparisons compared the group that received the IV acetaminophen (including both the preemptive and preventive groups) to the placebo group. For the secondary outcome analysis, variables were analyzed using a Chi-square test, Fisher’s exact test for categorical data, one-way ANOVA, or the Kruskal–Wallis test for continuous data.

A P value of less than 0.05 was considered statistically significant. In the pairwise group comparisons, significance was based on 0.05/3 = 0.017 using the Bonferroni correction.

Results

Between June 2021 and April 2022, a total of 169 pediatric and adolescent patients scheduled to undergo PSF were screened for eligibility, and 67 of them were excluded from the study (eight did not meet the inclusion criteria, and 59 declined to participate). The remaining 102 patients were assigned to one of the three groups (34 patients in each group). After excluding one patient in the preventive group due to not receiving the intervention, 101 patients were enrolled in the analysis. Two more patients were further lost to follow-up due to postoperative intubated status with sedation, leaving 33 patients in each group included in the final analysis. A CONSORT flow diagram of patient selection and dropout is displayed in Fig. 1. The baseline demographic characteristics showed no significant differences among the three groups (Table 1).

Primary outcome

The mean ± SD amount of opioid consumption during the first postoperative 24 h was 60.66 ± 23.84, 52.23 ± 22.43, and 66.70 ± 23.01 mg in the preemptive, preventive, and placebo groups, respectively (overall P = 0.043) (Fig. 2). Furthermore, the mean ± SD amount of opioid consumption per patient’s weight was 1.25 ± 0.45, 1.03 ± 0.43, and 1.34 ± 0.46 mg/kg in the preemptive, preventive, and placebo groups, respectively (overall P = 0.020). The mean differences with 95% CIs were: preemptive-placebo −0.08 (−0.30, 0.13), P = 0.443; preventive-placebo −0.30 (−0.52, 0.09), P = 0.007; and preemptive-preventive −0.22 (−0.00, 0.44), P = 0.050.

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) flowchart of the study population.
Table 1. Patient Characteristics and Perioperative Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Preemptive group (n = 33)</th>
<th>Preventive group (n = 33)</th>
<th>Placebo group (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>14.3 ± 2.3</td>
<td>14.7 ± 2.6</td>
<td>13.7 ± 1.4</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>3/30</td>
<td>4/29</td>
<td>6/27</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>19.0 ± 2.5</td>
<td>19.8 ± 2.9</td>
<td>19.1 ± 2.8</td>
</tr>
<tr>
<td>ASA-PS (I/II)*</td>
<td>4/29 (12.1/87.9)</td>
<td>6/27 (18.2/81.8)</td>
<td>5/28 (15.2/84.8)</td>
</tr>
<tr>
<td><strong>Intraoperative data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cobb’s angle (degrees)/operation level</td>
<td>53 (49, 62)/12 (11, 13)</td>
<td>56 (49, 59)/12 (11, 13)</td>
<td>52 (49, 57)/11 (11, 12)</td>
</tr>
<tr>
<td>Anesthetic (min)/operation time (min)</td>
<td>248 (233, 286)/203 (172, 239)</td>
<td>260 (243, 280)/209 (181, 224)</td>
<td>262 (238, 276)/200 (183, 223)</td>
</tr>
<tr>
<td>Total administered dose of remifentanil (µg)</td>
<td>3451 (2947, 3980)</td>
<td>3393 (3000, 4400)</td>
<td>3367 (2894, 3840)</td>
</tr>
<tr>
<td><strong>Preoperative laboratory data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST (U/L)/ALT (U/L)</td>
<td>16 (15, 18)/9 (8, 11)</td>
<td>17 (15, 20)/9 (8, 11)</td>
<td>19 (15, 21)/9 (7, 11)</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.64 (0.56, 0.69)</td>
<td>0.65 (0.56, 0.70)</td>
<td>0.61 (0.58, 0.71)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, number, *number (%) or median (Q1, Q3). BMI: body mass index, ASA-PS: American Society of Anesthesiologists physical status, AST: aspartate transaminase, ALT: alanine transferase.

Post hoc analysis indicated significant differences in the amount of opioid consumption between the preventive and placebo groups (P = 0.013) (Fig. 2). In addition, a significant difference was observed in opioid consumption per patient’s weight between the preventive and placebo groups (P = 0.007). Total opioid consumption and total opioid consumption per patient’s weight in the preventive group compared with the preemptive group were not different (P = 0.142, 0.050, respectively). Additionally, total opioid consumption and total opioid consumption per patient’s weight in the preemptive group were not different from those in the placebo group (P = 0.291, 0.443, respectively).

In the sensitivity analysis, the mean ± SD amount of cumulative opioid consumption during postoperative 24 h in the group that received IV acetaminophen (including both the preemptive and preventive groups) was less than that in the placebo group (56.45 ± 23.35 mg vs. 66.70 ± 23.01 mg, P = 0.041) (Supplementary Table 1). The mean ± SD amount of cumulative opioid consumption per patient’s weight in the combined preemptive and preventive group was less than that in the placebo group (1.14 ± 0.45 mg/kg vs. 1.34 ± 0.46 mg/kg, P = 0.048) (Supplementary Table 1).

### Secondary outcome

The total opioid consumption during postoperative 48 h was not different between the three study groups (101.36 ± 35.43 mg vs. 83.10 ± 41.47 mg vs. 90.54 ± 38.02 mg, overall P = 0.157). In addition, no significant difference was observed among the three groups in opioid consumption during postoperative 48 h divided by patient’s weight (2.03 ± 0.70 mg/kg vs. 1.62 ± 0.75 mg/kg vs. 1.86 ± 0.70 mg/kg, overall P = 0.070). No significant differences exist in resting, coughing, or the worst NRS pain scores in the PACU. Likewise, no differences were observed in resting, cough, and worst NRS pain scores at 4, 8, 24, and 48 h after surgery (Supplementary Table 2).

No difference was observed among the groups regarding the length of hospital stay (Table 2). Secondary clinical course charac-
teristics, including time to remove the urinary catheter, first sitting time, standing time, eating time, and defecation time between the three groups, were comparable (Table 2). Compared to preoperative laboratory data, the number of patients with elevated liver function tests, including AST, ALT, and creatinine values, did not differ in the three groups (Table 2). A self-rated questionnaire for early postoperative quality of recovery evaluated by QoR-15K showed no significant difference among the study groups (Table 2). Acetaminophen treatment was well tolerated, and most of the reported adverse events were mild. The frequency of adverse events, including respiratory depression, postoperative nausea and vomiting, pruritus, and constipation, was similar among the groups. No respiratory depression or acetaminophen-induced hepatic injury that required treatment was encountered in any patient (Table 3).

### Discussion

The results of this randomized controlled trial demonstrated that preventive administration of IV acetaminophen in adolescent and pediatric patients undergoing PSF reduced the cumulative 24-h opioid consumption compared to the placebo group but not in the preemptive group. This reduction in opioid consumption was 14.5 mg, exceeding the minimal clinically important difference of 10 mg reported in a previous study [14]. No significant differences were observed in pain scores, secondary clinical course characteristics, or self-reported patient satisfaction scores between the groups. The incidence of adverse events that prevent-

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### Table 2. Comparison of Patient's Satisfaction, Recovery Profile, and Laboratory Data

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Preemptive group (n = 33)</th>
<th>Preemptive group (n = 33)</th>
<th>Placebo group (n = 33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient's satisfaction (QoR-15)</td>
<td>84.4 ± 21.8</td>
<td>83.4 ± 27.0</td>
<td>89.9 ± 26.2</td>
<td>0.577</td>
</tr>
<tr>
<td>Duration of hospital stay (days)</td>
<td>7 (7.0, 7.0)</td>
<td>7 (7.0, 7.0)</td>
<td>7 (7.0, 7.0)</td>
<td>0.501</td>
</tr>
<tr>
<td>Recovery profile</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to remove urinary catheter (h)</td>
<td>94.0 (91.0, 96.0)</td>
<td>94.5 (91.5, 97.3)</td>
<td>92.0 (90.0, 96.0)</td>
<td>0.426</td>
</tr>
<tr>
<td>Time to first sitting (h)</td>
<td>70.0 (68.0, 72.0)</td>
<td>68.5 (64.8, 72.0)</td>
<td>68.0 (64.0, 70.0)</td>
<td>0.127</td>
</tr>
<tr>
<td>Time to first standing (h)</td>
<td>93.0 (90.0, 94.0)</td>
<td>92.0 (85.0, 94.0)</td>
<td>92.0 (87.0, 93.0)</td>
<td>0.227</td>
</tr>
<tr>
<td>Time to first solid feeding (h)</td>
<td>43.0 (40.0, 45.0)</td>
<td>43.0 (40.0, 44.0)</td>
<td>42.0 (40.0, 44.0)</td>
<td>0.770</td>
</tr>
<tr>
<td>Time to first defecation (h)</td>
<td>120.0 (88.0, 144.0)</td>
<td>98.0 (77.0, 123.0)</td>
<td>124.0 (123.0, 132.0)</td>
<td>0.129</td>
</tr>
<tr>
<td>Postoperative laboratory data†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST elevation*</td>
<td>6 (18.2)</td>
<td>5 (15.2)</td>
<td>9 (27.3)</td>
<td>0.542</td>
</tr>
<tr>
<td>ALT elevation*</td>
<td>1 (3.0)</td>
<td>1 (3.0)</td>
<td>3 (9.1)</td>
<td>0.614</td>
</tr>
<tr>
<td>Creatinine elevation*</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or median (Q1, Q3) or *number (%). †Normal range as defined for healthy subjects not undergoing anesthesia (AST, ALT: 0–40 IU/L, Creatinine: 0.7–1.4 mg/dl). QoR-15: Quality of recovery-15, AST: aspartate transaminase, ALT: alanine transferase, NA: not applicable.

### Table 3. Comparison of Adverse Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Preemptive group (n = 33)</th>
<th>Preemptive group (n = 33)</th>
<th>Placebo group (n = 33)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of adverse outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3 (9.1)</td>
<td>3 (9.1)</td>
<td>0 (0.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Constipation</td>
<td>8 (24.2)</td>
<td>10 (30.3)</td>
<td>8 (24.2)</td>
<td>1.000</td>
</tr>
<tr>
<td>PONV (0/1/2/3)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PACU</td>
<td>25/6/2 (75.8/18.2/6.1)</td>
<td>29/3/0 (90.6/9.4/0.0)</td>
<td>32/1/0 (97.0/3.0/0.0)</td>
<td>0.071</td>
</tr>
<tr>
<td>At postoperative 4 h</td>
<td>20/4/7 (64.5/12.9/22.6)</td>
<td>22/5/2 (75.9/17.2/6.9)</td>
<td>26/5/0 (83.8/16.1/0.0)</td>
<td>0.057</td>
</tr>
<tr>
<td>At postoperative 8 h</td>
<td>13/5/4 (59.1/22.7/18.2)</td>
<td>13/6/4 (56.5/26.1/17.4)</td>
<td>18/6/1 (72.0/24.0/4.0)</td>
<td>0.545</td>
</tr>
<tr>
<td>At postoperative 24 h</td>
<td>19/10/4 (57.6/30.3/12.1)</td>
<td>20/5/7 (62.5/15.6/21.9)</td>
<td>23/6/4 (69.7/18.2/12.1)</td>
<td>0.512</td>
</tr>
<tr>
<td>At postoperative 48 h</td>
<td>23/6/4 (69.7/18.2/12.1)</td>
<td>23/5/5 (69.7/15.2/15.2)</td>
<td>25/4/3 (78.1/12.5/9.4)</td>
<td>0.919</td>
</tr>
</tbody>
</table>

Values are presented as number (%). *PONV grades: 0 = absent, 1 = mild nausea, 2 = severe nausea, 3 = vomiting. NA: not applicable, PONV: postoperative nausea and vomiting, PACU: post-anesthesia care unit.

https://doi.org/10.4097/kja.23747
ed clinicians from administering IV acetaminophen to pediatric and adolescent patients did not increase compared to that in the placebo group.

Our study provides evidence of the additive effect of combining IV acetaminophen with systemic opioids, reducing opioid consumption in postoperative settings where moderate to severe pain is expected. This is consistent with previous findings that IV acetaminophen reduced opioid consumption in adult orthopedic surgery [15,16] and pediatric orthopedic surgery [17]. The different mechanisms of action of IV acetaminophen and systemic opioids, acting on different pathways and having complementary effects, may contribute to the observed additive analgesic effects. The predominant mechanisms of acetaminophen effects are central, and the most accepted theory for analgesic effects is the serotonergic descending inhibitory pathways [18,19]. However, systemic opioids exert an analgesic effect by acting on several opioid receptors in the central nervous system [20]. Therefore, these two drugs are effective as multimodal analgesia since they act on different pathways and have complementary actions. Despite this, there was no discernible disparity in the quality of pain relief as assessed by NRS scores among the three groups. This could be attributed to the effective use of PCA that allowed patients to self-administer opioids when their pain scores reached a certain threshold. The resting NRS score remained below the threshold throughout the study periods, indicating effective pain control.

The preventive administration of acetaminophen significantly reduced opioid consumption 24 h after surgery compared to the placebo group, while the preemptive administration of acetaminophen showed no difference compared to the placebo. This contradicts previous studies suggesting a preemptive analgesic effect of acetaminophen by blocking central sensitization resulting from surgical incisions [10,21]. Several reasons may be considered for these discrepancies. First, regarding the difference in the drug administration interval, the drug was administered at 8-h intervals from the end of surgery. Considering the operation time of PSF, the interval in the preemptive group was longer than 8 h. IV acetaminophen is known to have an analgesic effect within 15 min of administration, peak within 1 h, and last for 4–6 h [4,22,23]. Hence, the variation in the timing of administration between the groups likely contributed to the observed differences in the analgesic effect. Second, a potential synergistic effect may occur with the co-administration of IV acetaminophen and tramadol in the preventive group. At our institution, IV tramadol was administered when skin closure was performed to prevent remifentanil-induced hyperalgesia and to achieve a smooth awakening. Tramadol and acetaminophen do not overlap in their mechanisms of action and exhibit synergistic effects, thereby resulting in more rapid pain relief than tramadol alone and more persistent pain relief than acetaminophen alone [24,25].

The impact of reduced opioid consumption on postoperative recovery profiles was not evident in this study, indicating that the decrease in opioid usage may not be sufficient to influence postoperative recovery parameters. The adherence to established protocols for mobilization, diet, and bowel activity may have minimized differences in secondary clinical course characteristics. However, there was no difference in the incidence of adverse events among the groups, and no patients experienced hepatic injury due to IV acetaminophen exposure. According to previous studies, the estimated incidence of hepatic serious adverse events and drug-induced liver injury was only 3.2 and 0.4 per million patients, respectively [26], and most cases were related to other factors such as concomitant hepatotoxic medications, comorbid hepatic conditions, or medication errors [4]. Hence, when considering its capacity to reduce opioid usage and favorable safety profile, IV acetaminophen can be considered a valuable supplement for postoperative pain management.

A notable limitation of the current study is the relatively low dose of IV acetaminophen (45 mg/kg or 3 g per day) administered compared to the recommended dose. The recommended dose of IV acetaminophen is higher in pediatrics, with a maximum daily dose of IV acetaminophen of 60–75 mg/kg or 4 g per day [27]. The lower dose was chosen for safety concerns in the pediatric and adolescent population but may have impacted the outcomes. Future studies should investigate the relationship between drug dose and outcomes, including opioid consumption, adverse events, and recovery profiles. The second limitation is that the sample size calculation method does not take into account secondary outcomes. Nevertheless, our study was specifically structured to examine the disparity in opioid consumption with IV acetaminophen as the primary outcome, and we are confident that our sample size was adequate for this purpose.

In conclusion, the results of this study support the preventive administration of IV acetaminophen during the perioperative period in pediatric and adolescent patients undergoing a painful procedure. Moreover, it effectively reduces opioid consumption for 24 h postoperatively without increasing drug-induced adverse events and can be considered a valuable addition to postoperative pain management in this patient population.

**Funding**

None.
Conflicts of Interest

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

Data Availability

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

Author Contributions

Yeon Ju Kim (Data curation; Formal analysis; Investigation; Writing – original draft)
Ha-Jung Kim (Data curation; Formal analysis; Investigation; Methodology)
Sehee Kim (Data curation; Formal analysis)
Hyungtae Kim (Formal analysis; Methodology)
Choon Sung Lee (Methodology; Supervision)
Chang Ju Hwang (Data curation; Formal analysis)
Jae Hwan Cho (Data curation; Formal analysis)
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Supplementary Materials

Supplementary Fig. 1. Blinded piggy bags containing study drugs (acetaminophen or placebo normal saline). (A) The bag on the left, marked with green letters, contains acetaminophen (1 g in 100 ml). The bag on the right, marked with blue letters, contains placebo normal saline (100 ml). (B) The study drugs were obscured by wrapping the bags with non-transparent white tape. (C) To further ensure blinding, the wrapped bags were enclosed in a green-colored opaque envelope.

Supplementary Table 1. Cumulative opioid consumption in intravenous (IV) morphine milligram equivalents (MME) comparing the combined acetaminophen group (both preemptive and preventive groups) to the placebo group.

Supplementary Table 2. Postoperative pain assessment as measured by the numeric rating scale (NRS) score.

References

11. Doleman B, Read D, Lund JN, Williams JP. Preventive acetaminophen reduces postoperative opioid consumption, vomiting, and pain scores after surgery: systematic review and meta-analy-


Comparison of effects of telmisartan versus valsartan on post-induction hypotension during noncardiac surgery: a prospective observational study

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**Background:** Telmisartan is considered more potent than valsartan. Hemodynamic response during anesthesia induction may be influenced by anti-hypertension (HTN) medication. The present study compared the effect of anti-HTN medications on post-induction hypotension during noncardiac surgeries.

**Methods:** This observational study standardized the anesthetic regimen across patients, with hypotension defined as mean blood pressure (BP) of less than 65 mmHg. The hemodynamic changes within 5 min before and after endotracheal intubation, and within 10 min before and after surgical incision were measured. Transthoracic echocardiographic evaluation of the left ventricle (LV) during anesthesia induction was performed. The primary endpoint was the decline in mean BP after anesthetic administration in telmisartan and valsartan groups. Multivariate logistic regression analysis was used to identify predictors of post-induction hypotension.

**Results:** Data from 157 patients undergoing noncardiac surgery were analyzed. No significant differences were found in mean BP decline between the two groups during anesthesia induction. Hemodynamic changes and LV ejection fraction (EF) during anesthesia induction were similar between the groups. Age and preoperative initial mean BP in operation room (OR) were associated with post-induction hypotension in both groups.

**Conclusions:** The angiotensin receptor blocker (ARB) type did not influence post-induction hypotension during anesthesia induction. Age and preoperative initial mean BP in OR were associated with post-induction hypotension in patients taking ARBs.

**Keywords:** Anesthesia; Angiotensin receptor antagonists; General surgery; Hypotension; Telmisartan; Valsartan.

**Introduction**

Angiotensin receptor blockers (ARBs) are commonly used as effective first-line anti-hypertension (HTN) medications [1,2]. Recent guideline recommend ARBs as the primary anti-HTN treatment [3]. The hemodynamic effects of ARBs can vary based on their potency. Several studies have assessed the efficacy of ARBs in managing daily blood pressure (BP) [4,5]. Telmisartan stands out among ARBs because of its potency and prolonged duration of action compared to valsartan [6–8].

Fluctuations in hemodynamic response are common during anesthesia induction, of-
ten influenced by various factors. Typically, there is an initial decline in BP after anesthetic administration, followed by an increase after endotracheal intubation. Preoperative medications can significantly influence these hemodynamic responses. However, few studies have evaluated the hemodynamic responses related to specific ARBs during anesthesia induction.

We hypothesized that the hemodynamic response might differ based on the ARB type administered preoperatively. This study compared post-induction hypotension in patients taking telmisartan or valsartan as anti-HTN medication during non-cardiac surgery.

Materials and Methods

Study population

This was a prospective observational study of patients undergoing surgery under general anesthesia. The study protocol was approved by the Institutional Review Board (Konkuk University Medical Center, Seoul, Korea; Approval No, KUH1160077) which confirmed that the study was performed in accordance with the ethical standards of the Helsinki Declaration-2013, and was registered at http://cris.nih.go.kr (KCT0001595) prior to patient enrolment. All patients provided written informed consent before participation in the study. Patients who had been taking telmisartan or valsartan for a minimum of four weeks prior to the surgery were included. To further refine the study cohort, only those aged > 40 years, requiring general anesthesia for elective surgery, in the supine position, and classified as American Society of Anesthesiologists Physical Status (ASA-PS) class 2 were enrolled. The exclusion criteria were the use of either beta-blockers (BB) or calcium channel blockers (CCB), history of congestive heart failure (CHF), coronary artery disease (CAD), peripheral artery occlusive disease, cerebral infarction or hemorrhage, cardiac arrhythmia, orthostatic hypotension, and intraoperative change in position (Trendelenburg or reverse Trendelenburg position, beach chair position, prone position, or lateral position). Patients with abnormal intraoperative transthoracic echocardiographic measurements, such as poor echocardiographic view, left ventricular (LV) ejection fraction (EF) < 45%, and regional wall motion abnormality of LV wall, prior to anesthetic administration were excluded from further analysis.

Patients were allocated into two categories; those taking telmisartan (Telmisartan group) and those taking valsartan (Valsartan group). To optimize the effect of ARBs during anesthesia induction, all patients took their usual dose on the morning of the surgery. Anesthetists, surgeons, and nursing staff who participated in patient care were blinded to the study. Data were collected by trained observers who were blinded to the study and did not participate in patient care.

Anesthetic technique

No premedication was administered to any of the patients. Following standard monitoring, each patient was given an intravenous bolus infusion of 5 ml/kg balanced electrolyte solution before anesthesia induction. The anesthetic regimen remained consistent across all patients. Standard monitoring included electrocardiography, noninvasive BP monitoring, and pulse oximetry. Bispectral index monitoring was used to assess the depth of anesthesia. For anesthesia induction, 0.5 mg/kg lidocaine, 3 μg/ml propofol [9], and 5 ng/ml remifentanil using target control infusion (TCI) [10] set to last 5 min, were administered. Rocuronium (0.6 mg/kg) was administered for neuromuscular blockade, guided by peripheral neuromuscular transmission monitoring. Once the target plasma concentrations of propofol and remifentanil were achieved, endotracheal intubation was performed. Patients were subsequently ventilated using volume-controlled ventilation, maintaining tidal volume of 6 ml/kg and a positive end-expiratory pressure of 5 cmH₂O.

Hemodynamic management

Hypotension was defined as a mean arterial BP < 65 mmHg. From the time of propofol administration to 10 min after surgical incision, hemodynamic management was performed as follows: if the mean BP was less than 60 mmHg, 50 μg phenylephrine was administered intravenously; if the systolic BP was higher than 180 mmHg, 200 μg nicardipine was administered intravenously; if the heart rate (HR) was less than 40 beats/min, 4 mg ephedrine was administered intravenously. From the surgical incision to skin closure, if the mean BP was below 65 mmHg, a continuous intravenous infusion of phenylephrine was started with the dose adjusted to maintain a mean BP ≥ 65 mmHg.

Clinical measurements

The total amounts of anesthetic agents used during anesthesia induction were recorded. The total duration of anti-HTN medication, the interval between anti-HTN medication administration on the morning of the surgery and anesthesia induction, the entire anesthesia induction period, and the total anesthesia and surgical duration were measured. Preoperative laboratory values were also recorded.
Noninvasive BP and HR measurements were performed on the morning of the operation. After entering the operation room (OR), noninvasive BP measurements continued every minute from the start of patient monitoring to 5 min after surgical incision, and then every 2.5 min during the surgery. Hemodynamic values were recorded at several time points: the morning of the operation (Ward), the first hemodynamic monitoring values in OR (Initial OR), within 5 min before and after endotracheal intubation (Pre- and Post-intubation, respectively), and within 10 min before and after surgical incision (Pre-and Post-incision, respectively). Other monitored variables included the decline in mean BP after anesthetic administration, the incidence of mean BP < 65 mmHg, and the incidence of out-of-range mean BP, defined as 20% higher or lower than the baseline mean BP on the morning of the operation. The incidences of hemodynamic agent usage during anesthesia induction and phenylephrine infusion during the operation were also recorded.

**Transthoracic echocardiography (TTE) examination**

During anesthesia induction in the supine position, serial transthoracic echocardiography (TTE) evaluations were conducted using a 5 MHz transducer on a GE Vivid™ 7 (GE Healthcare). These measurements coincided with the hemodynamic value recording times, i.e., Initial OR, Pre-intubation, and Post-intubation. All TTE values were recorded at the end of the expiratory phase to exclude respiratory influences. These included left ventricular ejection fraction (LVEF) and tissue Doppler image (TDI) with pulsed wave Doppler in a two-dimensional image of the apical four-chamber view. LVEF was determined using the modified Simpson's method. TDI derived velocities of upward deflection during the systolic phase (s), along with the downward deflection during the early diastolic phase (e'), and the late diastolic phase (a') were measured at the septal annulus of the mitral valve (MV) from an average of 2 beats. A single cardiac anesthesiologist performed all TDI assessments that were subsequently reviewed by two independent anesthesiologists.

**Statistics**

The primary outcome was the difference in mean BP decrease from Initial OR to Post-incision between the Telmisartan and Valsartan groups. Based on the pilot study involving 18 patients, the mean BP decrease was 20.8 ± 5.2 mmHg and 24.6 ± 9.8 mmHg in the Telmisartan and Valsartan groups, respectively. *A priori* power analysis revealed an effect size of 0.47, resulting in a calculated sample size of 70 in each group for the primary outcome based on an α value of 0.05 and power of 0.8. Considering a 20% potential drop-out rate, we enrolled 85 patients in each group for a total of 170 participants.

For continuous variables, data distribution was first assessed for normality using the Shapiro-Wilk test. Independent two-tailed t-tests were utilized to compare the means of normally distributed continuous variables. For data not conforming to a normal distribution, the Mann-Whitney U test was used. The chi-square test was used for comparing categorical variables between the two groups. Intraclass correlation coefficients (ICCs) were calculated to assess the consistency of echocardiographic measurements, where ICC values ≥ 0.75 denoted satisfactory and excellent agreement.

A univariate logistic regression analysis was performed for each potential risk factor of post-induction hypotension including age, diabetes mellitus, total duration of anti-HTN medication, type of anti-HTN medication (telmisartan or valsartan), the interval between anti-HTN medication administration on the morning of the surgery and anesthesia induction, propofol dosage, mean BP on the morning of the surgery, initial mean BP in OR, and total duration of anesthesia induction. A multivariate logistic regression analysis, including these potential risk factors, was performed using enter method to identify the independent predictors for post-induction hypotension. The post-induction hypotension period was defined as a mean BP < 65 mmHg between the introduction of anesthetic agent and 10 min after surgical incision.

Normally distributed continuous data were presented as mean ± standard deviation. Non-normally distributed continuous data were presented as medians (Q1, Q3). For categorical variables, the numbers (n) and proportions (%) were calculated.

All statistical analyses were performed using the Statistical Package for Social Sciences 22® (IBM Corp.). P values < 0.05 were considered statistically significant.

**Results**

In total, 282 patients were eligible for the study between April 2017 and April 2018. Among them, 112 were excluded for the following reasons: 48 were on ARBs combined with either BB or CCB, six had a history of CHF, 15 had a history of CAD, two had a history of PADO, six had a history of cerebral infarction or hemorrhage, one had a history of cardiac arrhythmia, one had a history of orthostatic hypotension, and 26 were scheduled for surgeries requiring intraoperative position change. Additionally, 13 patients were excluded from the final analysis due to poor echocardiographic views. Consequently, 157 patients were included in the final analysis (78 in the Telmisartan group and 79 in the Valsartan group).
Both groups had similar demographic characteristics with age, gender, types of surgery, New York Heart Association class, ASA-PS, and medical history being comparable between the two groups (Table 1). There were no significant differences between the groups in terms of the total anesthetic amount used during anesthesia induction, duration of anti-HTN medication use, and the interval from taking anti-HTN medication on the morning of the surgery to anesthesia induction. Preoperative laboratory values were also similar between the two groups (Table 1).

The decline in mean BP during anesthesia induction for all patients was 27.7 ± 13.9 mmHg, with similar values for the Telmisartan and Valsartan groups (27.1 ± 15.3 mmHg vs. 28.3 ± 12.4 mmHg, respectively; P = 0.585) (Table 2). Overall, 36.3% of the patients experienced a mean BP < 65 mmHg from Initial OR to Post-incision, while 71.3% had a decline in mean BP > 20% of the morning BP from Initial OR to Post-incision. The incidence of the decline in mean BP decreasing below 65 mmHg and changes (either increase or decrease) exceeding 20% of the baseline morning BP from Initial OR to Post-incision was similar between the two groups (Table 2). There were no significant intergroup changes in mean BP during anesthesia induction between the two groups (Fig. 2A). The changes in HR during anesthesia induction were also similar between the groups (Fig. 2B), along with the use of hemodynamic agents including phenylephrine, ephedrine, or nicardipine (Table 2). During operation, the incidences of mean BP < 65 mmHg, with an increase or decrease greater than 20% of the morning BP, were also similar between the two groups. The highest intraoperative mean BP was significantly higher in the Telmisartan group than in the Valsartan groups (90.1 ± 10.6 mmHg vs. 87.1 ± 11.5 mmHg, respectively; P = 0.009). However, parameters such as lowest intraoperative mean BP, highest and
### Table 1. Demographic Profiles of the Telmisartan and Valsartan Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Telmisartan group (n = 78)</th>
<th>Valsartan group (n = 79)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>64 (56, 70)</td>
<td>65 (59, 72)</td>
<td>0.311</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.222</td>
</tr>
<tr>
<td>M</td>
<td>29 (37.18)</td>
<td>38 (48.10)</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>49 (62.82)</td>
<td>41 (51.90)</td>
<td></td>
</tr>
<tr>
<td>Height</td>
<td>159.8 ± 7.6</td>
<td>161.2 ± 7.3</td>
<td>0.239</td>
</tr>
<tr>
<td>Weight</td>
<td>65.2 ± 10.7</td>
<td>66.2 ± 11.1</td>
<td>0.575</td>
</tr>
<tr>
<td>BSA</td>
<td>1.70 ± 0.17</td>
<td>1.72 ± 0.17</td>
<td>0.485</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td>0.429</td>
</tr>
<tr>
<td>Head and neck surgery</td>
<td>0 (0)</td>
<td>4 (5.06)</td>
<td></td>
</tr>
<tr>
<td>General surgery</td>
<td>27 (34.62)</td>
<td>30 (37.97)</td>
<td></td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>7 (8.97)</td>
<td>6 (7.59)</td>
<td></td>
</tr>
<tr>
<td>Gynecologic surgery</td>
<td>11 (14.10)</td>
<td>6 (7.59)</td>
<td></td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td>21 (26.92)</td>
<td>21 (26.58)</td>
<td></td>
</tr>
<tr>
<td>Plastic surgery</td>
<td>2 (2.56)</td>
<td>3 (3.80)</td>
<td></td>
</tr>
<tr>
<td>Urologic surgery</td>
<td>10 (12.82)</td>
<td>9 (11.39)</td>
<td></td>
</tr>
<tr>
<td>NYHA I</td>
<td>37 (47.44)</td>
<td>33 (41.77)</td>
<td>0.580</td>
</tr>
<tr>
<td>NYHA II</td>
<td>41 (52.56)</td>
<td>46 (58.23)</td>
<td>1.000</td>
</tr>
<tr>
<td>ASA-PS II</td>
<td>78 (100)</td>
<td>79 (100)</td>
<td></td>
</tr>
<tr>
<td>Past medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (17.95)</td>
<td>14 (17.72)</td>
<td>1.000</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>29 (37.18)</td>
<td>30 (37.97)</td>
<td>1.000</td>
</tr>
<tr>
<td>Types of anti-HTN agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Telmisartan 40 mg</td>
<td>55 (70.51)</td>
<td>0 (0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Telmisartan 80 mg</td>
<td>23 (29.49)</td>
<td>0 (0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Valsartan 80 mg</td>
<td>0 (0)</td>
<td>58 (73.42)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Valsartan 160 mg</td>
<td>0 (0)</td>
<td>21 (26.58)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Thiazide</td>
<td>18 (23.08)</td>
<td>22 (27.85)</td>
<td>0.615</td>
</tr>
<tr>
<td>Total amounts of anesthetic agents during anesthesia induction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol (mg)</td>
<td>120 (120, 145)</td>
<td>120 (113, 149)</td>
<td>0.805</td>
</tr>
<tr>
<td>Rocuronium (mg)</td>
<td>39 ± 6</td>
<td>40 ± 7</td>
<td>0.603</td>
</tr>
<tr>
<td>Remifentanil (μg)</td>
<td>153 (138, 175)</td>
<td>162 (142, 175)</td>
<td>0.635</td>
</tr>
<tr>
<td>Duration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HTN medication (month)</td>
<td>60 (24, 120)</td>
<td>74 (36, 120)</td>
<td>0.123</td>
</tr>
<tr>
<td>PO interval (min)</td>
<td>245 (135, 375)</td>
<td>295 (130, 405)</td>
<td>0.495</td>
</tr>
<tr>
<td>Induction (min)</td>
<td>6 (6, 8)</td>
<td>6 (6, 8)</td>
<td>0.849</td>
</tr>
<tr>
<td>Anesthesia (min)</td>
<td>154 (98, 210)</td>
<td>171 (124, 215)</td>
<td>0.160</td>
</tr>
<tr>
<td>Operation (min)</td>
<td>115 (70, 170)</td>
<td>140 (95, 178)</td>
<td>0.136</td>
</tr>
<tr>
<td>Preoperative laboratory values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG</td>
<td>130 (100, 168)</td>
<td>128 (99, 161)</td>
<td>0.611</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>175.96 ± 37.87</td>
<td>179.87 ± 41.76</td>
<td>0.540</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>98.59 ± 35.33</td>
<td>100.03 ± 35.26</td>
<td>0.799</td>
</tr>
<tr>
<td>eGFR</td>
<td>83.5 (67.0, 91.0)</td>
<td>76.0 (67.0, 91.0)</td>
<td>0.412</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3), incidence (%), or mean ± SD. BSA: body surface area, NYHA: New York Heart Association, ASA-PS: American Society of Anesthesiologists physical status, HTN: hypertension, TG: triglyceride, LDL: low-density lipoprotein, eGFR: estimated glomerular filtration rate, PO interval: the interval between taking anti-HTN medication on the morning of the operation to anesthesia induction, Induction: duration of anesthesia induction.
lowest HR, and the incidence of phenylephrine infusion during operation, were similar between the groups (Table 2).

The ICC for LVEF measurements at Initial OR, Pre-intubation, and Post-intubation were 0.773 (95% CI [0.702, 0.829]), 0.808 (95% CI [0.746, 0.856]), and 0.789 (95% CI [0.722, 0.841]), respectively. Regarding TDI values including s, e', and a’, the lowest coefficient was 0.864, signifying excellent agreement. LVEF during anesthesia induction decreased after anesthetic administration, but increased after intubation, with no significant intergroup differences between the Telmisartan and Valsartan groups (Table 3). The TDI values (s, e’, and a’) during anesthesia induction were also comparable between the groups (Table 3).

Multivariate logistic regression analysis identified age and the mean BP at initial OR as independent predictors for a mean BP < 65 mmHg from Initial OR to Post-incision (OR [95% CI]; 1.06 [1.01, 1.11] and 0.94 [0.90, 0.97]; P = 0.020 and P = 0.001, respectively) (Fig. 3) (Supplementary Table 1).

Discussion

The present study demonstrated that telmisartan and valsartan had comparable effects on the decline in mean BP during anesthesia induction. There were no significant differences in the LVEF and longitudinal contraction of LV between the two groups during anesthesia induction. The highest and lowest intraoperative hemodynamic values were also comparable between the two groups. These results suggest the type of ARB administered on the morning of the surgery does not influence the hemodynamic changes during anesthesia induction.

Previous clinical studies comparing the effects of telmisartan and valsartan on HTN management [4,11–13] have demonstrated the superiority of telmisartan in controlling BP. This is because of the high protein-binding affinity [8] and pronounced norepinephrine suppression [6] of telmisartan compared to valsartan. However, telmisartan may lead to a decline in BP, potentially causing post-induction hypotension after anesthetic administration. Therefore, we anticipated a greater decline in mean BP in the Telmisartan group compared to the Valsartan group. However, there was no discernible difference in BP reduction during anesthesia induction between the two groups.

The similar changes in BP during anesthesia induction for the Telmisartan and Valsartan groups could be attributed to several factors. A BP fluctuation, under the influence of reduced systemic vascular resistance or cardiac contractility after anesthetic administration, sympathetic stimulation due to endotracheal intubation, and various factors, are common during anesthesia induction. However, various vasopressors or sympathetic antagonists may be administered to attenuate these fluctuations. Moreover, fluid administration during anesthesia induction may also significantly influence the hemodynamics. Under these conditions, the effects of ARBs may be overshadowed, resulting in indistinguishable post-induction hypotension. Consequently, the present study demonstrated consistent intraoperative BP fluctuations, regardless of the specific ARB used. While previous research has demonstrated that telmisartan offers a more potent BP control than valsartan, its influence could be attenuated by several clinical variables during practical application.

Chronic ARB therapy has been shown to interfere with the
Table 2. Comparison of Hemodynamic Profiles and Left Ventricular Ejection Fraction (LVEF) between the Telmisartan and Valsartan Groups during Anesthesia

<table>
<thead>
<tr>
<th>Hemodynamic value</th>
<th>Telmisartan group (n = 78)</th>
<th>Valsartan group (n = 79)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>During anesthesia induction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decline in mean BP (mmHg)</td>
<td>27.1 ± 15.3</td>
<td>28.3 ± 12.4</td>
<td>0.585</td>
</tr>
<tr>
<td>Incidence of mean BP &lt; 65 mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial OR</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NS</td>
</tr>
<tr>
<td>Pre-intubation</td>
<td>11 (14.10)</td>
<td>7 (8.86)</td>
<td>0.435</td>
</tr>
<tr>
<td>Post-intubation</td>
<td>6 (7.69)</td>
<td>2 (2.53)</td>
<td>0.268</td>
</tr>
<tr>
<td>Pre-incision</td>
<td>22 (28.21)</td>
<td>22 (27.85)</td>
<td>1.000</td>
</tr>
<tr>
<td>Post-incision</td>
<td>2 (2.56)</td>
<td>7 (8.86)</td>
<td>0.176</td>
</tr>
<tr>
<td>Incidence of out of range of mean BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 20% of baseline</td>
<td>18 (23.08)</td>
<td>29 (36.71)</td>
<td>0.091</td>
</tr>
<tr>
<td>&lt; 20% of baseline</td>
<td>58 (74.36)</td>
<td>54 (68.35)</td>
<td>0.512</td>
</tr>
<tr>
<td>Incidence of hemodynamic agent administration during anesthesia induction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>9 (11.54)</td>
<td>7 (8.86)</td>
<td>0.771</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>2 (2.56)</td>
<td>3 (3.80)</td>
<td>1.000</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>6 (7.69)</td>
<td>3 (3.80)</td>
<td>0.480</td>
</tr>
<tr>
<td>During operation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of mean BP &lt; 65 mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraoperative</td>
<td>32 (41.03)</td>
<td>30 (37.97)</td>
<td>0.820</td>
</tr>
<tr>
<td>Incidence of out of range of mean BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 20% of baseline</td>
<td>5 (6.41)</td>
<td>6 (7.59)</td>
<td>1.000</td>
</tr>
<tr>
<td>&lt; 20% of baseline</td>
<td>58 (74.36)</td>
<td>59 (74.68)</td>
<td>1.000</td>
</tr>
<tr>
<td>Intraoperative highest and lowest mean BP and HR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest mean BP (mmHg)</td>
<td>90.1 ± 10.6</td>
<td>87.1 ± 11.5</td>
<td>0.009</td>
</tr>
<tr>
<td>Lowest mean BP (mmHg)</td>
<td>66.7 (63.0, 75.0)</td>
<td>67.0 (62.3, 72.3)</td>
<td>0.578</td>
</tr>
<tr>
<td>Highest HR (beats/min)</td>
<td>64 ± 11</td>
<td>64 ± 9</td>
<td>0.835</td>
</tr>
<tr>
<td>Lowest HR (beats/min)</td>
<td>60 (55, 67)</td>
<td>60 (53, 63)</td>
<td>0.252</td>
</tr>
<tr>
<td>Incidence of hemodynamic agent infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>7 (8.97)</td>
<td>9 (11.39)</td>
<td>0.813</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, incidence (%), or median (Q1, Q3). BP: blood pressure, OR: operation room, HR: heart rate, Initial OR: at the first time of patient hemodynamic monitors in operation room, Pre-intubation: lowest values within 5 min before endotracheal intubation, Post-intubation: lowest values within 5 min after endotracheal intubation, > 20% of range: higher blood pressure than 120% of mean blood pressure which was measured on the morning of operation, < 20% of range, lower blood pressure than 80% of mean blood pressure which was measured on the morning of operation, Pre-incision: within 10 min before surgical incision, Post-incision: within 10 min after surgical incision.

sympathetic nervous system functioning, while enhancing the parasympathetic activity [14]. Consequently, recent guidelines recommend discontinuation of ARBs prior to cardiac surgery for mitigating the risk of perioperative hypotension [15]. However, these recommendations remain a topic of debate, because the potential deleterious effects of ARBs on perioperative hypotension may vary with the type of surgery, i.e., cardiac or noncardiac surgery. Several recent studies have demonstrated that ARBs do not exacerbate perioperative hypotension during noncardiac surgeries, nor do they correlate with increased morbidity and mortality [16,17]. The present study showed that the incidence of mean BP < 65 mmHg was 36.3%, while that of a decline exceeding 20% of the morning BP was 71.3% in both groups. Moreover, the average reduction in mean BP during anesthesia induction was approximately 28 mmHg in both groups. These changes may be tolerable in noncardiac surgeries because the EF and longitudinal performance of LV were within the acceptable range on echocardiography, and the cardiac contractility remained relatively tolerable during anesthesia induction. Additionally, the relatively low incidence of vasopressor administration compared to previous studies suggests that clinically significant hypotension was a rare occurrence in the present study. Yoon et al. [17] recently demonstrated that the incidence of vasopressor use during anesthesia induction was 37% in patients taking ARBs that was higher than that in the
### Table 3. Transthoracic Echocardiographic Values during Anesthesia Induction

<table>
<thead>
<tr>
<th>Echocardiographic value</th>
<th>Telmisartan group (n = 78)</th>
<th>Valsartan group (n = 79)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left ventricular ejection fraction (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial OR</td>
<td>65.0 (64.0, 66.5)</td>
<td>64.8 (63.8, 67.8)</td>
<td>0.926</td>
</tr>
<tr>
<td>Pre-intubation</td>
<td>61.5 (60.5, 62.5)</td>
<td>61.0 (60.0, 62.5)</td>
<td>0.591</td>
</tr>
<tr>
<td>Post-intubation</td>
<td>66.5 (65.0, 68.5)</td>
<td>66.0 (65.0, 67.3)</td>
<td>0.202</td>
</tr>
<tr>
<td><strong>Tissue Doppler image-derived values at septal annulus of mitral valve</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>s Initial OR</td>
<td>9.84 (9.56, 10.29)</td>
<td>9.79 (9.45, 10.10)</td>
<td>0.309</td>
</tr>
<tr>
<td>Pre-intubation</td>
<td>9.34 (8.89, 9.57)</td>
<td>9.10 (8.76, 9.43)</td>
<td>0.125</td>
</tr>
<tr>
<td>Post-intubation</td>
<td>9.90 (9.64, 10.52)</td>
<td>9.80 (9.35, 10.56)</td>
<td>0.460</td>
</tr>
<tr>
<td>e' Initial OR</td>
<td>10.94 (10.65, 11.6)</td>
<td>10.73 (10.44, 11.34)</td>
<td>0.097</td>
</tr>
<tr>
<td>Pre-intubation</td>
<td>10.06 (9.59, 10.55)</td>
<td>9.69 (8.93, 10.37)</td>
<td>0.073</td>
</tr>
<tr>
<td>Post-intubation</td>
<td>11.98 (11.27, 12.52)</td>
<td>12.09 (11.73, 12.35)</td>
<td>0.524</td>
</tr>
<tr>
<td>a' Initial OR</td>
<td>8.82 ± 1.00</td>
<td>8.62 ± 0.59</td>
<td>0.134</td>
</tr>
<tr>
<td>Pre-intubation</td>
<td>8.89 (8.61, 9.22)</td>
<td>8.91 (8.61, 9.14)</td>
<td>0.955</td>
</tr>
<tr>
<td>Post-intubation</td>
<td>9.69 (9.40, 10.02)</td>
<td>9.71 (9.40, 9.94)</td>
<td>0.955</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3) or mean ± SD. OR: operation room, Initial OR: at the first time of patient hemodynamic monitors in operation room, Pre-intubation: lowest values within 5 min before endotracheal intubation, Post-intubation: lowest values within 5 min after endotracheal intubation.

**Fig. 3.** Multivariate logistic regression analysis for post-induction hypotension. DM: diabetes mellitus, HTN: hypertension, PO: per oral, BP: blood pressure, OP: operation, OR: operation room, Telmisartan: use of telmisartan as anti-HTN medication (reference value: use of valsartan), PO interval: the interval between taking anti-HTN medication on the morning of the operation and anesthesia induction, OP morning: on the morning of the operation, Initial OR: at the first time of patient hemodynamic monitors in the operation room, Duration of induction: total duration of anesthesia induction, OR: odds ratio.
present study. We hypothesized that the measured and gradual infusion of anesthetics through programmed TCI for total intravenous anesthesia may have played a role in limiting the incidences of post-induction hypotension and vasopressor use during anesthesia induction [18,19].

The present study showed that age and initial mean BP in OR were associated with post-induction hypotension. In particular, initial mean BP in OR was inversely related to post-induction hypotension that was in accordance with previous studies demonstrating that a lower pre-induction BP increased the incidence of post-induction hypotension [20,21]. Theoretically, increased sympathetic activity related to preoperative anxiety, such as white coat HTN, can be rapidly blunted by anesthetic administration. Crowther et al. [22] demonstrated in a prospective study that high preoperative BP was not associated with intraoperative hypotension or related complications. These inconsistent results highlight the need for a more comprehensive randomized control trial to validate these observations.

This study had several limitations. First, not all patients underwent invasive BP monitoring, although noninvasive BP was measured every minute for all patients. Second, the potential for heterogeneity in variables influencing intraoperative hypotension exists in the present study. Finally, patients classified as ASA-PS class III were not included. Therefore, in the future, meticulously planned, large-scale randomized trials are imperative to investigate the effects of ARBs on perioperative hypotension.

In conclusion, the ARB type did not significantly influence post-induction hypotension during general anesthesia induction. Age and initial mean BP in OR were significantly associated with post-induction hypotension in patients on ARBs.

**Funding**

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**Conflicts of Interest**

Seong-Hyop Kim has been an editor for the Korean Journal of Anesthesiology since 2019. However, he was not involved in any process of review for this article, including peer reviewer selection, evaluation, or decision-making. There were no other potential conflicts of interest relevant to this article.

**Data Availability**

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

**Author Contributions**

Chung-Sik Oh (Conceptualization; Data curation; Formal analysis; Writing – original draft)
Jun Young Park (Data curation; Investigation)
Seong-Hyop Kim (Supervision)

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**Supplementary Material**

Supplementary Table 1. Univariate analysis and multivariate logistic regression analysis of variables associated with post-induction hypotension.

**References**


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Efficacy of intraoperative blood salvage and autotransfusion in living-donor liver transplantation: a retrospective cohort study

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¹Yonsei University College of Medicine, ²Department of Anesthesiology and Pain Medicine, Anesthesia and Pain Research Institute, Yonsei University College of Medicine, ³Department of Transplantation Surgery, Yonsei University College of Medicine, Seoul, Korea

Background: Liver transplantation (LT) may be associated with massive blood loss and the need for allogeneic blood transfusion. Intraoperative blood salvage autotransfusion (IBSA) can reduce the need for allogeneic blood transfusion. This study aimed to investigate the effectiveness of blood salvage in LT.

Methods: Among 355 adult patients who underwent elective living-donor LT between January 1, 2019, and December 31, 2022, 59 recipients without advanced hepatocellular carcinoma received IBSA using Cell Saver (CS group). Based on sex, age, model for end-stage liver disease (MELD) score, preoperative laboratory results, and other factors, 118 of the 296 recipients who did not undergo IBSA were matched using propensity score (non-CS group). The primary outcome was the amount of intraoperative allogenic red blood cell (RBC) transfusion. Comparisons were made between the two groups regarding the amount of other blood components transfused and postoperative laboratory findings.

Results: The transfused allogeneic RBC for the CS group was significantly lower than that of the non-CS group (1,506.0 vs. 1,957.5 ml, P = 0.026). No significant differences in the transfused total fresh frozen plasma, platelets, cryoprecipitate, and estimated blood loss were observed between the two groups. The postoperative allogeneic RBC transfusion was significantly lower in the CS group than in the non-CS group (1,500.0 vs. 2,100.0 ml, P = 0.039). No significant differences in postoperative laboratory findings were observed at postoperative day 1 and discharge.

Conclusions: Using IBSA during LT can effectively reduce the need for perioperative allogeneic blood transfusions without causing subsequent coagulopathy.

Keywords: Autologous blood transfusion; Autotransfusion; Blood coagulation; Blood transfusion; Liver transplantation; Operative blood salvage; Postoperative complications.

Introduction

Liver transplantation (LT) is a surgical procedure indicated for patients with end-stage liver disease or acute liver failure that cannot be treated with medication or other therapies. High intraoperative blood loss is anticipated during LT owing to coagulopathy, portal hypertension, collateral vessels, and complex surgical procedures including anastomosis of major vessels [1]. Therefore, allogeneic blood transfusion is common, and rates of perioperative allogeneic blood transfusion remain elevated in patients undergoing LT (50.5%–62.6%) [2,3]. However, allogeneic blood transfusion causes immunosuppression...
and can lead to complications, such as anaphylaxis, transfusion-associated circulatory overload, or transfusion-related acute lung injury [5,6]. The risk of infection and graft failure is also high in patients who receive allogeneic blood transfusion, with significantly longer wound healing and hospitalization periods [7,8].

In an effort to reduce the need for allogeneic blood transfusions, intraoperative blood salvage autotransfusion (IBSA) has been developed. Moreover, the IBSA system collects and processes blood from the operative field, allowing it to be reinjected into the patient [9].

Studies have reported that IBSA reduces the amount of intraoperative allogeneic red blood cell (RBC) transfusion in LT [10,11]; however, some studies have suggested otherwise [12,13]. Additionally, several reports revealed that higher intraoperative blood loss may be owing to IBSA-related fibrinolysis during LT [14,15]. The relationship between IBSA and the coagulative and fibrinolytic laboratory parameters has not been studied in detail. Moreover, some reports have shown that IBSA can cause side effects, such as coagulopathy, infection, and salvaged blood syndrome [6,16].

Currently there is no consensus on the efficacy and safety of IBSA in LT, and the impact of IBSA on the early and long-term outcomes is unclear. Therefore, this study aimed to evaluate the efficacy of IBSA during LT, with the goal of providing insight into its potential role in reducing the need for allogeneic blood transfusions and improving patient outcomes. Additionally, we verified the efficacy of blood salvage throughout the perioperative period of LT by showing the reduced amount of postoperative allogeneic blood transfusion.

Materials and Methods

This study has been approved by the Institutional Review Board (IRB) of Severance Hospital (IRB No. 4-2022-1629). The requirement for informed consent was waived by the IRB owing to the retrospective nature of this study.

This was a single-center, retrospective cohort study. Data were collected from electronic medical records. Patients who underwent LT between January 1, 2019, and December 31, 2022, were enrolled. The exclusion criteria were ages below 18 years, emergency surgery, deceased donor LT, and incomplete data. Incomplete data refers to data omissions, inadequately recorded information, or data presented in inappropriate formats. Patients undergoing elective living-donor LT were divided into two groups based on usage of IBSA: Cell Saver (CS) group and non-CS group.

Patient demographics (sex, age, height, weight, body mass index, and the model for end-stage liver disease [MELD]), symptoms related with end-stage liver disease (ascites, encephalopathy, and varices), preoperative laboratory findings, perioperative outcomes, and transplantation-related complications were recorded. The MELD score was calculated using the preoperative values for international normalized ratio (INR), serum bilirubin, and serum creatinine. Aspartate transaminase, alanine transaminase, total bilirubin, direct bilirubin, prothrombin time (PT), INR, activated partial thromboplastin time (aPTT), hemoglobin, and platelet count were involved in preoperative laboratory findings within one month prior to surgery. Intraoperative parameters include the amount of crystalloid, albumin input, RBC count, fresh frozen plasma (FFP), platelet count, cryoprecipitate transfusion, urine output, and estimated blood loss. Hemoglobin level, platelet count, PT, INR, aPTT, and fibrinogen were recorded on postoperative day 1 (POD1) and on discharge. Postoperative transfusion was calculated as the total amount of transfused blood from admission to the surgical intensive care until discharge. Clinical outcomes including length of hospital, intensive care unit (ICU) stay and ventilation duration were recorded. We examined transplantation-related complications (graft failure, bile duct complication, and vascular complication) using follow-up data. Patients who underwent surgery between January 1, 2019, and December 31, 2021, were included and followed up until June 2022. The follow-up period ranged from 80 to 1,234 days, with a median of 501 days. These variables were compared between the CS group and non-CS group.

According to our institutional policy, IBSA was used in the elective living-donor LT, whereas it was contraindicated in patients with advanced hepatocellular carcinoma. Blood was salvaged using Cell Saver 5 (Haemonetics®). The shed blood from the operative field was suctioned into the reservoir of a device containing anticoagulant. If sufficient blood was collected, it underwent centrifugation and washing, and was processed to a hematocrit of approximately 60%. The target blood hemoglobin concentration was 8.0 g/dl, and salvaged blood was autotransfused in the CS group when RBC transfusion was indicated. Salvaged blood was used only during surgery.

Intra- and postoperatively, allogeneic blood transfusion was performed based on the hospital guidelines. Allogeneic transfusion was considered based on tolerance when the hemoglobin concentration dropped below 8.0 g/dl that was determined by arterial blood gas analysis or complete blood count.

Statistical analysis

Continuous variables are presented as median (Q1, Q3) or mean ± SD and were compared using a Mann-Whitney U test or
independent t-test. Categorical variables are presented as frequency and proportions and were compared using Fisher's exact test or a chi-square test. The cumulative survival probabilities were estimated by the Kaplan-Meier method and compared between the groups by the log-rank test.

Propensity score matching was performed to correct baseline selection bias. Using logistic regression, a propensity score was constructed based on the predicted probability of IBSA. Selected covariates are variables associated with the degree of liver dysfunction and blood loss during LT. These include sex, age, MELD score, American Society of Anesthesiologists classification, preoperative hemoglobin, platelet count, PT, and INR [17–19]. Covariate matching was performed in a 1:2 ratio between the CS group and non-CS group using an optimal matching algorithm without replacement and caliper. Matching quality was evaluated using standardized mean differences between the CS group and non-CS group. A standardized mean difference < 0.1 indicated a negligible imbalance between the groups.

All two-sided P values < 0.050 were considered statistically significant. Statistical analysis was performed using R package, version 4.2.2 (R Development Core Team, R Foundation for Statistical Computing®). Propensity score matching was performed using the Matchit package of the R software.

### Results

A total of 455 LT procedures were performed between January 1, 2019, and December 31, 2022, in our institution. We excluded 100 patients for the following reasons: (1) emergency operation or deceased donor LT (n = 74) and (2) ages under 18 years (n = 26). The remaining 355 adult patients who underwent elective living-donor LT were included in this study.

Of these, 59 (16.6%) received IBSA and 296 (83.4%) did not. Baseline characteristics are shown in Table 1. Before matching, significant differences were observed between the two groups, including MELD score, ascites, encephalopathy, bilirubin, PT, INR, aPTT, and hemoglobin. The MELD score was significantly higher in the CS group than in the non-CS group (10.6 [7.7, 15.7] vs. 15.8 [12.9, 21.6], P < 0.001), indicating an imbalance in baseline liver function between the two groups.

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before matching</th>
<th>After matching</th>
<th>P value</th>
<th>SMD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non-CS group (n = 296)</td>
<td>CS group (n = 59)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>P value</td>
<td>SMD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex (M)</td>
<td>205 (69.3)</td>
<td>36 (61.0)</td>
<td>0.278</td>
<td>0.174</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>57.0 (51.0, 63.0)</td>
<td>55.0 (48.5, 61.5)</td>
<td>0.111</td>
<td>0.197</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.9 (21.7, 26.3)</td>
<td>23.9 (21.5, 26.6)</td>
<td>0.685</td>
<td>0.097</td>
</tr>
<tr>
<td>MELD score</td>
<td>10.6 (7.7, 15.7)</td>
<td>10.6 (7.7, 15.7)</td>
<td>0.000</td>
<td>0.785</td>
</tr>
<tr>
<td>ASA ≥ 3</td>
<td>291 (98.3)</td>
<td>59 (100.0)</td>
<td>0.689</td>
<td>0.185</td>
</tr>
<tr>
<td>ESLD symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ascites</td>
<td>167 (56.4)</td>
<td>48 (81.4)</td>
<td>0.001</td>
<td>0.559</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>54 (18.2)</td>
<td>19 (32.2)</td>
<td>0.025</td>
<td>0.326</td>
</tr>
<tr>
<td>Varices</td>
<td>190 (64.2)</td>
<td>41 (69.5)</td>
<td>0.528</td>
<td>0.113</td>
</tr>
<tr>
<td>Preop laboratories</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>35.5 (25.0, 48.0)</td>
<td>40.0 (30.5, 52.5)</td>
<td>0.081</td>
<td>0.078</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>19.0 (13.0, 26.0)</td>
<td>16.0 (11.0, 25.5)</td>
<td>0.242</td>
<td>0.019</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>1.5 (0.9, 3.1)</td>
<td>2.4 (1.7, 5.1)</td>
<td>&lt; 0.001</td>
<td>0.253</td>
</tr>
<tr>
<td>Direct bilirubin (mg/dl)</td>
<td>0.6 (0.3, 1.5)</td>
<td>1.2 (0.8, 2.5)</td>
<td>&lt; 0.001</td>
<td>0.305</td>
</tr>
<tr>
<td>PT (s)</td>
<td>14.1 (12.8, 16.5)</td>
<td>16.5 (15.0, 19.6)</td>
<td>&lt; 0.001</td>
<td>0.457</td>
</tr>
<tr>
<td>INR</td>
<td>1.2 (1.1, 1.4)</td>
<td>1.4 (1.2, 1.6)</td>
<td>&lt; 0.001</td>
<td>0.484</td>
</tr>
<tr>
<td>aPTT (s)</td>
<td>34.3 (30.9, 38.2)</td>
<td>36.9 (33.7, 41.5)</td>
<td>0.001</td>
<td>0.150</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>10.6 (9.1, 12.4)</td>
<td>8.9 (8.0, 10.3)</td>
<td>&lt; 0.001</td>
<td>0.121</td>
</tr>
<tr>
<td>Platelet count (10⁴/L)</td>
<td>750 (54.5, 112.0)</td>
<td>67.0 (43.0, 96.0)</td>
<td>0.054</td>
<td>0.316</td>
</tr>
</tbody>
</table>

Values are presented as numbers (%), mean ± SD or median (Q1, Q3), except for categorical variables, for which values represent numbers of patients with percentages. CS: Cell Saver; SMD: standardized mean difference; BMI: body mass index; MELD: model for end-stage liver disease, ASA: American Society of Anesthesiologists classification, ESLD: end-stage liver disease, AST: aspartate transaminase, ALT: alanine transaminase, PT: prothrombin time, INR: international normalized ratio, aPTT: activated partial thromboplastin time.

https://doi.org/10.4097/kja.23599
Propensity score matching between the two groups was performed in a 1:2 ratio. After matching, the CS group and non-CS group were in balance for baseline characteristics including MELD score (16.0 [11.3, 21.5] vs. 15.8 [12.9, 21.6], P = 0.437, Table 1). Follow-up data were collected from 127 patients in the study population to evaluate transplantation-related complications (graft failure, bile duct complication, and vascular complication). Among these patients, after propensity score matching, those who underwent surgery until the year 2021 were included and followed up until June 2022.

The median blood volume autotransfused in the CS group was 550 ml (314, 1,186). No significant difference in crystalloid and albumin input was observed between the two groups. The median amount of transfused allogeneic RBC was significantly lower in the CS group (1,506.0 ml [896.5, 2,170.5] for the CS group vs. 1,957.5 ml [900.0, 3,294.0] for the non-CS group, P = 0.026). No significant difference in the total amount of transfused FFP, platelets, and cryoprecipitate was observed between the two groups. Estimated blood loss during surgery was not significantly different between the groups (P = 0.611, Table 2).

Both groups showed similar postoperative laboratory findings on POD1 and at the time of discharge (Table 3). The total amount of postoperative RBC transfusion until discharge was significantly lower in the CS group than in the non-CS group (1,500.0 ml [300.0, 3,600.0] vs. 2,100.0 ml [600.0, 4,800.0], P = 0.039). No significant difference was observed between the groups regarding the total amount of postoperative FFP, platelet, and cryoprecipitate transfusion until discharge. The length of hospital and ICU stay and ventilation duration were similar between the groups. Additionally, no significant difference in transplantation-related complications was observed between the two groups, including graft failure, bile duct complication, vascular complication, and one-year mortality (Table 4).

The one-year survival after LT between the CS group and non-CS group was analyzed. The one-year mortality rate was 10% in the CS group, compared to 19.6% in the non-CS group (P = 0.349, Table 4). No significant difference in cumulative survival probabilities was observed between the two groups (P = 0.500, Fig. 1).

Discussion

Our study has demonstrated that IBSA effectively reduces the need for allogeneic blood transfusion during LT throughout the postoperative period until discharge. Moreover, no significant differences in length of hospital and ICU stay, ventilation duration, one-year mortality, and transplantation-related complications were observed between the groups.

The efficacy and safety of IBSA use has been well-established in other surgical domains. A previous systematic review demonstrated that IBSA lowered intraoperative allogeneic RBC transfusion by 38% in orthopedic and cardiac surgery without additional worsening of clinical outcomes [20]. A meta-analysis that included various types of surgery, predominantly consisting of orthopedic, cardiac, and vascular surgeries, demonstrated that IBSA reduced the rate of exposure to allogeneic RBC transfusion by a relative 39%, as well as the risk of infection and length of hospital stay [21]. Compared to research on IBSA in other surgical fields, studies on IBSA in LT are relatively scarce in terms of quantity and sample size. The use of IBSA in LT has been analyzed in several observational studies. Similar to the results of our study, a reduction in intraoperative allogeneic transfusion owing to IBSA use was reported by several studies [22–24].

In addition to the significant reduction in intraoperative RBC

| Table 2. Intraoperative Parameters after Matching |
|---|---|---|---|
| Variable | Non-CS group (n = 118) | CS group (n = 59) | P value |
| Intake (ml) | | | |
| IBSA volume | 0.0 (0.0, 0.0) | 550.0 (314.0, 1,186.0) | < 0.001 |
| Crystalloid | 6,209.5 (4,628.0, 9,147.0) | 5,900.0 (4,771.5, 7,855.0) | 0.433 |
| Albumin | 3,500.0 (2,500.0, 4,600.0) | 3,500.0 (3,000.0, 5,000.0) | 0.200 |
| RBC | 1,957.5 (900.0, 3,294.0) | 1,506.0 (896.5, 2,170.5) | 0.026 |
| FFP | 317.5 (0.0, 759.0) | 450.0 (0.0, 674.0) | 0.619 |
| Platelet | 265.5 (0.0, 499.0) | 236.0 (0.0, 304.0) | 0.310 |
| Cryoprecipitate | 240.0 (77.0, 480.0) | 242.0 (233.5, 480.0) | 0.507 |
| Urine output (ml) | 1,057.5 (630.0, 1,560.0) | 1,050.0 (640.0, 1,615.0) | 0.854 |
| Estimated blood loss (ml) | 6,175.0 (3,850.0, 8,900.0) | 5,900.0 (3,676.0, 8,200.0) | 0.611 |

Values are presented as median (Q1, Q3). CS: Cell Saver, IBSA: intraoperative blood salvage autotransfusion, RBC: red blood cell, FFP: fresh frozen plasma.
Table 3. Postoperative Outcomes after Matching

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-CS group (n = 118)</th>
<th>CS group (n = 59)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory finding on POD1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>8.3 (7.6, 9.0)</td>
<td>8.3 (7.6, 9.1)</td>
<td>0.957</td>
</tr>
<tr>
<td>Platelet count (× 10^9/L)</td>
<td>55.0 (44.0, 70.0)</td>
<td>61.0 (45.5, 75.5)</td>
<td>0.261</td>
</tr>
<tr>
<td>Prothrombin time (s)</td>
<td>19.5 (16.8, 22.3)</td>
<td>18.5 (16.6, 20.6)</td>
<td>0.409</td>
</tr>
<tr>
<td>INR</td>
<td>1.6 (1.4, 1.9)</td>
<td>1.5 (1.4, 1.7)</td>
<td>0.140</td>
</tr>
<tr>
<td>aPTT (s)</td>
<td>42.2 (37.5, 52.1)</td>
<td>40.6 (36.7, 46.6)</td>
<td>0.200</td>
</tr>
<tr>
<td>Fibrinogen (mg/dl)</td>
<td>94.0 (73.0, 139.0)</td>
<td>104.0 (86.5, 127.5)</td>
<td>0.190</td>
</tr>
<tr>
<td>Laboratory finding on discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>9.2 ± 1.4</td>
<td>9.0 ± 1.2</td>
<td>0.167</td>
</tr>
<tr>
<td>Platelet count (× 10^9/L)</td>
<td>155.0 (92.0, 243.0)</td>
<td>178.0 (93.0, 303.0)</td>
<td>0.133</td>
</tr>
<tr>
<td>Prothrombin time (s)</td>
<td>12.1 (11.3, 13.8)</td>
<td>12.4 (11.6, 13.6)</td>
<td>0.327</td>
</tr>
<tr>
<td>INR</td>
<td>1.0 (0.9, 1.2)</td>
<td>1.0 (1.0, 1.1)</td>
<td>0.690</td>
</tr>
<tr>
<td>aPTT (s)</td>
<td>30.7 (27.9, 35.0)</td>
<td>30.2 (28.0, 34.5)</td>
<td>0.854</td>
</tr>
<tr>
<td>Postoperative total transfusion*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC (ml)</td>
<td>2,100.0 (600.0, 4,800.0)</td>
<td>1,500.0 (300.0, 3,600.0)</td>
<td>0.039</td>
</tr>
<tr>
<td>FFP (ml)</td>
<td>3,300.0 (1,800.0, 4,500.0)</td>
<td>3,750.0 (2,700.0, 5,025.0)</td>
<td>0.120</td>
</tr>
<tr>
<td>Platelet (ml)</td>
<td>900.0 (300.0, 2,250.0)</td>
<td>600.0 (300.0, 1,800.0)</td>
<td>0.120</td>
</tr>
<tr>
<td>Cryoprecipitate (ml)</td>
<td>240.0 (240.0, 240.0)</td>
<td>240.0 (240.0, 240.0)</td>
<td>0.728</td>
</tr>
<tr>
<td>Clinical outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of hospital stay (d)</td>
<td>48.0 (33.0, 70.5)</td>
<td>51.0 (30.5, 66.5)</td>
<td>0.510</td>
</tr>
<tr>
<td>Length of ICU stay (d)</td>
<td>4.0 (3.0, 6.0)</td>
<td>5.0 (4.0, 6.0)</td>
<td>0.169</td>
</tr>
<tr>
<td>Ventilation duration (d)</td>
<td>2.0 (2.0, 4.5)</td>
<td>2.0 (2.0, 4.0)</td>
<td>0.950</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3) or mean ± SD. CS: Cell Saver, POD: postoperative day, INR: international normalized ratio, aPTT: activated partial thromboplastin time, RBC: red blood cell, FFP: fresh frozen plasma, ICU: intensive care unit. *Postoperative transfusion: the total amount of transfused blood from admission to the surgical intensive care center until discharge.

Table 4. Transplantation-related Complications

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-CS group (n = 97)</th>
<th>CS group (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transplantation-related</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>One-year mortality</td>
<td>19.6 (6.2)</td>
<td>10 (6.2)</td>
<td>0.349</td>
</tr>
<tr>
<td>Graft failure</td>
<td>6 (6.2)</td>
<td>2 (6.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Bile duct complication</td>
<td>45 (46.4)</td>
<td>14 (46.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Total vascular complication</td>
<td>21 (21.6)</td>
<td>6 (20.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hepatic artery</td>
<td>8 (8.2)</td>
<td>2 (6.7)</td>
<td>1.000</td>
</tr>
<tr>
<td>Portal vein</td>
<td>10 (10.3)</td>
<td>1 (3.3)</td>
<td>0.415</td>
</tr>
<tr>
<td>Hepatic vein</td>
<td>5 (5.2)</td>
<td>3 (10.0)</td>
<td>0.600</td>
</tr>
</tbody>
</table>

Values are presented as number (%). CS: Cell Saver.

transfusion, our study found a noteworthy decrease in postoperative RBC transfusion from the patients’ arrival in the ICU until discharge. This finding is clearly different from that of previous studies that primarily focused on the amount of blood transfused solely during the surgery. However, it aligns with some existing literature [24,25] and suggests a potential correlation with the ad-
verse effects of intraoperative allogeneic transfusion that can cause dilutional coagulopathy and subsequent increase in postoperative bleeding [11]. Based on these observations, it can be speculated that IBSA may enhance postoperative outcomes by reducing the need for intraoperative RBC transfusions without introducing any additional side effects. Although our study did not directly measure postoperative estimated blood loss in the ICU, our results indicated that IBSA did not cause postoperative coagulopathy. These findings suggest that IBSA can be a valuable approach in LT, as it not only reduces the risks associated with allogeneic blood transfusions but contributes to improved postoperative outcomes without compromising coagulation.

Monitoring perioperative blood coagulation in LT is crucial as patients with end-stage liver disease often experience impaired coagulation. In our study, no significant differences were observed intraoperatively between the two groups regarding the transfusion of FFP, platelets, and cryoprecipitate. Furthermore, no notable variations in postoperative laboratory parameters, including platelet count, PT, INR, aPTT, and fibrinogen levels, on POD 1 were observed between the two groups. Since IBSA replaces only RBCs and no other clotting factors or platelets, there is a concern that dilution of clotting factors could potentially lead to clinical coagulopathy [9,26]. However, it is essential to note that several studies have reported that IBSA does not significantly affect the total amount of intraoperative FFP and platelet transfusions, nor does it have a notable impact on postoperative coagulation parameters [20,27]. Additionally, a previous study reported that the volume of IBSA used was associated with the severity of blood coagulation impairment [28]. In studies where clinical coagulopathy was reported, the volume of IBSA used was approximately 1,000 ml that was larger than that used in other studies [28,29]. However, in our study, the average autotransfusion volume was 550 ml that indicates that the volume did not significantly affect blood coagulation. Therefore, based on the findings from our study and existing literature [20,27], it can be suggested that a mean IBSA autotransfusion volume of 550 ml in LT, as used in our research, is unlikely to have a significant effect on blood coagulation. Nevertheless, continuous monitoring and further investigation of perioperative coagulation status remain essential to ensure patient safety during the LT procedures.

This study offers a distinctive and valuable contribution to the existing literature by exploring the cumulative perioperative transfusion volume until discharge. Unlike previous studies that focused solely on the intraoperative outcome, our approach provides a more comprehensive and thorough evaluation of the efficacy of blood salvage throughout the perioperative period of LT. This broader perspective allows for a better understanding of the overall impact and benefits of blood salvage techniques in LT, making our study a valuable addition to the existing body of knowledge in this field.

This study has some limitations. First, being a retrospective study, there may be inherent biases and limitations associated with the use of electronic medical records for data collection, such as potential confounding variables and missing data, and the effect of anesthesiologists or operating surgeons. However, we made efforts to address these limitations by conducting rigorous data collection and employing propensity score matching. Propensity score matching allowed us to minimize selection bias and enhance the comparability between the CS and non-CS groups. Second, the study was conducted at a single center that may restrict the generalizability of our findings to other institutions. To validate and strengthen our results, multi-center studies with larger sample sizes are warranted. Furthermore, the follow-up period in our study was relatively short, ranging from 80 to 1,234 days, with a median of 501 days. Longer-term follow-up is essential to assess the effect of IBSA on outcomes such as overall survival, graft survival, and long-term complications. Future research should focus on evaluating the longer-term effects of IBSA on patient outcomes to gain a more comprehensive understanding of its benefits.

In conclusion, our study presents compelling evidence that the implementation of IBSA during LT is highly effective in reducing the necessity for allogeneic blood transfusions. Our findings hold crucial implications for clinical practice, as IBSA has the potential to substantially decrease the reliance on allogeneic blood transfusions, thereby minimizing transfusion-related complications and ultimately leading to improved patient outcomes. Continued investigation into IBSA's benefits and appropriate indications could bring about meaningful advancements in the field of LT and enhance patient care in the future.

**Funding**

None.

**Conflicts of Interest**

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

**Data Availability**

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

Jongchan Lee (Data curation; Formal analysis; Investigation; Visualization; Writing – original draft)
Sungji Choo (Investigation; Visualization; Writing – original draft)
Jae Geun Lee (Data curation)
Sujung Park (Formal analysis; Investigation; Validation; Writing – review & editing)
Bon-Nyoeo Koo (Conceptualization; Project administration; Supervision; Writing – review & editing)

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Comparison of lung aeration loss in open abdominal oncologic surgeries after ventilation with electrical impedance tomography-guided PEEP versus conventional PEEP: a pilot feasibility study

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Background: Existing literature lacks high-quality evidence regarding the ideal intraoperative positive end-expiratory pressure (PEEP) to minimize postoperative pulmonary complications (PPCs). We hypothesized that applying individualized PEEP derived from electrical impedance tomography would reduce the severity of postoperative lung aeration loss, deterioration in oxygenation, and PPC incidence.

Methods: A pilot feasibility study was conducted on 36 patients who underwent open abdominal oncologic surgery. The patients were randomized to receive individualized PEEP or conventional PEEP at 4 cmH₂O. The primary outcome was the impact of individualized PEEP on changes in the modified lung ultrasound score (MLUS) derived from preoperative and postoperative lung ultrasonography. A higher MLUS indicated greater lung aeration loss. The secondary outcomes were the PaO₂/FiO₂ ratio and PPC incidence. An intraoperative PaO₂/FiO₂ ratio was recorded. The post-hoc analysis showed that the increase in lung aeration loss and deterioration of intraoperative oxygenation correlated with the deviation from the individualized PEEP.

Results: A significant increase in the postoperative MLUS (12.0 ± 3.6 vs 7.9 ± 2.1, P < 0.001) and a significant difference between the postoperative and preoperative MLUS values (7.0 ± 3.3 vs 3.0 ± 1.6, P < 0.001) were found in the conventional PEEP group, indicating increased lung aeration loss. In the conventional PEEP group, the intraoperative PaO₂/FiO₂ ratios were significantly lower, but not the postoperative ratios. The PPC incidence was not significantly different between the groups. Post-hoc analysis showed the increase in lung aeration loss and deterioration of intraoperative oxygenation correlated with the deviation from the individualized PEEP.

Conclusions: Individualized PEEP appears to protect against lung aeration loss and intraoperative oxygenation deterioration. The advantage was greater in patients whose individualized PEEP deviated more from the conventional PEEP.

Keywords: Electric impedance; Feasibility studies; General anesthesia; Laparotomy; Lung compliance; Positive-pressure respiration; Pulmonary atelectasis; Ultrasonography; Surgical oncology; Tomography.
Introduction

Major surgical procedures are associated with postoperative pulmonary complications (PPCs) [1]. Various strategies have been recommended to reduce PPCs and evidence suggests that intraoperative lung-protective ventilation plays a major role [1,2]. The concept of lung-protective ventilation evolved from acute respiratory distress syndrome (ARDS). Iatrogenic lung injury due to positive pressure ventilation, called ventilator-induced lung injury, occurs due to an interplay of volutrauma, barotrauma, atelectrauma, biotrauma, and oxytrauma [3]. A ventilatory strategy with low tidal volume ($V_t$), high positive end-expiratory pressure (PEEP), low plateau pressure, and low driving pressure ($\Delta P$) has been found to be beneficial in patients with ARDS [4]. Extrapolating this concept into intraoperative ventilation, researchers are evaluating various lung protective ventilation strategies to reduce the incidence of PPCs [3].

One strategy involves the delivery of high PEEP in the intraoperative setting. However, the evidence for this is mixed, with some studies showing benefits [5,6], and others showing no benefit [7–9]. This might be due to the variable patient profiles, body habitus, body mass index (BMI), lung dimensions, and pleural pressures included in these studies. Thus, the concept of individualized PEEP for intraoperative ventilation has evolved. The methods used to arrive at the ideal PEEP for a patient include best compliance, best oxygenation, esophageal manometry, the pressure–volume curve, stress index, end-expiratory lung volume, computed tomography (CT), lung ultrasonography, and electrical impedance tomography (EIT) [10].

EIT is a bedside, radiation-free, real-time, and noninvasive monitoring modality used to measure regional ventilation. EIT can measure overdistended or collapsed lung fields. During decremental PEEP titration, the appropriate PEEP can be identified based on the balance between overdistended and collapsed areas [11,12]. Studies have shown that EIT can be used to identify the ideal PEEP for each patient [13–15].

Atelectasis following general anesthesia is a major contributing factor to the development of PPCs. Although CT is considered the gold standard for detecting and quantifying atelectasis, it has many disadvantages, such as radiation exposure, the need to shift the patient to the radiology suite, high cost, and limited availability. Recently, lung ultrasonography has been explored as an alternative to CT for identifying lung aeration loss [16]. Lung ultrasonography has been found to correlate with thoracic CT [17,18] and magnetic resonance imaging [19] for identifying lung atelectasis.

We hypothesized that EIT-derived PEEP would reduce the severity of postoperative lung aeration loss. In this pilot feasibility study, we investigated lung aeration loss using lung ultrasonography in patients who underwent open abdominal oncologic surgery after ventilation with conventional or individualized PEEP.

Materials and Methods

Study setting and participants

This prospective, randomized, participant- and outcome-assessor-blinded pilot feasibility study was conducted at the Dr. Bhimrao Ramji Ambedkar Institute Rotary Cancer Hospital, All India Institute of Medical Sciences in New Delhi, India, from August 2019 to September 2021. This study was approved by the Institute Ethics Committee for Postgraduate Research of the All India Institute of Medical Sciences in New Delhi, India (No. IECPG/357/5/2019) and was registered at https://ctri.nic.in/ (No. CTRI/2019/07/020351); principal investigator: Karthik AR, date of registration: July 24, 2019) prior to patient enrolment. Written informed consent was obtained from all participants before enrolment in the study. Patients aged 18–65 years with American Society of Anesthesiologists (ASA) physical statuses of I, II, or III who underwent elective open abdominal oncologic surgery and provided consent were included in the study. Patients who met the following criteria were excluded from the study: (1) BMI < 18.5 kg/m$^2$ or > 35 kg/m$^2$; (2) moderate to severe pulmonary function test abnormalities (i.e., less than 80% predicted forced vital capacity [FVC] or forced expiratory volume in the first second [FEV$_1$] or FEV$_1$/FVC); (3) serum albumin levels < 3.0 g/dl; (4) presence of a pacemaker; (5) undergoing surgery involving an incision not extending above the level of the umbilicus; and (6) undergoing surgery lasting < 2 h in duration. All the procedures were performed in accordance with the Declaration of Helsinki, 2013. This manuscript adheres to the Consolidated Standards of Reporting Trials (CONSORT) format.

Study protocol

A total of 40 patients were enrolled in the study. The patients were eventually randomized to receive either EIT-derived PEEP (EIT PEEP group) or conventional PEEP (PEEP 4 group) ventilation at a 1:1 ratio. Computer-generated block randomization was performed using block sizes of 2, 4, and 6. Patients who satisfied the inclusion criteria and provided consent were enrolled in the study the day before the procedure. The patients and outcome assessors were blinded to group allocation. Allotment concealment was achieved using sequentially numbered opaque sealed envelopes.

After enrolment in the study, an arterial blood gas (ABG) anal-
ysis was performed with the patients on room air the evening before surgery on a GEM Premier 3000 machine (Instrumentation Laboratory). On the day of surgery, patients were attached to the following standard monitors in the operating room: electrocardiography, pulse oximetry, and noninvasive blood pressure.

A baseline chest ultrasonography was performed using an Edge II ultrasound machine (FUJIFILM Sonosite) with a low-frequency (5–2 MHz) convex probe. The long axis of the probe was placed perpendicular to the long axis of the intercostal space. Ultrasonography was performed in 12 areas, divided by the anterior and posterior axillary lines into anterior, lateral, and posterior zones. The anterior and lateral zones were further divided into superior and inferior areas at the line across the nipples, and the posterior zone was divided below the level of the scapula into medial and lateral areas, to a total of 12 areas, six on each side (Supplementary Figs. 1–3). Given that ultrasonography of the scapula cannot be used to study the lungs, this area was omitted. Short video clips from each area were taken and labelled with the participant number and recorded in the ultrasound machine.

After securing the intravenous lines, patients underwent epidural catheter placement, unless contraindicated, at a vertebral level appropriate for the surgery. An EIT belt was placed along the fourth or fifth intercostal space and EIT monitoring (PulmoVis-ta® 500, Dräger Medical) was initiated (Supplementary Figs. 4–7). A Primus® (Dräger Medical) anesthesia workstation was used to administer the general anesthesia. After pre-oxygenation with 100% oxygen for 5 min, general anesthesia induction and endotracheal intubation were performed with intravenous fentanyl 2 μg/kg, propofol 2.5 mg/kg, and rocuronium 1 mg/kg. Mechanical ventilation was initiated in volume-controlled ventilation (VCV) mode with a $V_t$ of 6 ml/kg of predicted body weight (PBW), PEEP of 4 cmH$_2$O, inspiratory pause of 30%, and FiO$_2$ of 50% with an appropriate respiratory rate (RR) to maintain end-tidal carbon dioxide (ETCO$_2$) at 35–45 mmHg. The PBW was calculated using the following formulae: [20] PBW (kg) for males = 50 + 0.91 (height [cm] – 152.4); PBW (kg) for females = 45.5 + 0.91 (height [cm] – 152.4).

An arterial line was placed in one of the radial arteries, and invasive blood pressure monitoring was initiated. ETCO$_2$ and anesthesia gas were monitored using a side-stream monitor. Central venous access was obtained as required. Anesthesia was maintained using an oxygen-air mixture, sevoflurane, and intermittent rocuronium boluses. Analgesia was maintained via the epidural route along with intermittent intravenous fentanyl boluses.

Lung recruitment was performed in a graded fashion in pressure-controlled ventilation mode with a $P_{\text{mip}}$ of 25 cmH$_2$O, PEEP of 10 cmH$_2$O for 45 s; and $P_{\text{mip}}$ of 35 cmH$_2$O, PEEP of 20 cmH$_2$O for 45 s. The I:E ratio was set at 1:1, and the RR was set at 10/min during recruitment. After recruitment, the ventilation mode was changed to VCV mode with a $V_t$ of 6 ml/kg of PBW, I:E ratio of 1:2, inspiratory pause of 30%, and PEEP of 20 cmH$_2$O with an appropriate RR to maintain ETCO$_2$ at 35–45 mmHg. Decremental PEEP titration was performed in VCV mode by decreasing the PEEP in increments of 2 cmH$_2$O every 45 s up to zero PEEP. The PEEP trial analysis was performed using an EIT monitor.

The EIT monitor was used to measure the compliance loss at various levels of PEEP and plotted on two lines, one each for compliance loss at high and low PEEP. The compliance loss at the high and low PEEP lines measured compliance loss due to alveolar hyperdistension and collapse, respectively. The point at which both lines intersected was considered the point of compromise between alveolar hyperdistension and collapse. The nearest PEEP value above this point was considered the individual’s ideal PEEP (Fig. 1 and Supplementary Fig. 8).

The patients were randomized to the EIT PEEP or PEEP 4 group. After randomization, the patients underwent a second recruitment maneuver, similar to the first. After the second recruitment, ventilation was changed to the VCV mode with PEEP set to the EIT PEEP value or to 4 cmH$_2$O according to the randomized group. The rest of the surgery proceeded using the new PEEP value in VCV mode with other ventilatory parameters as before.

If the target ETCO$_2$ was not achieved with a maximum RR of 20/min, the $V_t$ was increased to a maximum of 8 ml/kg PBW. Fluid management, blood products, and anesthetic regimens were administered at the discretion of the attending anesthesiologist. If hypotension (defined as a decrease in mean arterial pressure > 20% of the baseline) occurred at any point, it was managed with vasopressors, the choice of which was at the discretion of the attending anesthesiologist. Extubation was performed in pressure support ventilation mode with the allocated PEEP. One hour after extubation, a similar chest ultrasonography was performed and short video clips were labelled and saved. The video clips contained only the patient sequence number; no information about the randomization group or the patient’s identity was included.

ABGs were obtained at various time points (Supplementary Fig. 9). Analgesia was titrated to a Numeric Rating Scale score for pain of 3/10. The patients were followed up for up to three post-operative days for the development of PPCs, if any.

**Data collection**

The following data were collected: (1) modified lung ultrasound score (MLUS), (2) PaO$_2$/FiO$_2$ ratio, (3) hemodynamic variables
(pulse rate and blood pressure), and (4) PPCs. The pre- and post-operative ultrasound video clips for all patients were recorded by the same anesthesiologist, with more than three years of experience in lung ultrasonography. The video clips were analyzed by two pulmonologists, each with more than five years of experience in lung ultrasonography. An MLUS, as described Monastesse et al. [16], was generated. The MLUS was chosen over the original lung ultrasound score as the former was found to be more sensitive [16]. Each of the 12 areas of the lung was assigned a score between 0 and 3 as follows: (a) up to 2 B lines: score 0, (b) more than 3 B lines or small subpleural consolidations separated by a normal pleural line: score 1, (c) multiple coalescent B lines or multiple small subpleural consolidations separated by a thickened or irregular pleural line: score 2, and (d) lung consolidation or small subpleural consolidation > 1 × 2 cm in diameter: score 3. A total score ranging from 0 to 36 was calculated by adding the individual scores for each of the 12 areas (with a higher score indicating greater lung aeration loss). The two pulmonologists were informed of the scoring system before the analysis was conducted. Representative lung ultrasound images are shown in Supplementary Figs. 10 and 11. The pulmonologists were blinded to the randomization groups as the video clips did not contain any identifying information.

The PPCs studied were respiratory infection, respiratory failure, pleural effusion, atelectasis, pneumothorax, bronchospasm, and aspiration pneumonitis, as described previously by Canet et al. [21]. The primary outcome was the impact of individualized PEEP on the change in the MLUS between the pre- and post-operative lung ultrasound. The secondary outcomes were the PaO₂/FiO₂ ratio and PPC incidence. Fig. 2 presents a procedural flow diagram of the study.

**Statistical analysis**

Given the nature of this study as a pilot, we postulated that a mean 2-point difference in the MLUS calculated at each time

![Fig. 1. PEEP titration analysis in the EIT monitor. The white and orange lines in the lower portion of the image denote the compliance loss at low and high PEEP levels, respectively. The values on the lines denote the percentage compliance loss. Timepoints A–J denote each step in the PEEP titration, with A at a PEEP of 20 cmH₂O and J at a PEEP of 2 cmH₂O. The lines intersect between points G and H, with G at a PEEP of 8 cmH₂O and H at a PEEP of 6 cmH₂O. The greater PEEP value of 8 cmH₂O is taken as the EIT-derived PEEP for this patient. PEEP: positive end expiratory pressure, EIT: electrical impedance tomography, C loss HP: compliance loss towards higher PEEP levels, C loss LP: compliance loss towards lower PEEP levels.](https://doi.org/10.4097/kja.23858)
point with a standard deviation of 2 would be observed. Assuming a power of 80%, a level of significance (two-tailed) of 5%, and an incomplete dataset of 15% of the patients, we estimated that 20 patients would need to be enrolled in each group. The data was analyzed using STATA® software version 14.0 (StataCorp.). Categorical variables are presented as numbers and percentages (%), and continuous variables are presented as the mean ± standard deviation (SD). The normality of the data was tested using the Shapiro-Wilk test. The duration of surgery was not normally distributed. The unpaired Student's t-test was applied for normally distributed data, and the Mann-Whitney U test was applied if normality was not assumed for between-group comparisons.

Qualitative variables were compared using the χ² test or Fisher's exact test. The Spearman's rank correlation test was used to observe the correlation between quantitative variables, as appropriate. Interobserver reliability in lung ultrasound scores were assessed using the intraclass correlation coefficient (ICC) and Cronbach’s α. Differences were considered statistically significant at P < 0.05.

**Results**

Forty patients were randomized into two groups, the EIT PEEP group and the PEEP 4 group (20 patients per group). One patient in the EIT PEEP group was extubated on the first postoperative day because of intraoperative hemodynamic instability. One patient with stomach carcinoma in the PEEP 4 group underwent a thoracotomy and one-lung ventilation during the intraoperative period. Another patient in the PEEP 4 group was extubated on the third postoperative day because of severe hemodynamic instability and postoperative hepatic and renal dysfunction. A third patient in the PEEP 4 group was reintubated in the immediate postoperative period because of hypoventilation and sedation. All four of these patients were excluded from the final analysis. Thus, data from a total of 19 patients in the EIT PEEP group and 17 patients in the PEEP 4 group were analyzed. The CONSORT flow diagram of the study is shown in Fig. 3.

The baseline patient characteristics were comparable between the two groups (Table 1). Some correlations between the BMI and EIT-derived PEEP values were found in all 36 patients in both groups ($r = 0.567, P < 0.001$) (Supplementary Fig. 12). The EIT-derived PEEP of all 36 patients ranged from 4 to 14 cmH₂O (mean ± SD: 8.4 ± 2.8 cmH₂O). Perioperative patient parameters were comparable between the two groups (Supplementary Table 1). For the duration of surgery, two outliers were noted in the PEEP 4 group.

Fig. 4 shows the MLUS values for the two groups. The baseline preoperative MLUS values were comparable between the two groups (5.0 ± 3.8 vs 4.8 ± 1.7, $P = 0.823$); however, the postoperative MLUS was significantly higher in the PEEP 4 group (denoting a higher degree of lung aeration loss) than in the EIT PEEP group (12.0 ± 3.6 vs 7.9 ± 2.1, $P < 0.001$). Similarly, the difference between the post- and preoperative MLUS values was significantly higher in the PEEP 4 group than in the EIT PEEP group (7.0 ± 3.3 vs 3.0 ± 1.6, $P < 0.001$).

The ABG parameters are presented in Supplementary Table 2. The PaCO₂, pH, HCO₃⁻, and lactate levels were comparable between the two groups at all time points. PaO₂/FiO₂ ratios were comparable between the two groups at baseline and after the sec-
ond recruitment. However, the PaO$_2$/FiO$_2$ ratio was significantly lower in the PEEP 4 group than in the EIT PEEP group at one hour after randomization and before extubation. In addition, the PaO$_2$/FiO$_2$ ratio at one hour after extubation and one day after extubation were lower in the PEEP 4 group than in the EIT PEEP group, though this difference was not statistically significant.

The interobserver reliability of the lung ultrasound scores between the two observers is presented in Supplementary Table 3. For the individual video clips, the ICC between the two observers ranged from 0.722 to 0.989 (P < 0.001). The ICC between the two observers for the total pre- and post-operative MLUS values were 0.987 and 0.988, respectively (P < 0.001), denoting good reliability between the observers.

A post-hoc analysis was performed to study the correlation between the delta PEEP (ΔPEEP) and various parameters (Table 2). The ΔPEEP was calculated as the difference between the EIT-derived PEEP and the set PEEP for all 36 patients. This analysis was possible because data was collected on the EIT PEEP in all patients.

ΔPEEP = EIT-derived PEEP – set PEEP

Since all patients in the EIT PEEP group had their intraoperative PEEP set to the EIT-derived PEEP value, their ΔPEEP was zero. Three patients in the PEEP 4 group had an EIT-derived PEEP of 4 cmH$_2$O; thus, their ΔPEEP was also zero. The remaining 14 patients in the PEEP 4 group had a ΔPEEP ranging from 2 to 10 cmH$_2$O (Supplementary Table 4).

A strong positive correlation was found between the ΔPEEP and the difference between the postoperative and preoperative MLUS values. The negative correlation between the ΔPEEP and the PaO$_2$/FiO$_2$ ratios at one hour after randomization, before extubation, and 24 h after extubation was significant. However, the negative correlation between the ΔPEEP and PaO$_2$/FiO$_2$ ratio at one hour after extubation was not significant.

The PPCs are presented in Supplementary Table 5. The incidence of PPCs was not significantly different between the groups. Neither of the outliers for the duration of surgery in the PEEP 4 group had PPCs. Hence, these outliers should not have influenced the results.

Discussion

High-quality evidence regarding the ideal intraoperative setting
for PEEP to minimize PPCs or improve clinical outcomes is not available in the existing literature. Most studies have recommended avoiding zero PEEP and high V\textsubscript{T} during the intraoperative period. However, the exact value of PEEP for improving postoperative outcomes remains unclear. Given the growing evidence that a single PEEP value may not be ideal for all patients, or even for the same patient at various time points, the concept of individualized PEEP has been evaluated. However, the optimal method for identifying these PEEP values remains unclear. We chose EIT monitoring because preliminary evidence has suggested that EIT-guided PEEP titration might be superior to the most commonly used conventional best compliance method \[13\]. However, various PEEP titration methods are available for EIT monitoring, such as using the point of balance between lung collapse and hyperdistension or using the regional ventilation delay index. As no current literature has confirmed the superiority of either method, we chose the former.

The methods used to evaluate the effectiveness of intraoperative ventilation strategies need to be simple, accurate, reproducible, and available at the point of care. EIT and lung ultrasonography are radiation-free point-of-care modalities. However, their utility in the exploration of ideal intraoperative PEEP needs to be evaluated. We chose the following subset of surgeries in which PPCs are expected: open abdominal surgeries with the patient in various positions, with an incision extending above the umbilicus and lasting more than two hours. Because our institute is an on-

### Table 1. Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>EIT PEEP group (n = 19)</th>
<th>PEEP 4 group (n = 17)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>9/10</td>
<td>9/8</td>
<td>0.738</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>45.8 ± 11.7</td>
<td>46.4 ± 14.2</td>
<td>0.896</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenal mass</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ca cervix</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ca colon</td>
<td>1</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Ca duodenum</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ca endometrium</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Ca gall bladder</td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ca ovary</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ca pancreas</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ca rectum</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Ca stomach</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Gastric GIST</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Germ cell tumor testis</td>
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<td>1</td>
<td></td>
</tr>
<tr>
<td>Periampullary carcinoma</td>
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<td>1</td>
<td></td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Retroperitoneal sarcoma</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.6 ± 8.3</td>
<td>157.0 ± 10.2</td>
<td>0.254</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>59.9 ± 11.1</td>
<td>62.8 ± 10.3</td>
<td>0.429</td>
</tr>
<tr>
<td>BMI (kg/m\textsuperscript{2})</td>
<td>23.3 ± 4.4</td>
<td>25.7 ± 4.7</td>
<td>0.128</td>
</tr>
<tr>
<td>PBW (kg)</td>
<td>55.3 ± 9.4</td>
<td>52.3 ± 10.7</td>
<td>0.374</td>
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<tr>
<td>ASA-PS (I/II/III)</td>
<td>10/7/2</td>
<td>8/9/0</td>
<td>0.150</td>
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<tr>
<td>Comorbidities</td>
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<tr>
<td>Diabetes</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
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<td>5</td>
<td></td>
</tr>
<tr>
<td>Jaundice</td>
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<td>0</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Mild restrictive lung disease</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Preoperative chemotherapy</td>
<td>3</td>
<td>3</td>
<td>1.0</td>
</tr>
<tr>
<td>Preoperative radiotherapy</td>
<td>1</td>
<td>1</td>
<td>1.0</td>
</tr>
<tr>
<td>Serum albumin (g/dl)</td>
<td>4.1 ± 0.5</td>
<td>4.1 ± 0.5</td>
<td>0.727</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>11.7 ± 1.0</td>
<td>11.6 ± 0.8</td>
<td>0.750</td>
</tr>
<tr>
<td>Pulmonary function tests</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>% predicted FEV\textsubscript{1}</td>
<td>83.7 ± 5.8</td>
<td>83.8 ± 5.4</td>
<td>0.963</td>
</tr>
<tr>
<td>% predicted FVC</td>
<td>87.4 ± 7.5</td>
<td>87.5 ± 5.9</td>
<td>0.962</td>
</tr>
<tr>
<td>% predicted FEV\textsubscript{1}/FVC</td>
<td>96.1 ± 5.2</td>
<td>95.9 ± 4.0</td>
<td>0.917</td>
</tr>
</tbody>
</table>

Values are presented as number or mean ± SD. EIT: electrical impedance tomography, PEEP: positive end expiratory pressure, Ca: carcinoma, GIST: gastrointestinal stromal tumor, BMI: body mass index, PBW: predicted body weight, ASA-PS: American Society of Anesthesiologists physical status, FEV\textsubscript{1}: forced expiratory volume in the first second, FVC: forced vital capacity.
Table 2. Correlation between the ΔPEEP and Various Parameters

<table>
<thead>
<tr>
<th>Correlation with ΔPEEP</th>
<th>Spearman correlation coefficient (r)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference between postoperative and preoperative MLUS value</td>
<td>0.790</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PaO\textsubscript{2}/FiO\textsubscript{2} ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>One hour after randomization</td>
<td>−0.498</td>
<td>0.002</td>
</tr>
<tr>
<td>Before extubation</td>
<td>−0.485</td>
<td>0.003</td>
</tr>
<tr>
<td>One hour after extubation</td>
<td>−0.237</td>
<td>0.165</td>
</tr>
<tr>
<td>One day after extubation</td>
<td>−0.478</td>
<td>0.003</td>
</tr>
</tbody>
</table>

PEEP: positive end expiratory pressure, ΔPEEP: difference between electrical impedance tomography derived PEEP and set PEEP; MLUS: modified lung ultrasound score; PaO\textsubscript{2}/FiO\textsubscript{2}: ratio of arterial oxygen saturation to inspired oxygen fraction.

Pulmonary medicine and Généreux et al. [22] observed that intraoperative individualized PEEP did not extend into the postoperative period. This is consistent with the observations presented by Nestler et al. [22] and Généreux et al. [23] and suggests that the lung aeration advantage in the EIT PEEP group was lost during the postoperative period. Thus, measures to keep the alveoli recruited during the postoperative period may be necessary to sustain improvements in oxygenation.

The PPC-related secondary outcomes did not support our hypothesis. Although the incidence of PPCs was higher in the PEEP 4 group, the difference was not statistically significant.

The EIT-derived PEEP of all 36 patients ranged from 4 to 14 cmH\textsubscript{2}O. This correlated reasonably well with the BMI of the patients, such that patients with a higher BMI demonstrated a higher ideal PEEP. This is consistent with the findings of Pereira et al. [14]. As we had determined the ideal PEEP values for the patients in both groups, we were able to evaluate whether lung aeration loss was greater with increased deviation from the ideal PEEP value. To examine this correlation, we performed a post-hoc analysis. We defined the deviation from the ideal PEEP as the ΔPEEP. As expected, the ΔPEEP value correlated well with the change in the MLUS. In other words, the more the set PEEP value deviated from the ideal PEEP value, the greater the lung aeration loss. This correlation was also reflected in a decrease in arterial oxygenation: the greater the deviation from the ideal PEEP, the greater the decrease in oxygenation intraoperatively. However, this correlation disappeared in the immediate postoperative period. A moderate correlation was found between the ΔPEEP and the decrease in oxygenation one day after extubation. We could not find any previous study that evaluated the correlation between the deviation from the ideal PEEP and various respiratory parameters.

Our study has certain limitations. First, it was performed as a pilot study to determine feasibility and offer information to refine the methodology for a larger study. Thus, it was conducted on a small sample size at a single center and was not adequately powered to study the outcomes. Additionally, this study was conducted only on patients undergoing oncologic surgery. Thus, the applicability of these results to the general population may not be valid. Second, the EIT belt was attached along the fourth or fifth intercostal space, and information gathered by the EIT monitor...
was consistent with the region of the lungs only at that level. Lung regions above or below this level may have a different balance of collapse and hyperdistension; thus, a global picture may not be possible. Third, the study population had low ASA physical status scores. The hemodynamic implications of PEEP titration and maintenance of EIT-derived PEEP throughout surgery have not been studied in more unstable patients. CT of the thorax is considered the gold standard for quantifying lung atelectasis. However, given the risk of radiation exposure and the need to shift the immediate postoperative patient to the CT suite, we chose to perform lung ultrasonography. Preliminary literature suggests that lung ultrasonography correlates well with other modalities for identifying lung aeration loss. Because ultrasonography is also known for its operator dependency, we established the interobserver reliability of the MLUS before using it for outcome measurements. However, adequately powered studies with larger sample sizes are required to validate the score and establish the inter- and intra-observer reliabilities of the MLUS.

In conclusion, patients ventilated with EIT-derived PEEP experienced less lung aeration loss than those ventilated with conventional PEEP. Intraoperative oxygenation was better in the EIT PEEP group than in the conventional PEEP group. However, sustained oxygenation was lost in the postoperative period after the removal of the EIT PEEP. No significant difference was found in the incidence of PPCs between the groups. Additionally, significant correlations were found between deviation from the ideal PEEP and lung aeration loss and deterioration in intraoperative oxygenation. This suggests that the more a patient’s ideal PEEP deviates from the conventional PEEP, the more benefits are expected from an individualized PEEP titration protocol. Further adequately powered studies are required to validate our results. We intend to perform a definitive randomized controlled trial with a larger sample size and methodological improvements based on the results of this study.

Acknowledgements

The authors would like to thank Dr. Maroof Ahmad Khan and Dr. Rajeev Kumar Malhotra for their support in the statistical analysis.

Funding

None.
Supplementary Materials

Supplementary Fig. 1. Ultrasound areas in the anterior chest wall. Supplementary Fig. 2. Ultrasound areas in the lateral chest wall. Supplementary Fig. 3. Ultrasound areas in the posterior chest wall. Supplementary Fig. 4. Electrical Impedance Tomography (EIT) monitor. Supplementary Fig. 5. EIT belt attached around the chest – anterior view. Supplementary Fig. 6. EIT belt attached around the chest – lateral view. Supplementary Fig. 7. Screenshot of EIT monitoring screen. Supplementary Fig. 8. PEEP titration analysis of a patient in EIT monitor. Supplementary Fig. 9. Timepoints of arterial blood gas measurement. Supplementary Fig. 10. Snapshot from an ultrasound clip showing a normal pleural line. Supplementary Fig. 11. Snapshot from an ultrasound clip showing a thickened and irregular pleural line along with a small subpleural consolidation. Supplementary Fig. 12. Scatter plot of BMI and EIT derived PEEP. Supplementary Table 1. Perioperative patient parameters. Supplementary Table 2. Arterial blood gas parameters. Supplementary Table 3. Inter-observer reliability of modified lung ultrasound score. Supplementary Table 4. EIT derived PEEP and ΔPEEP of the participants. Supplementary Table 5. Incidence of postoperative pulmonary complications.

References

16. Monastesse A, Girard F, Massicotte N, Charttrand-Lefebvre C,


Background: In recent years, the suprainguinal fascia iliaca compartment block (SFICB) has become more common in clinical practice. This assessor-blinded dose-finding study aimed to determine the minimum effective concentration (MEC90, MEC95) of bupivacaine for a single-injection SFICB in patients undergoing arthroscopic anterior cruciate ligament repair.

Methods: This prospective study was conducted at a tertiary hospital (postoperative recovery room and ward). The SFICB was performed as a postsurgical intervention after spinal anesthesia. Seventy patients were allocated using the biased-coin design up-and-down sequential method. The ultrasound-guided SFICB was performed using different bupivacaine concentrations, and standard multimodal analgesia was administered to all patients. Block success was defined as the absence of pain or presence of only tactile sensation during the pinprick test conducted on the anterior and lateral regions of the mid-thigh six hours postoperatively.

Results: According to isotonic regression and bootstrap CIs, the MEC90 value of bupivacaine for a successful SFICB was 0.123% (95% CI [0.098, 0.191]) and the MEC95 value was 0.188% (95% CI [0.113, 0.223]).

Conclusions: Our study showed that the MEC90 and MEC95 values for bupivacaine administered via an SFICB for analgesia were 0.123% and 0.188%, respectively. One advantage of using lower concentrations of bupivacaine is the associated reduction in quadriceps weakness.

Keywords: Analgesia; Bupivacaine; Local anesthetics; Nerve block; Pain management; Regional anesthesia.

Introduction

The fascia iliaca compartment (FIC) is a funnel-shaped adipose space between the epimysium of the iliopsoas muscle and the fascia iliaca, which covers the muscle but is
not attached to it [1]. The FIC contains the femoral (FN) and lateral femoral cutaneous nerves (LFCN) but not the obturator nerve (ON) [2].

In 1989, Dalens et al. [3] were the first to describe a conventional infrainguinal fascia iliaca compartment block (FICB) for lower-limb orthopedic surgery. Despite earlier publications (3:1 block), this approach has been shown to be incapable of blocking all nerves of the lumbar plexus [4–6]. Stevens et al. first described the suprainguinal fascia iliaca compartment block (SFICB) approach in 2007 [7] and in 2011, Hedbard et al. [8] were the first to define the longitudinal ultrasound (US)-guided SFICB in cadavers. Using this suprainguinal longitudinal approach, studies have shown that the ON, FN, and LFCN can all be anesthetized when a large volume is injected underneath the fascia iliaca [9]. This approach has also proven to be superior to the classic infrainguinal approach [4,10]. The SFICB may provide analgesia comparable to a lumbar plexus block in patients undergoing hip, femur, and upper thigh surgery, which explains why the authors refer to the SFICB as an “anterior lumbar plexus block” [8,9,11].

Some studies on the minimal effective volume (MEV) for the SFICB have also been performed, but none are available on the minimum effective concentration (MEC) of various local anesthetic agents [2,12,13]. For patient safety, particularly in patients who are elderly and frail, determining the lowest clinically significant concentration that blocks the major nerves targeted by the SFICB is critical and may provide an advantage by minimizing block-induced complications such as muscle weakness, local anesthetic systemic toxicity, and myotoxicity.

In this assessor-blinded dose-finding study, we aimed to detect the MEC90 and MEC95 of bupivacaine for a single-injection SFICB in patients undergoing arthroscopic anterior cruciate (ACL) ligament repair.

## Materials and Methods

### Study design

In this study, we investigated the MEC of bupivacaine at a fixed volume of 40 ml that achieved 90% and 95% blockade success in a population of patients undergoing arthroscopic knee surgery.

To achieve study homogeneity, all surgeries were performed by the same surgeon (LK) and the same anesthetist performed all blocks (ST). A designated participant prepared the predetermined concentration of bupivacaine. The concentration was concealed from the patient, anesthesiologist, surgeon, data collector, and evaluator (CG).

This study was approved by the local ethics committee (OMUKAE:2021/630) and the Ministry of Health (TTTCK:22-AKD-08). Following registration at clinicaltrials.gov (NCT05408585), the study was conducted between June 7, 2022 and February 27, 2023 in accordance with the principles of the Declaration of Helsinki (2013), and all patients involved in the study provided written informed consent.

This study was prospectively conducted at a tertiary hospital (Samsun University Education and Research Hospital) and included American Society of Anesthesiologists (ASA) Class I–II patients (aged 18–65 years) with a body mass index (BMI) between 19 and 30 kg/m² scheduled for ACL repair under spinal anesthesia. Patients with contraindications for regional anesthesia (e.g., bleeding-coagulation disorders, infection at the injection site) were excluded, as were patients with neurological or psychiatric diseases that would impair pain assessment, orientation-cooperation issues, or a history of allergy to local anesthetics. To homogenize the samples, cases with a surgical duration < 30 min or > 60 min were excluded from the analysis.

Only the researcher responsible for randomization and drug preparation had access to the block success status of the patients during service follow-ups. The biased-coin design up-down sequential method (BCD-UDSM) was used, with the previous patient’s block success determining the bupivacaine concentration to be administered to the next patient. Based on previous studies, the initial concentration of bupivacaine was determined to be 0.25% and the up-down concentration was 0.025% [14–16]. Randomization was performed using the closed-envelope technique: one hundred sealed envelopes were placed in a pouch, 89 of which indicated that the bupivacaine concentration be maintained (89%) and 11 indicated the concentration be reduced (11%). Following a successful block, an envelope was drawn from the bag randomly to determine the following patient’s bupivacaine concentration, with an 11% probability (b = 0.11) it would be decreased by 0.025% and an 89% probability (1-b = 0.89) it would be maintained at the same concentration. If the block failed, the next patient was administered a 0.025% higher concentration of bupivacaine. The same probability was maintained for each patient, as the envelope that was drawn was returned to the bag after each drawing.

### Anesthesia and analgesia management

All patients received standard monitoring (non-invasive arterial blood pressure, electrocardiography, and pulse oximetry) and none received any premedications. All patients received spinal anesthesia with 12–15 mg of heavy bupivacaine (2.4–3.0 ml) without
an adjuvant via a midline approach at the L4–L5 interval. All arthroscopic ACL repair surgeries were performed by a single expert surgeon using the same surgical approach.

All patients underwent standard preoperative, perioperative, and postoperative analgesia protocols. At the conclusion of surgery, each patient received 20 mg intravenous (IV) tenoxicam and 1 g IV acetaminophen. The postoperative analgesia regimen consisted of IV tenoxicam every 12 h and IV paracetamol every 8 h.

**Block performance**

Since we excluded long- and short-term surgeries (< 30 min, > 60 min) and could not predict the complications that may develop during the operation, the block procedures were performed postoperatively under standard ASA monitoring in the post-anesthesia care unit (PACU). All blocks were performed by an experienced anesthesiologist who had successfully completed the procedure (SFICB) at least 100 times previously.

The patients were placed in the supine position after skin disinfection and draping, and a high-frequency linear US transducer (10–18 MHz, Esoate MyLab™30Gold) was placed longitudinally at the level of the anterior superior iliac spine. The iliacus muscle and the overlying hyperechoic fascia iliaca were visualized by shifting the US probe in the caudal and medial directions. The US transducer was positioned slightly obliquely superomedially and inferolaterally and the internal oblique (cephalad) and the sartorius (caudad) muscles overlying the iliacus muscle were visualized, yielding a “bow-tie sign” image. The deep circumflex iliac artery, which is an important ultrasonographic landmark, was identified. In this position, an 80-mm block needle (Vygon Echoplex, 85 mm, 21 G) was advanced from the transducer’s caudal side using the in-plane technique, and 0.5 ml of the prepared local anesthetic solution was administered between the fascia iliaca and iliacus muscle with real-time US guidance (Fig. 1). The injection site was confirmed on US imaging. All patients then received a 40-ml local anesthetic injection at a predetermined concentration. Patients were monitored in the PACU for 20 min after the block and then transferred to the ward.

**Patient follow-up**

A blinded anesthetist conducted patient follow-ups in the ward. This anesthetist was not involved in any aspect of determining the bupivacaine concentration for the block, the preparation or administration of the block, or the surgical procedure. The exclusive role of the anesthetist was limited to conducting postoperative service follow-ups at 6, 12, 18, and 24 h postoperatively. Similar to the study conducted by Aliste et al. [14], our first patient follow-up was planned to be performed 6 h postoperatively to ensure that spinal anesthesia had worn off and to evaluate the patient for quadriceps weakness, which can develop due to the block. Moreover, the cutaneous and motor functions of the contralateral thigh were examined and compared 6 h postoperatively to confirm that quadriceps weakness was not due to spinal anesthesia. During patient visits at 6, 12, 18, and 24 h postoperatively, pain was assessed using the Numeric Rating Scale (NRS). Additionally, nurses assessed pain during the hourly patient follow-ups in the ward. At these intervals, block success was evaluated using the pinprick score, pain intensity using the NRS, and quadriceps muscle weakness using the Bromage score. Patients with an NRS

![Fig. 1. (A, B) Relevant sonoanatomy for ultrasound-guided suprainguinal fascia iliaca compartment block (SFICB). (A) Natural ultrasound image of the SFICB. (B) Sonoanatomy of the muscles and fascia during an SFICB. The dashed white line represents the fascia iliaca, and the black arrow indicates the deep circumflex iliac artery. SC: subcutaneous tissue, SM: sartorius muscle, IOM: internal oblique muscle, IM: iliacus muscle, IB: iliac bone, LA: local anesthetic.](https://doi.org/10.4097/kja.23710)
score ≥ 4 received 50 mg of IV tramadol as a rescue analgesic.

To examine sensory block, the pinprick test was conducted using a 27-gauge hypodermic needle (0 = no sensory block; 1 = tactile sense present, no pain; 2 = no tactile sense, no pain). The mid-thigh was assessed separately in three quadrants: the anterior, lateral, and medial. Blockage of the FN, LFCN, and ON was recorded separately. The pinprick test conducted 6 h postoperatively was used to determine block success: the block was considered “successful” if the pinprick score was 1 or 2 in the anterior and lateral parts of the mid-thigh and unsuccessful or “failed” if the pinprick score was 0 in the anterior or lateral parts of the mid-thigh. The medial aspect of the thigh was evaluated and the results were documented; however, these findings were not used to determine block success. The Bromage score was used to assess the motor weakness of the quadriceps muscle (0 = full flexion of feet and knees, 1 = only able to move knees, 2 = only able to move feet, and 3 = unable to move feet or knees). A Bromage score of 2–3 at 6 h postoperatively was classified as “quadriceps muscle weakness.”

Outcome measurements

The primary outcome of the study was block success as this was used to determine the bupivacaine concentration administered to the subsequent patient (BCD-UDSM). The secondary outcomes included quadriceps muscle weakness, NRS scores, total number of analgesics required in 24 h, opioid-related side effects (nausea/vomiting), and block-related complications (vascular puncture, hematoma, local anesthetic toxicity, etc.).

Statistical analysis

This dose-finding study aimed to estimate the MEC90 and MEC95 for the US-guided SFICB. Based on the up-and-down sequential method described by Dixon [15,16], the first patient received bupivacaine at a concentration of 0.25%. The sample size for our study was dynamically determined using the BCD-UDSM, targeting a minimum of 48 successful blocks based on the dose-block success ratio observed in our previous cases. To accommodate for potential losses and setbacks during follow-up, we increased the sample size by 30%, aiming for 63 successful blocks. This approach aligns with recommendations in the literature and our clinical experience, ensuring a robust study while meeting the ethical requirements for maximum patient enrollment [15]. In comparable studies using the biased-coin model, sample size ranges between 50 and 70 were used [17–20].

Analyses were performed using R version 4.2.2 (R Foundation for Statistical Computing). Patient characteristics and results were reported using descriptive tests. The MEC90 and MEC95 were calculated using isotonic regression (updown package, version 0.1.0). To calculate the 95% CI, the data frame was bootstrapped 2000 times (boot package, version 1.3-28.1). A P value < 0.05 was considered statistically significant.

Results

Seventy participants were recruited and assigned to the study groups (Fig. 2). The demographic characteristics of the patients are delineated in Table 1.

According to isotonic regression and bootstrap CIs, the MEC90 and MEC95 values of bupivacaine for a successful SFICB were 0.123 (95% CI [0.098, 0.191]) and 0.188 (95% CI [0.113, 0.223]), respectively. Of the total 70 blocks performed, 63 were successful and seven were unsuccessful. Additionally, sensory loss was observed in 36 patients, demonstrating the efficacy of the ON block. Table 2 shows the proportion of patients that exhibited successful blocks along with observed ON block efficacy according to the bupivacaine concentration. The number of failed blocks according to bupivacaine concentration was as follows: one patient at 0.225%, one patient at 0.15%, one patient at 0.125%, one patient at 0.1%, and three patients at 0.075%. Five of the failed blocks were conducted on males and two were conducted on females. Fig. 3 depicts all the blocks applied in the study and their success statuses.

Motor weakness was noted in 48 patients at 6 h postoperatively. In 33 of these patients, motor weakness resolved in subsequent follow-ups but persisted for up to 24 h in the remaining 15 patients. In the first 9 h of follow-up, all patients reported NRS scores < 4. After 9 h postoperatively, 9 patients reported an NRS score of 4. After the administration of rescue analgesics, the NRS score decreased to < 4 in all patients. NRS scores according to the bupivacaine concentration are presented in Table 3. No patient received more than one rescue analgesic during the first 24 h postoperatively, and all patients who required rescue analgesics did so at 9 h postoperatively or later. Table 2 shows the number of patients who required rescue analgesia according to the bupivacaine concentration. None of the patients experienced nausea or vomiting. No complications related to the spinal anesthesia or SFICB occurred in the PACU or in the ward up to 24 h postoperatively. Table 2 shows the number of successful and unsuccessful blocks; observed response rate; and the number of patients with successful ON blocks, quadriceps weakness, and requiring rescue analgesics according to the bupivacaine concentration.
**Table 1.** Patient Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
<th>Median (Q1, Q3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>30.8 ± 9.5</td>
<td>29 (23, 36)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>173.9 ± 5.7</td>
<td>175 (172, 178)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78.2 ± 5.9</td>
<td>79 (74, 82)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.8 ± 1.9</td>
<td>25.8 (24.7, 27.3)</td>
</tr>
<tr>
<td>Surgical duration (min)</td>
<td>48.4 ± 4.3</td>
<td>47 (46, 52)</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>10/60</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, median (Q1, Q3) or number of patients. BMI: body mass index.

**Discussion**

Our study revealed that the MEC90 and the MEC95 values of bupivacaine for the SFICB in arthroscopic knee surgeries was 0.123% and 0.188%, respectively. The incidence of SFICB-related motor weakness appears to be higher at relatively high bupivacaine concentrations.

Postoperative pain varies in intensity and duration based on factors such as surgical type, individual pain tolerance, and efficacy of pain management. Adequate perioperative pain management is crucial because poorly managed pain can prolong recovery, increase complications, and impact the overall patient experience. Consequently, a comprehensive approach to postoperative pain management should be adopted that incorporates both pharmacological and non-pharmacological interventions. In this study, a MEC analysis of the SFICB was conducted.

Studies on the MEC and MEV in relation to regional anesthesia

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**Fig. 2.** Flowchart of the study.
Fig. 3. The up-and-down sequence. The black dots represent successful blocks and the white dots represent unsuccessful blocks with varying concentrations of bupivacaine. The horizontal lines represent the calculated minimum effective bupivacaine concentrations. MEC: minimum effective concentration.

Table 2. Observed Response Rates

<table>
<thead>
<tr>
<th>Bupivacaine concentration</th>
<th>Total blocks</th>
<th>Successful blocks (response rate)</th>
<th>Patients with obturator nerve block</th>
<th>Patients requiring rescue analgesia</th>
<th>Quadriceps muscle weakness at 6 h</th>
<th>Quadriceps muscle weakness at 24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25%</td>
<td>7</td>
<td>7 (100)</td>
<td>2</td>
<td>2</td>
<td>7 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>0.225%</td>
<td>8</td>
<td>7 (87)</td>
<td>3</td>
<td>-</td>
<td>7 (87)</td>
<td>3 (42)</td>
</tr>
<tr>
<td>0.2%</td>
<td>6</td>
<td>6 (100)</td>
<td>2</td>
<td>-</td>
<td>6 (100)</td>
<td>5 (83)</td>
</tr>
<tr>
<td>0.175%</td>
<td>9</td>
<td>9 (100)</td>
<td>7</td>
<td>1</td>
<td>9 (100)</td>
<td>5 (55)</td>
</tr>
<tr>
<td>0.15%</td>
<td>11</td>
<td>10 (90)</td>
<td>8</td>
<td>1</td>
<td>10 (90)</td>
<td>2 (20)</td>
</tr>
<tr>
<td>0.125%</td>
<td>11</td>
<td>10 (90)</td>
<td>8</td>
<td>-</td>
<td>8 (72)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>0.1%</td>
<td>12</td>
<td>11 (91)</td>
<td>3</td>
<td>2</td>
<td>1 (8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>0.075%</td>
<td>6</td>
<td>3 (50)</td>
<td>3</td>
<td>3</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Values are presented as number or number (%).

Table 3. Pain Scores according to Bupivacaine Concentrations

<table>
<thead>
<tr>
<th>Bupivacaine concentration</th>
<th>Total blocks</th>
<th>6 h</th>
<th>12 h</th>
<th>18 h</th>
<th>24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25%</td>
<td>7</td>
<td>2 (1, 2)</td>
<td>2 (2, 2)</td>
<td>2 (2, 3.5)</td>
<td>2 (1, 2)</td>
</tr>
<tr>
<td>0.225%</td>
<td>8</td>
<td>2 (2, 2)</td>
<td>2 (1.7, 2)</td>
<td>2 (1, 2)</td>
<td>1 (1, 1)</td>
</tr>
<tr>
<td>0.20%</td>
<td>6</td>
<td>2 (2, 2)</td>
<td>2 (1.2, 2)</td>
<td>2 (1, 2)</td>
<td>1 (1, 1,7)</td>
</tr>
<tr>
<td>0.175%</td>
<td>9</td>
<td>2 (2, 3)</td>
<td>2 (2.3)</td>
<td>2 (2, 2)</td>
<td>2 (1.2)</td>
</tr>
<tr>
<td>0.15%</td>
<td>11</td>
<td>2 (1, 3)</td>
<td>3 (2, 3)</td>
<td>2 (1.5, 2)</td>
<td>1 (1, 2)</td>
</tr>
<tr>
<td>0.125%</td>
<td>11</td>
<td>2 (2.3)</td>
<td>2 (1.5, 2)</td>
<td>2 (1, 2)</td>
<td>1 (1, 2)</td>
</tr>
<tr>
<td>0.10%</td>
<td>12</td>
<td>2 (2, 2.25)</td>
<td>2 (2, 3)</td>
<td>2 (2, 3)</td>
<td>1 (1, 2)</td>
</tr>
<tr>
<td>0.075%</td>
<td>6</td>
<td>2 (1.2, 2.7)</td>
<td>3 (2.25, 3)</td>
<td>3 (2, 3.7)</td>
<td>1 (1, 1)</td>
</tr>
</tbody>
</table>

Values are presented as number or median (Q1, Q3). NRS: Numerical Rating Scale.

Techniques have focused primarily on peripheral nerve blocks [21,22]. As the number of fascial plane blocks performed in clinical practice has increased in recent years, various studies on the MEC and MEV have also been conducted. Similar to other plane and sheath blocks, the volume and concentration of the injected local anesthetic are crucial for the success of the SFICB, for which the local anesthetic is injected between the fascia iliaca and iliacus muscle. Nevertheless, when a high volume of local anesthetic is
required, caution is advised to avoid local anesthetic systemic toxicity, particularly in elderly and frail patients.

Bupivacaine is a potent local anesthetic commonly used for regional anesthesia and pain management. It belongs to the amide class of local anesthetics and is known for its long duration of action, making it suitable for various medical procedures. However, excessive systemic absorption or accidental intravascular injections can lead to bupivacaine toxicity, affecting the central nervous and cardiovascular systems. Symptoms include dizziness, confusion, seizures, and, in severe cases, cardiac arrhythmias or cardiac arrest.

Comparative studies evaluate the effects of different predetermined volumes and concentrations. Gül et al. [23] compared three different volumes of bupivacaine (0.3 ml/kg, 0.4 ml/kg, 0.5 ml/kg) with a fixed 0.25% bupivacaine concentration with the FICB and found that 0.5 ml/kg provides more effective analgesia.

The literature includes MEV studies on cadavers and patients undergoing the SFICB [2,12,13,20]. For example, Zhang et al. [20] determined that the MEV95 of ropivacaine was 34.6 ml for the SFICB. In a cadaveric study, Kantakam et al. [12] found that the MEV90 value required for the diffusion of the dye to the FN, LFCN, and ON was 62.5 ml. In a similar study, Vermeylen et al. [2] reported that the volume of local anesthetic that could reach the FN, LFCN, and ON was 40 ml. The different values of MEV90 reported in the cadaveric study can be attributed to the lack of passive muscle movements in cadavers, the freshness of the cadavers, and the effects of these factors on the spread of the dye [24]. This is an important limitation of human cadaver studies. To our knowledge, this is the first MEC investigation of bupivacaine for the SFICB.

While the local anesthetic is likely to reach the FN and LFCN with the SFICB, involvement of the ON remains unclear. Although involvement of the ON is possible, numerous hypotheses currently exist regarding its “mechanism of action.” The most widely accepted mechanism is the involvement of the ON through cranial spread of the local anesthetic [9]. Another mechanism could be the migration of the local anesthetic from the fascia ilia-
cosaic to the retroperitoneum, close to the iliac vessels and ON [12]. The possible effect of biodynamics due to the passive muscle mobilization on the distribution of local anesthetics itself might also be important.

The most significant disadvantage of most regional anesthesia techniques used in lower extremity surgical procedures is that they may lead to motor block [25]. Carella et al. [26] performed the SFICB on patients undergoing hip surgery and evaluated their walking performance on the first and second postoperative days. In this study, the SFICB had positive results regarding postoperative functional recovery, both in terms of walking performance and incidence of orthostatic intolerance, as well as opioid-sparing effects and reduced opioid-related side effects. The effectiveness of the SFICB has also been investigated in different age groups and has been reported to provide an opioid-sparing effect in hip surgery in elderly and fragile patients [27].

The motor-sparing effect is one of the most influential factors in current studies on patients undergoing knee surgery [28]. Quadriceps muscle weakness may develop even after a single-shot adductor canal blockade if the local anesthetic dose is increased [29]. Therefore, researchers are continually searching for new techniques that preserve motor function while providing effective postoperative analgesia. The 4-in-1 block, modified 4-in-1 block, infiltration between the popliteal artery and capsule of the knee block, and adductor canal block could be included in the newer motor-sparing peripheral nerve block techniques for analgesia after total knee arthroplasty [28,30,31]. In our study, we found that the motor blockage was lower with a lower concentration of bupivacaine, and therefore, the SFICB could be used as an alternative to motor-sparing analgesia in patients undergoing knee surgery.

A local anesthetic injected into the fascia iliaca can similarly reach the FN with the SFICB, resulting in motor block. We assessed quadriceps muscle strength at 6 h postoperatively using the Bromage score and discovered that the incidence of motor block decreased as the local anesthetic concentration decreased (Table 2). The incidence of quadriceps weakness was 23% on average, especially when a bupivacaine concentration < 0.15% was administered. Most studies have evaluated quadriceps muscle weakness after various regional anesthesia techniques, aiming to identify the most appropriate technique for providing adequate analgesia while preserving motor function. For instance, in a study conducted by Vamshi et al. [32] designed to compare quadriceps weakness in patients undergoing total hip arthroplasty, the pericapsular nerve group (PENG) block and the SFICB were each applied to 30 patients. Similar to our study, the authors assessed quadriceps weakness at 6 h postoperatively; however, they used a local anesthetic mixture consisting of 30 ml 0.25% bupivacaine with 1 µg/kg clonidine for the SFICB procedure. They found that five patients in the SFICB group and none in the PENG group had quadriceps weakness and thus reported that the PENG block resulted in less quadriceps weakness than the SFICB. In our study, varying bupivacaine concentrations were administered at a fixed volume of 40 ml. The relatively higher incidence of quadriceps muscle weakness observed in our study could thus be attributed to this higher volume. Consequently, if the SFICB is administered for perioperative analgesia, a lower bupivacaine concentration is
likely advantageous, particularly if early rehabilitation is crucial. At bupivacaine concentrations \( \leq 0.10\% \), quadriceps weakness was negligible or nearly nonexistent.

Our study underscores the vital role of postoperative mobilization in patient care, which is consistent with the existing literature, and emphasizes the potential benefits, including the mitigation of complications, such as deep vein thrombosis and pulmonary embolism. Furthermore, our findings highlight the positive impact of early ambulation on musculoskeletal factors, emphasizing its crucial role in preventing postoperative muscle atrophy and joint stiffness post-surgery [33]. The ongoing search for regional anesthesia techniques that enable early patient mobilization while ensuring effective perioperative pain management is critical. Research into the concentration and volume of relevant regional techniques are a notable focus of these investigations.

This study had several limitations. First, we were unable to record the onset time of analgesia because the patients received the block whilst under the effect of spinal anesthesia, and we were also unable to determine the block duration because we did not observe the patients for more than 24 h. Levente et al. [34] reported that the median duration of a conventional fascia iliaca block with 40 ml of 0.5% ropivacaine is 48 h and can be prolonged by increasing the volume and concentration of the local anesthetic. However, caution is advised to not exceed the limits for local anesthetic systemic toxicity when using high volumes and concentrations [35]. This is particularly crucial for the elderly and fragile patients. Second, we used the pinprick test to evaluate block success even though the use of the pinprick test for sensory testing is controversial. In similar studies using the pinprick test for cutaneous testing among patients and healthy volunteers for an erector spinae plane block, the authors reported highly variable results [36,37]. In addition, evaluating block success using the pinprick test after ON block application is controversial. Bouaziz et al. [38] performed a selective ON block with 7 ml of 0.75% ropivacaine in patients scheduled for knee surgery and stated that cutaneous examination alone was insufficient to determine block success and that the adductor muscle tension should also be evaluated. Third, to assess motor block, more objective and non-biased data can be obtained using techniques such as dynamometry to measure quadriceps muscle strength [39,40].

This study demonstrated that the MEC90 and MEC95 of bupivacaine for the SFICB in arthroscopic knee surgeries were 0.123% and 0.188%, respectively. Reduced motor blockade is an advantage of using a lower concentration of bupivacaine. Further research is needed to determine the efficacy of the SFICB using varying concentrations and various local anesthetic agents.

### Funding
None.

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

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

### Author Contributions
Caner Genc (Data curation; Project administration; Visualization; Writing – original draft; Writing – review & editing)
Serkan Tulgar (Investigation; Methodology; Writing – original draft; Writing – review & editing)
Murat Unal (Investigation; Methodology)
Ahmet Serhat Genc (Investigation; Methodology)
Basar Erdivanli (Software; Validation; Visualization; Writing – original draft)
Kris Vermeylen (Writing – original draft; Writing – review & editing)
Ersin Koksal (Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing)

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### References


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Introduction

With the increasing rates of cesarean section (CS) worldwide, there has been growing interest among clinicians on the effective management of postoperative pain following CS [1]. Adequate postoperative pain control is crucial for promoting mobility, ensuring emotional well-being, and preventing chronic pain. Insufficient pain control in the postpartum period negatively affects maternal birth experiences and hinders newborn care.
and breastfeeding [2,3]. Given the major impact of postoperative pain on newborn health and maternal–neonate bonding, diligent efforts by clinicians are required to achieve optimal analgesia [3,4]. Programmed intermittent epidural bolus (PIEB) infusion is a novel technique that delivers local anesthetics at programmed intervals and has gained increasing popularity as a form of labor analgesia [5–7]. Previous studies on PIEB for labor analgesia demonstrated that it reduced the incidence of motor blockade [5,6], decreased local anesthetic consumption [5], and yielded comparable or improved pain control than continuous epidural infusion (CEI) [5,6]. Furthermore, two studies comparing PIEB and CEI for post-CS analgesia reported that the PIEB also provided effective analgesia, reduced ropivacaine consumption, and decreased the need for patient-controlled epidural analgesia (PCEA) [8,9]. However, the available evidence is not sufficient to recommend PIEB for post-CS analgesia. In addition, the optimal regimen of PIEB for post-CS analgesia has not yet been established.

In this study, we aimed to compare the analgesic effects of PIEB and CEI based on pain scores at 36 h after CS. We hypothesized that PIEB would be a more effective analgesia than CEI after CS. Additionally, we compared total local anesthetic consumption, need for PCEA, and safety profiles between the PIEB and CEI groups.

Materials and Methods

This single-center, prospective, two-arm randomized controlled trial was conducted at the Samsung Medical Center in Korea between October 2022 and April 2023.

Ethics

This study protocol adheres to the Consolidated Standard of Reporting Trials (CONSORT) guidelines and the principles of the Declaration of Helsinki of 2013. The study protocol was approved by the Samsung Medical Center Institutional Review Board (SMC 2022-08-073 on September 15, 2022) and registered prospectively on the Clinical Research Information Services (KCT0007756; September 29, 2022). Informed consent was obtained from all participants prior to their enrollment in the study.

Study participants

Pregnant women scheduled for elective CS under combined spinal epidural anesthesia (CSE) were assessed for eligibility. The inclusion criteria were as follows: age between 19 and 45 years, American Society of Anesthesiologists physical status II, full-term pregnancy, parity with fewer than three previous births, and singleton pregnancy. Patients were excluded from the study if the body mass index was over 40 kg/m², known fetal abnormalities were present, the study protocol could not be understood, or if participation was refused.

Randomization and blinding

Participants were randomly allocated to the CEI (control group) or PIEB groups in a 1:1 ratio. A randomization table with a block size of four was generated using a web service (www.sealedenvelope.com). Allocation information was concealed using a sealed envelope technique by independent staff not involved in the study. The anesthesia nurse sequentially opened the envelope and set up the PCEA infusion pump (Accumate 1200®, Wooyoun Medical Co., Ltd.) according to group allocation in a separate room. With its monitor veiled, the infusion pump was delivered to the post-anesthesia care unit (PACU) to initiate epidural infusion. Participants, anesthesia providers, outcome assessors, and obstetricians were blinded to group assignment.

Anesthesia and postoperative management

In the operating room, CSE was performed, with participants in the lateral decubitus position, according to institutional protocols [10]. A standard sterile technique was followed. An 18-gauge Tuohy needle (Portex® epidural minipack, ICU Medical, Inc.) was inserted in the L2–L3 intervertebral space. The epidural spaces were identified using the loss of resistance technique with air, and a multi-orifice epidural catheter was threaded 4–5 cm into the epidural space. Following epidural catheter placement, spinal anesthesia was performed at the L3–L4 intervertebral space using a 25-gauge Whitacare needle (BD® Whitacare needle, Becton, Dickinson and Company). Confirmation of free flow of cerebrospinal fluid was followed by the intrathecal administration of 8 mg of 0.5% hyperbaric bupivacaine and 100 μg of morphine sulfate to all participants. The block height for surgery was confirmed when the dermatome was desensitized up to T4 and assessed using an alcohol swab. All participants received prophylactic intravenous phenylephrine continuous infusion at a rate of 100 μg/h. Additional phenylephrine boluses (50 to 100 μg) were administered to maintain the mean blood pressure within 20% of the baseline value.

All participants received standardized postoperative analgesia according to the institutional protocol, with the mode of epidural infusion changed based on grouping. Epidural infusion was initiated in the PACU and maintained until postoperative day (POD).
2. Additionally, intravenous ketorolac 30 mg was administered every 8 h for 24 h after surgery; this was then switched to oral acetaminophen 650 mg every 8 h from POD 2 to POD 3. If pain control with PCEA was inadequate, intramuscular ketoprofen 100 mg was administered upon the participant's request. Participants also received regular doses of intravenous ramosetron 0.3 mg every 8 h for POD 2.

**Intervention**

According to an institutional protocol, the regimen for epidural infusion consisted of a mixture of 20 ml of 1,000 μg fentanyl, 40 ml of 0.75% ropivacaine, and 210 ml of 0.9% saline (i.e., total 270 ml of 0.11% of ropivacaine). An epidural infusion pump was initiated in the PACU once the first complaint of pain or resolution of spinal anesthesia to a level of T10 was achieved. Both pumps were equipped with PCEA, allowing a 2-ml bolus with a lockout time of 15 min and a maximum volume of 12 ml. The CEI group received a constant rate of 4 ml/h of 0.11% ropivacaine. In the PIEB group, the infusion pump was programmed to deliver a 4-ml bolus every hour at a rate of 120 ml/h. The first intermittent bolus through the epidural catheter was delivered immediately after connecting the epidural pump. The PIEB dosing guideline was based on our institutional experience. Access to the epidural infusion regimen described above was available to all participants until POD 2; however, the infusion pump was temporarily stopped by nursing staff if the participants reported subjective motor weakness in the lower extremities. The pump was restarted once the motor weakness resolved.

**Measurements and outcomes**

The primary outcome of the study was the pain score at rest at 36 h after CS. Secondary outcomes included pain scores at rest and during mobilization, total volume of epidural infusion, time to first PCEA, total volume of PCEA, number of PCEA requests, incidence of motor blockade, presence of paresthesia in the lower extremity, and postoperative recovery profiles over a 36-h period after CS.

An independent outcome assessor visited each participant and assessed outcomes at a predetermined time. Pain scores at rest were assessed at 1, 8, 24, and 36 h after CS using a numeric rating scale (NRS) (0–10; 0 = no pain, 10 = worst imaginable pain). Pain scores during mobilization were assessed at 8, 24, and 36 h after CS, considering that spinal anesthesia had not fully worn off at 1 h after CS. The incidence of motor blockade and numbness or paresthesia in the lower extremities were assessed at 8, 24, and 36 h after CS. Motor blockade was defined as a score of 1 or more on the modified Bromage score that ranges from 0 to 3 (0 = able to lift legs against gravity, 1 = able to flex knee but unable to flex legs, 2 = able to move feet but unable to flex the knee, 3 = unable to move any joints) [12]. Data for epidural infusion, including the total volume of epidural infusion, time to first PCEA, total volume of PCEA, and number of PCEA requests, were automatically recorded on the epidural pump. The logs on epidural infusion were extracted to an Excel file upon study completion.

Complications related to epidural infusion, such as hypotension, nausea, pruritus, and urinary retention, were evaluated during the epidural infusion. Hypotension was defined as a reduction of 20% or more from the baseline value or a mean blood pressure of less than 65 mmHg. All participants were requested to log the time of the first ambulation, self-voiding, and flatus. Time to voiding was defined as the interval from Foley catheter removal to self-voiding. Urinary retention was defined as self-voiding failure for 6 h after Foley catheter removal. To assess post-CS recovery, participants were asked to complete the Obstetric Quality of Recovery-11, Korean version (ObsQoR-11K) questionnaires and rate their health status using a visual analog scale, 0–100 mm (0 = worst imaginable health, 100 = best imaginable health), at 36 h after CS [13]. Patient-centered outcomes, including satisfaction with postoperative analgesia and recovery, were assessed using the NRS (0 = not satisfied at all, 10 = very satisfied) at 36 h after CS.

**Sample size calculation and statistical analysis**

The sample size was calculated based on the results of a pilot study (unpublished data). In the pilot study, we assessed the pain scores 36 h after CS in the patient using PCEA with the CEI method. The mean pain score at rest at 36 h after CS was 4.5 ± 1.9 (mean ± standard deviation [SD]) on the NRS in the pilot study. We assumed that the pain scores at rest of the PIEB group had to decrease by 1.5 or more [14] to detect clinically meaningful differences compared with the CEI group. With an alpha error of 5% and a power of 90%, 34 participants for each group were required using two-sample t-test. Accounting for a potential dropout rate of 10%, we enrolled 37 participants in each group.

All data were tested for normality using the Shapiro–Wilk test. Normally distributed data are presented as mean ± SD and were compared using two-sample t-test. Non-normally distributed data are presented as median (Q1, Q3) and were analyzed using the Mann–Whitney U test. Categorical variables are presented as the number (%) and were compared using a chi-square test or Fisher's exact test, as appropriate. The NRS data were analyzed using repeated-measures analysis of variance to identify the interaction.
between time and group for variables of multiple testing. Pain scores at each time point were compared using the Mann–Whitney U test. The time-weighted pain score was calculated as the area under the curve (AUC<sub>0–36 h</sub>) of the time–pain score curve for each participant in both groups. For post hoc analysis, the Bonferroni correction was applied in multiple comparisons of pain scores. Statistical significance was set at P < 0.05. All statistical analysis was performed using SPSS® 27.0 (IBM Inc.).

**Results**

Between October 2022 and April 2023, 87 women scheduled for elective CS were assessed for eligibility. Among them, three women did not meet the inclusion criteria, and ten women refused to participate in the study. All enrolled women (n = 74) were randomly assigned to either the CEI or PIEB group and completed the intervention (Fig. 1). There were no significant differences in baseline patient characteristics between the groups (Table 1).

Median pain scores (Q1, Q3) at rest measured at 8 and 24 h after CS were significantly lower in the PIEB group compared with those in the CEI group (0 [0, 1] vs. 2 [1, 3], P < 0.001; 0 [0, 2] vs. 2 [1, 3], P = 0.005, respectively (Fig. 2A). Pain score at rest at 36 h after CS, the primary outcome, was also significantly lower in the PIEB group than in the CEI group (3 [2, 4] vs. 0 [0, 2]; median difference: 2, 95% CI [1, 2], P < 0.001) (Fig. 2A). Pain scores during mobilization were significantly lower in the PIEB group than in the CEI group at all time points (8, 24, and 36 h) (Fig. 2B). Repeatedly measured pain scores at rest had a significant time–group interaction (P < 0.001). In contrast, no significant time–group interaction was observed in pain during mobilization (P = 0.079). The mean time-weighted pain score using AUC<sub>0–36 h</sub> was significantly lower in the PIEB group than in the CEI group (Pain at rest: 65.4 ± 31.4 vs. 27.9 ± 23.4, P < 0.001; Pain during mobilization: 136.3 ± 39.1 vs. 79.7 ± 33.4, P < 0.001).

There were no significant differences in the total volume of epidural infusion, total volume of PCEA, and number of PCEA re-

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**Table 1. Demographic Data and Baseline Characteristics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CEI group (n = 37)</th>
<th>PIEB group (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>35.3 ± 3.2</td>
<td>35.4 ± 3.6</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.1 ± 5.0</td>
<td>162.5 ± 5.1</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.7 ± 10.4</td>
<td>71.0 ± 8.5</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.9 ± 3.4</td>
<td>26.9 ± 3.5</td>
</tr>
<tr>
<td>Primipara</td>
<td>23 (62.2)</td>
<td>19 (51.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reasons for CS</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal presentation</td>
<td>3 (8.1)</td>
<td>2 (5.4)</td>
</tr>
<tr>
<td>Placenta abnormality</td>
<td>7 (18.9)</td>
<td>5 (13.5)</td>
</tr>
<tr>
<td>Repeated CS</td>
<td>14 (37.8)</td>
<td>16 (43.2)</td>
</tr>
<tr>
<td>Maternal choice</td>
<td>7 (18.9)</td>
<td>8 (21.6)</td>
</tr>
<tr>
<td>Others</td>
<td>1 (2.7)</td>
<td>3 (8.1)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number (%). CEI: continuous epidural infusion, PIEB: programmed intermittent epidural boluses, CS: cesarean section.

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**Fig. 1.** Consolidated Standards of Reporting Trials (CONSORT) flow diagram illustrating the participant enrollment and allocation during the study period. CEI: continuous epidural infusion, PIEB: programmed intermittent epidural boluses.
quests between the groups, except for the total volume of PCEA at 24 h (Table 2). The total volume of PCEA administered over a 24-h period was significantly lower in the PIEB group (2 [0, 9]) than in the CEI group (10 [4, 15], P = 0.016). The median time to the first PCEA was significantly longer in the PIEB group (9.0 [5.5, 24.2] h) than in the CEI group (5.3 [2, 10.8] h, P = 0.038).

The satisfaction score for analgesia at 36 h after CS was significantly higher in the PIEB group than in the CEI group (P = 0.018; Table 3). As regards postoperative recovery profiles, participants in the PIEB group showed significantly higher ObsQoR-11K

### Table 2. The Variables of Epidural Infusion and Rescue Analgesic Administration between the CEI and PIEB Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CEI group (n = 37)</th>
<th>PIEB group (n = 37)</th>
<th>Differences (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total volume of epidural infusion (ml)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 h</td>
<td>2 (0, 3.2)</td>
<td>4 (4, 4)</td>
<td>-2 (-2.5, 0)</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>8 h</td>
<td>32 (29.9, 36)</td>
<td>34 (32, 36)</td>
<td>-0.6 (-2.3, 2)</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>24 h</td>
<td>103 (96.0, 110)</td>
<td>96 (94, 100)</td>
<td>7 (1.9, 12.9)</td>
<td>0.068</td>
</tr>
<tr>
<td>36 h</td>
<td>147.9 (138.1, 165.3)</td>
<td>145 (134, 153)</td>
<td>6.9 (-3.4, 18)</td>
<td>0.944</td>
</tr>
<tr>
<td>Ropivacaine dose per h (mg/h)</td>
<td>4.9 (4.7, 5.4)</td>
<td>4.7 (4.5, 5.1)</td>
<td>0.2 (0, 0.4)</td>
<td>0.124</td>
</tr>
<tr>
<td>Time to first PCEA (h)</td>
<td>5.3 (2.0, 10.8)</td>
<td>9.0 (5.5, 24.2)</td>
<td>-3.9 (-7.7, -0.1)</td>
<td>0.038</td>
</tr>
<tr>
<td>Total volume of PCEA (ml)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 h</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>8 h</td>
<td>2 (0, 4)</td>
<td>0 (0, 3)</td>
<td>0 (0, 2)</td>
<td>0.612</td>
</tr>
<tr>
<td>24 h</td>
<td>10 (4, 15)</td>
<td>2 (0, 9)</td>
<td>6 (0, 10)</td>
<td>0.016</td>
</tr>
<tr>
<td>36 h</td>
<td>14 (6, 32)</td>
<td>7 (3.5, 17)</td>
<td>6 (0, 12)</td>
<td>0.096</td>
</tr>
<tr>
<td>The number of PCEA request*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 h</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>8 h</td>
<td>1 (0, 3)</td>
<td>0 (0, 2)</td>
<td>0 (0, 0)</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>24 h</td>
<td>5 (2.5, 11.5)</td>
<td>1 (0.5, 8.5)</td>
<td>3 (0, 5)</td>
<td>0.085</td>
</tr>
<tr>
<td>36 h</td>
<td>8 (5, 20)</td>
<td>4.5 (2, 19.5)</td>
<td>2 (-1, 6)</td>
<td>0.950</td>
</tr>
<tr>
<td>Rescue analgesic requirement</td>
<td>0 (0, 1)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>0.606</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3). *Individual P value was adjusted using a Bonferroni correction. CEI: continuous epidural infusion, PIEB: programmed intermittent epidural boluses, PCEA: patient-controlled epidural analgesia.
scores compared with those for participants in the CEI group (87.0 ± 15.2 vs. 73.0 ± 16.9; mean difference: −14, 95% CI [−21.4, −6.5], P < 0.001). Differences in each item of the ObsQoR-11K between the groups is presented in Supplementary Fig. 1.

The incidence of adverse events, such as hypotension, nausea, pruritus, urinary retention, and paresthesia in the lower extremities, was not significantly different between the groups (Table 3). Notably, motor blockade, assessed within 36 h after CS, was observed in 14 participants (37.8%) in the CEI group, whereas only one participant (2.7%) in the PIEB group experienced motor blockade (P < 0.001). In the PIEB group, epidural catheter repositioning was needed in two participants (5.4%) due to unilateral block. Epidural catheter occlusion occurred in one participant (2.7%) in each group. No other adverse events were observed in both groups during the study period.

### Discussion

Our findings demonstrated that PIEB provided more effective analgesia 36 h after CS than CEI without increasing the risk of motor deficits. The superior analgesic effects of PIEB were observed in pain scores at rest and during mobilization. In addition, PIEB was associated with a lower incidence of motor blockade, longer time to first PCEA, a lower volume of PCEA during the 24 h following CS, and higher maternal satisfaction with pain relief.

Our findings are consistent with those of previous studies showing that PIEB yielded more effective analgesia after CS than CEI [8,9]. Specifically, a previous study reported that PIEB using a 6-ml bolus of 0.1% ropivacaine every hour reduced the pain score of uterine contraction after CS compared to that with CEI (6 ml/h) [8]. The greater analgesic effect of PIEB over CEI can be attributed to the difference in local anesthetic spread in the epidural space. In PIEB, the higher bolus delivery rate generates a higher injection pressure of local anesthetics [15,16]. A cadaveric study demonstrated that local anesthetics tended to spread more evenly in the epidural space when administered by bolus injection compared with continuous infusion, and the spread was correspondingly uniform with high injection pressure [17]. Moreover, studies in porcine models have shown that bolus epidural injection of a dye solution produced a more extensive longitudinal and circumferential spread compared with continuous infusion, suggesting that PIEB can be more evenly distributed in the epidural space.

### Table 3. Perioperative Clinical Outcomes between the CEI and PIEB Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CEI group (n = 37)</th>
<th>PIEB group (n = 37)</th>
<th>Differences (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satisfaction for analgesia (0-10)</td>
<td>8 (7, 10)</td>
<td>10 (9, 10)</td>
<td>−1 (−2, −1)</td>
<td>0.018</td>
</tr>
<tr>
<td>Satisfaction for recovery (0-10)</td>
<td>8 (7, 9)</td>
<td>9 (8, 10)</td>
<td>−1 (−1, 0)</td>
<td>0.067</td>
</tr>
<tr>
<td>ObsQoR-11K (0-10)</td>
<td>73.0 ± 16.9</td>
<td>87.0 ± 15.2</td>
<td>−14.0 (−21.4, −6.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Global health status (0-100)</td>
<td>70 (60, 80)</td>
<td>80 (70, 90)</td>
<td>−6 (−15, 0)</td>
<td>0.049</td>
</tr>
<tr>
<td>Time to first flatus (h)</td>
<td>18.8 (11.3, 23.5)</td>
<td>14.7 (10.3, 25.8)</td>
<td>2.1 (−2.8, 7.0)</td>
<td>0.099</td>
</tr>
<tr>
<td>Time to voiding (h)</td>
<td>3.8 (3.0, 4.0)</td>
<td>3.5 (1.8, 4.0)</td>
<td>0.5 (0, 1)</td>
<td>0.129</td>
</tr>
<tr>
<td>Time to ambulation (h)</td>
<td>26.3 ± 2.0</td>
<td>25.8 ± 2.1</td>
<td>0.5 (−0.5, 1.5)</td>
<td>0.306</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4 (10.8)</td>
<td>6 (16.2)</td>
<td>0.736</td>
<td></td>
</tr>
<tr>
<td>1/8/24/36 h h</td>
<td>1/1/2/2</td>
<td>1/1/3/1</td>
<td>&gt; 0.99</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (16.2)</td>
<td>6 (16.2)</td>
<td>&gt; 0.99</td>
<td></td>
</tr>
<tr>
<td>1/8/24/36 h h</td>
<td>0/4/3/1</td>
<td>0/3/3/1</td>
<td>&gt; 0.99</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>22 (59.5)</td>
<td>22 (59.5)</td>
<td>&gt; 0.99</td>
<td></td>
</tr>
<tr>
<td>1/8/24/36 h h</td>
<td>2/10/17/9</td>
<td>3/10/14/6</td>
<td>&gt; 0.99</td>
<td></td>
</tr>
<tr>
<td>Antihistamine requirements</td>
<td>5 (13.5)</td>
<td>8 (21.6)</td>
<td>0.240</td>
<td></td>
</tr>
<tr>
<td>Urinary retention</td>
<td>2 (5.6)</td>
<td>0 (0.0)</td>
<td>&gt; 0.99</td>
<td></td>
</tr>
<tr>
<td>24/36 h h</td>
<td>2/0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor blockade</td>
<td>14 (37.8)</td>
<td>1 (2.7)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>8/24/36 h h h</td>
<td>5/10/6</td>
<td>1/0/0</td>
<td>&gt; 0.99</td>
<td></td>
</tr>
<tr>
<td>Paresthesia in the lower extremity</td>
<td>4 (10.8)</td>
<td>3 (8.1)</td>
<td>&gt; 0.99</td>
<td></td>
</tr>
<tr>
<td>8/24/36 h h h</td>
<td>1/4/1</td>
<td>0/3/1</td>
<td>&gt; 0.99</td>
<td></td>
</tr>
<tr>
<td>Epidural catheter repositions</td>
<td>0 (0.0)</td>
<td>2 (5.4)</td>
<td>0.493</td>
<td></td>
</tr>
<tr>
<td>Epidural catheter occlusion</td>
<td>1 (2.7)</td>
<td>1 (2.7)</td>
<td>&gt; 0.99</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3), mean ± SD, or number (%). CEI: continuous epidural infusion, PIEB: programmed intermittent epidural boluses, ObsQoR-11K: Obstetric Quality of Recovery-11 Korean version.
Consequently, the greater analgesic effect of PIEB over CEI can be attributed to the uniform spread of local anesthetics in the epidural space due to the higher injection pressure compared to CEI.

In this study, the delivery rate of PIEB (120 ml/h) was relatively low compared with that in previous studies (ranging from 250 to 360 ml/h) [5,8]. We chose a delivery rate of 120 ml/h for PIEB for several reasons. To prioritize the safety of participants, a cautious approach was adopted when configuring the epidural pump settings. A previous study at our institution demonstrated the superior analgesic effect of PIEB over CEI in labor analgesia with a delivery rate of 240 ml/h [11]. Considering the extended duration of epidural infusion and the limited availability of safety data in the CS population, we selected a reduced delivery rate of 120 ml/h, half the rate employed in the aforementioned study. In addition, a higher delivery rate was associated with occlusion of the infusion pump [16], thus prompting us to choose a relatively lower delivery rate. Finally, a previous study showed that PIEB of 100 ml/h had similar analgesia compared to PIEB of 300 ml/h [20], suggesting that a delivery rate of 120 ml/h would be sufficient to achieve effective analgesia.

The most important benefit of PIEB is that it can reduce the incidence of motor blockades [8]. Achieving the conflicting goals of ensuring adequate pain control while avoiding unnecessary sensory block and motor blockade in epidural analgesia for CS presents a major challenge. Indeed, the mechanism by which PIEB reduced the incidence of motor blockade might be attributed to differences in local anesthetic concentrations depending on the injection methods. When given in PIEB, the intraneural concentration of local anesthetics reduces as they diffuse out between bolus intervals. In contrast, the concentration of local anesthetics remains consistently higher in the extraneural spaces in the CEI, generating a concentration gradient with the intraneural space [21]. This concentration gradient causes local anesthetics to persistently move into the intraneural space, leading to motor blockade [16,21]. The lower incidence of motor blockade observed in postpartum women using PIEB in this study may be associated with the benefits of early ambulation, as recommended by the Enhanced Recovery After Surgery (ERAS) guidelines [22,23]. Early ambulation is an important clinical indicator for maternal health and neonatal care as it indicates better postoperative recovery and ensures maintenance of maternal independence during the postpartum period [24].

Another benefit of PIEB presented in previous studies is its local anesthetic-sparing effect [9,25]. Specifically, a previous study comparing PIEB and CEI for post-CS analgesia reported that PIEB (3 ml bolus of 2% ropivacaine every hour) reduced 48-h ropivacaine consumption by 20 mg compared to CEI (3 ml/h), while providing comparable analgesia [9]. However, in our study, as shown in Table 2, there was no significant difference in local anesthetic consumption between the groups. This discrepancy could be explained by methodological differences in the epidural pump start time. In this study, the epidural infusion pump was started at the same time point in both groups, and the infusion pump in the PIEB group was programmed to deliver the first intermittent bolus at the start of the epidural infusion pump. In contrast, in previous studies the first intermittent bolus in the PIEB group was administered 30 min or 1 h later compared to CEI [9,25]. A recent review article also discussed that reduced local anesthetic consumption with PIEB may result from artifacts of epidural pump start times [16]. Another possible reason is the strategy for managing epidural analgesia in our institution. The epidural infusion pump was temporarily stopped by the nursing staff if the participants reported subjective motor weakness in the lower extremities. In the CEI group, seven participants experienced subjective motor weakness, but in the PIEB group, only three participants experienced subjective motor weakness that made the epidural pump off-time longer in the CEI group. In addition, routine multimodal analgesia, including intrathecal morphine and regular acetaminophen that was administered to the patients in our study could have made a negligible difference in local anesthetic consumption.

As an exploratory finding, we noted that the ObsQoR-11K scores related to maternal independence and neonatal care (item number 7: able to mobilize independently; 8: hold baby; 9: feed/nurse baby; 10: look after personal hygiene, see online Supplementary Fig. 1) were significantly higher in the PIEB group compared with those in the CEI group. While our results suggested that a greater analgesic effect and less motor blockade with PIEB might be associated with maternal and neonatal well-being, we cannot provide conclusive evidence.

This study has several limitations. First, we included both parous and multiparous women in our study. Since postpartum pain might be different according to parity, stratified randomization by parity would be ideal to exclude baseline imbalances between groups. However, there was no statistically significant difference in parity in this study. In addition, a previous study reported no significant differences in adequate analgesia and analgesic consumption after CS according to parity [26]. Second, our participants were limited to pregnant women undergoing CS under the CSE technique. Of the neuraxial anesthesia options for CS, spinal anesthesia is preferred in many countries [27–29]. Thus, it is difficult to generalize our results to CS under other anesthetic techniques. Third, the “gold standard” in acute pain management...
following CS is intrathecal or epidural opioids combined with systemic analgesia, rather than the epidural infusion of local anesthetics \[22,23,30\]. Even when employing CSE for CS, the additional epidural infusion of local anesthetics beyond a single-shot technique is not generally encouraged due to concerns about complications, such as infection, hematoma formation, and hindering early ambulation \[30,31\]. However, the findings of this study suggest that the use of PIEB allows for effective pain control without the risk of motor weakness in the lower extremities, addressing the concerns about obstacles to early ambulation. Fourth, the optimal regimen (concentration, volume, interval, and delivery rate) for PIEB has not been determined. According to an institutional protocol, we used the same concentration and volume of epidural solution in PIEB as CEI (4 ml/h of 0.11% ropivacaine). Our results might differ with different anesthetic concentrations, bolus volume, interval, and delivery rates. Further studies are necessary to determine the optimal PIEB setting to maximize its analgesic effect. Lastly, in our study, the reduced incidence of the motor blockade did not shorten the time to first ambulation. The Foley catheter was removed about 20–24 h from the CSE induction time according to obstetrics protocols due to concerns of urinary retention. This might delay ambulation and mobilization in all participants and attenuated the differences in time to the first ambulation between the groups.

In conclusion, postoperative epidural analgesia with PIEB is more effective than CEI in patients undergoing elective CS under CSE. Future work is needed to determine the ideal PIEB settings to optimize its superior analgesic effect after CS.

**Funding**

None.

**Conflicts of Interest**

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

**Data Availability**

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials. Individual participant data and additional data are available from the corresponding author, RAK, on request indefinitely.

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**Supplementary Material**

Supplementary Fig. 1. Numeric rating scale of Obstetric Quality of Recovery-11 Korean version (ObsQoR-11K) 36 h after cesarean section. *indicates P < 0.05. †indicates P < 0.001.

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Neuroprotective effect of erythropoietin on anesthesia-induced neurotoxicity through the modulation of autophagy in Caenorhabditis elegans

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Background: The anti-oxidative, anti-inflammatory, and anti-apoptotic effects of erythropoietin may provide neuroprotective effects. Erythropoietin also modulates autophagy signaling that may play a role in anesthesia-induced neurotoxicity (AIN). Herein, we investigated whether AIN can be attenuated by the neuroprotective effect of erythropoietin in the Caenorhabditis elegans (C. elegans).

Methods: Synchronized worms were divided into the control, Iso, EPO, and EPO-Iso groups. The chemotaxis index (CI) was evaluated when they reached the young adult stage. The lgg-1::GFP-positive puncta per seam cell were used to determine the autophagic events. The erythropoietin-mediated pathway of autophagy was determined by measuring the genetic expression level of let-363, bec-1, atg-7, atg-5, and lgg-3.

Results: Increased lgg-1::GFP puncta were observed in the Iso, EPO, and EPO-Iso groups. In the Iso group, only the let-363 level decreased significantly as compared to that in the control group (P = 0.009). bec-1 (P < 0.001), atg-5 (P = 0.012), and lgg-3 (P < 0.001) were expressed significantly more in the EPO-Iso group than in the Iso groups. Repeated isoflurane exposure during development decreased the CI. Erythropoietin could restore the decreased CI by isoflurane significantly in the EPO-Iso group.

Conclusions: Erythropoietin showed neuroprotective effects against AIN and modulated the autophagic pathway in C. elegans. This experimental evidence of erythropoietin-related neuroprotection against AIN may be correlated with the induced autophagic degradation process that was sufficient for handling enhanced autophagy induction in erythropoietin-treated worms.

Keywords: Anesthesia-induced neurotoxicity; Autophagy; Caenorhabditis elegans; Erythropoietin; Isoflurane; Neuroprotection; Toxicity.

Introduction

Volatile anesthetics can cause apoptosis or degeneration of nervous cells in the developing brain in several experimental animal models [1–3]. This is known as anesthesia-induced neurotoxicity (AIN). Several mechanisms such as rapid increase in oxidative stress [4] and reactive oxygen species [5–7] are known to be two of the causes of AIN. Additionally, the potential role of autophagy is proposed in the AIN [8], and the modulation of autophagy may minimize the AIN [9,10]. Autophagy is a lysosome-mediated pathway for the degradation of misfolded proteins [11]. Recent studies showed the accumulation...
of autophagosomes and increased expression of autophagy-related markers in various pathologic conditions [12–14].

Erythropoietin is a representative hematopoietic cytokine. In the field of neuroscience, erythropoietin is being studied for its neuroprotective function. Erythropoietin is known to inhibit glutamate cytotoxic action, increase the expression of antioxidant enzymes, suppress the production of free radicals, and affect the secretion of neurotransmitters [15–17]. The anti-oxidative, anti-inflammatory, and anti-apoptotic effects of erythropoietin can result in neuroprotection, and it also modulates autophagy signaling [18,19].

Caenorhabditis elegans (C. elegans) does not have a vascular system; therefore, the hematopoietic effect of erythropoietin can be excluded from this model and the neuroprotective effect against AIN can be identified. Additionally, C. elegans is a proper animal model for studying autophagy due to the characterized autophagic genes and reliable visual monitoring of autophagy [20].

Herein, we investigated whether AIN can be attenuated by the neuroprotective effect of erythropoietin. Accordingly, we aimed to identify the step of the genetic pathways related to autophagy that is affected by AIN and protected by erythropoietin in C. elegans.

Materials and Methods

Worm strains, culture, synchronization, and pharmacologic application

Wild-type N2 and adIs2122 [lgg-1p::GFP::lgg-1 + rol-6(su1006)] that were obtained from the Caenorhabditis Genetics Center (Minneapolis, MN, USA) were used. Escherichia coli strain OP50 was seeded in the nutrient growth medium (NGM) petri plates (OP50 plates) and all the worms were maintained on OP50 plates at 20°C. Egg-laying adult worms were incubated for 1 h and removed. Newly laid eggs hatched after 12 h; thus, synchronized L1 larvae were obtained for the next experiments.

Synchronized worms were divided into the following four subgroups: the control, Iso, EPO, or EPO-Iso group. All worms of the Iso and EPO-Iso groups were exposed to isoflurane four times, for 1 h at each larval stage. C. elegans was anesthetized as described previously [21,22]. Briefly, petri plates containing C. elegans were placed in a sealed glass chamber. Thereafter, liquid isoflurane was administered through a port mounted on the glass chamber; the isoflurane vaporized inside, anesthetizing the exposed worms. The isoflurane concentration was 99% effective dose for the worms. The worms of the EPO and EPO-Iso groups were treated with erythropoietin during the development period. Erythropoietin of the designated volume and concentration was spread with OP50 in the NGM plate. The erythropoietin-containing OP50 plates were replaced every 12 h. Erythropoietin concentrations of 3, 10, 30, 100, and 300 IU/ml were tested in each OP50 plate to determine the appropriate neuroprotective erythropoietin concentration (Supplementary Fig. 1), and 5 IU/ml of erythropoietin was used in the subsequent experiments.

Chemotaxis assay

Nine centimeter NGM petri plates were prepared, with the starting (S) point marked at the center, attractant (A) point marked on one side, and control (C) point marked on the other side (Fig. 1). Then, 30 µl of OP50 suspension was seeded at point S.

![Fig. 1. The chemotaxis assay. (A) When approximately 50 worms reached the young-adult stage, they were washed three times with S-basal buffer. (B) The worms were moved to the center (S point) of the chemotaxis petri plate. (C) After 1 h, the chemotaxis index was obtained: (Worm count of A point – worm count of C point)/total count of worms x 100 (%). A: attractant point by placing OP50, S: worm starting point, C: control point, OP50: Escherichia coli strain, CI: chemotaxis index.](https://doi.org/10.4097/kja.23789)
A for the attractant, while points S and C were left unseeded. When approximately 50 worms reached the young adult stage, they were moved to the point S of the chemotaxis petri plate after being washed three times with S-basal buffer. The worms in the chemotaxis plate were allowed to move for 1 h, and the number of worms in each section was counted under microscopy. The chemotaxis index (CI) was calculated using the following equation:

\[
\text{worm count of point A} - \text{worm count of point C} / \text{total count of worms} \times 100 (%). 
\]

Analysis of autophagic events

A synchronized adIs2122 strain expressing lgg-1::GFP was used for the autophagy analysis. They were exposed to isoflurane four times as described above and cultured on erythropoietin-containing NGM petri plates or not according to the group arrangement. When they reached the young adult stage, the transgenic worms were mounted on a 2% agarose pad in M9 buffer containing 0.1% NaN₃, onto microscope slides and imaged using a fluorescence confocal microscope. Autophagic events were observed by evaluating the lgg-1::GFP-positive puncta per seam cell. Five independent experiments were performed and 10 worms were evaluated in each experiment. At least 5–10 seam cells from each worm were examined.

RNA preparation and real-time polymerase chain reaction (PCR)

The erythropoietin-mediated pathway of autophagy was determined by measuring the genetic expression levels of let-363, bec-1, and atg-7 using real-time PCR. RNA was extracted from young adult worms in each group with TRIzol™ reagent (Invitrogen). The quality-controlled RNA (OD 260/280 > 1.5 and OD 260/230 > 1.0) was confirmed by a NanoDrop™ (ND-2000, Thermo Fisher Scientific) and an Agilent 2100 Bioanalyzer™ (Agilent Technologies). The first-strand cDNA was synthesized by Maxima H minus First-strand cDNA Synthesis Kit™ (Thermo Fisher Scientific), and each of the gene-specific primers was as follows:

- let-363 (forward): 5’-TGC TAT CGC TGC ACA GTT TC-3’
- let-363 (reverse): 5’-TGA GCA TCC GAG ATG AGC TTC-3’
- bec-1 (forward): 5’-CTG TCA GCA GCA GTT GAG GT-3’
- bec-1 (reverse): 5’-CGT TCC TCC GTG GCT CAA TGG-3’
- atg-7 (forward): 5’-TGG AGA ATG GTT GCT CAA TGG-3’
- atg-7 (reverse): 5’-TAT AAT TAT AGA TTA CCC TGT TCC ACC A-3’
- atg-3 (forward): 5’-TGG AGA ATG GTT GCT CAA TGG-3’
- atg-3 (reverse): 5’-TGG AGA ATG GTT GCT CAA TGG-3’

GCA AA-3’ (reverse); and pan-actin, 5’-TCG GTA TGG GAC AGA AGG AC-3’ (forward) and 5’-CAT CCC AGT TGG TGA CGA TA-3’ (reverse).

Statistics

Data are presented as the mean ± standard deviation; they were tested for normality using the Shapiro-Wilk test. Normally distributed data were analyzed using a one-way analysis of variance; for post-hoc analysis, Bonferroni or Games-Howell correction was used according to equal or unequal variances, respectively. Statistical analyses were performed using the SPSS® 27.0 version (IBM Co.) and P values of 0.05 were considered statistically significant.

Results

The autophagic marker, lgg-1::GFP, was observed in young adult worms. The control group displayed little localization of lgg-1::GFP (Fig. 2A). An increased lgg-1::GFP expression was observed in the Iso and EPO groups (Figs. 2B and C), suggesting that autophagy in C. elegans was enhanced by either repeated isoflurane exposure or erythropoietin treatment. When C. elegans was pretreated with erythropoietin, the increase of lgg-1::GFP continued even after isoflurane exposure (Fig. 2D). The Iso, EPO, and EPO-Iso groups presented significantly higher numbers of lgg-1::GFP puncta per hypodermal seam cell than did the control group (Fig. 2E).

The up-regulation of autophagy can be either beneficial or harmful to organelles. To discriminate between these two roles, the expression of several autophagy-related genes was evaluated, such as let-363, bec-1, atg-7, atg-5, and lgg-3 in C. elegans (Fig. 3). The let-363 expression was significantly lower in the Iso group than in the control group (P = 0.009); however, the bec-1, atg-7, atg-5, and lgg-3 expressions did not differ significantly between the control and Iso groups. The let-363 expression in the EPO-Iso group was significantly lower than that in the control group (P < 0.001); however, it did not differ significantly from that in the ISO group (P = 0.176). bec-1 (P < 0.001), atg-5 (P = 0.012), and lgg-3 (P < 0.001) were expressed significantly more in the EPO-Iso group than in the Iso groups.

Repeated isoflurane exposure during the developmental period decreased the CI significantly (P < 0.001; Fig. 4) as shown in our previous studies [23,24]. Erythropoietin treatment without isoflurane exposure did not affect the CI. Erythropoietin in the EPO-Iso group could restore the decreased CI by isoflurane significantly (P < 0.001 for ISO vs. EPO-Iso); however, it did not recover the
Fig. 2. The expression pattern of \( lgg-1::GFP \). (A) Control group, (B) Iso group, (C) EPO group, (D) EPO-Iso group, (E) number of \( lgg-1::GFP \) puncta per seam cell. Five independent experiments were performed and 10 worms were evaluated in each experiment. White dashed lines indicate seam cells; 5–10 seam cells were screened for each worm. The scale bar is 20 µm. *P < 0.05 compared to the control group. Other intergroup comparisons revealed no significant differences.

Fig. 3. The expression level of autophagy-related genes. Graphs shown are averages with the standard deviation from five independent experiments including at least six petri plates per group in each experiment. Each petri plate contained at least 50 worms. *P < 0.05 compared to the control group, †P < 0.05 compared to the Iso group.

CI to the level in the control group (P = 0.018 for control vs. EPO-Iso).

**Discussion**

In the present study, repeated isoflurane exposure induced an increase in autophagosome formation without altering the autophagic degradation process in *C. elegans*. Neurotoxic effects were determined on the basis of the decrease in the CI in the isoflurane-treated worms. Erythropoietin pretreatment may reduce the neurotoxic effects of repeated isoflurane exposure by inducing autophagic degradation.

Autophagy is a fundamental degradation process to maintain homeostasis by eliminating misfolded proteins or damaged organelles. Considering that the extinction of autophagy causes axonal degradation and neural death in animal models [25,26], this

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Autophagy is also induced by various stressful conditions, such as nutritional deprivation, hypoxia, endoplasmic reticulum stress, and pathogens [28]. Inhalation anesthesia was proposed to induce autophagy that interestingly plays a dual role, cytotoxic or cytoprotective [9,29]. The role of autophagy in the AIN has been evaluated in previous studies that reported that cognitive impairment or neurotoxicity by sevoflurane was related to excessive autophagy in the brains of young mice and fetal rats [10,30]. Prolonged anesthetic exposure can cause excessive autophagy and apoptosis that ultimately determines neural cell injury by anesthetic agents [31]. In our model, induced autophagy was also presented by repeated anesthesia exposure with decreased CI.

Erythropoietin fundamentally stimulates red blood cells in the bone marrow; however, its role in neuroprotection and neurogenesis has been studied in various neurodegenerative diseases, such as Alzheimer’s [32,33] and Parkinson’s diseases [34,35]. Autophagy is reported as a major neuroprotective mechanism of erythropoietin [36]. Jang et al. [17] demonstrated the erythropoietin-induced neuroprotection showing the experimental evidence that the autophagy-related signaling pathway was enhanced by erythropoietin in the rotenone-induced neurotoxicity model. Additionally, erythropoietin is reported to generate a protective effect by modifying the autophagic activity in oxygen-induced neurotoxicity [37]. Besides the neuroprotective effect of erythropoietin, it activated autophagy in other conditions, such as inflammatory microenvironment [38], spinal cord injury [18], or hepatic steatosis [39].

The neuroprotective effect of erythropoietin in AIN has been reported previously. Erythropoietin treatment attenuated sevoflurane-induced neuronal cell apoptosis in rat cortical neurons, where the other mechanism, the EPOR-Erk1/2-Nrf2/Bach1 signal pathway, was proposed [40]. Single treatment of erythropoietin could reduce both apoptosis and late neurologic disorders in newborn rats exposed to sevoflurane [41]. Autophagy-related neuroprotection by erythropoietin in AIN was first observed in the present study. The gene 

The expression of let-363 changed significantly on repeated sevoflurane and erythropoietin pretreatment. The let-363 in C. elegans that is an ortholog of the target of rapamycin kinase in humans negatively regulates autophagy induction [42]. When considering the decrease of let-363 by sevoflurane and erythropoietin, repeated anesthetic exposure and erythropoietin pretreatment may activate autophagy induction. Additionally, several cellular stresses such as nutrient deficiency, hypoxia, oxidative stress, and accumulation of protein aggregates are known to induce autophagy [28]. Repeated sevoflurane exposure also increased oxidative stress in C. elegans that might have contributed to autophagy induction.

However, the bec-1, atg-5, and lgg-3 levels differed significantly between the Iso and EPO-Iso groups. Although the atg-7 expression did not differ significantly between these two groups, it was increased by EPO treatment. Both bec-1 and atg-7 are related to the autophagic pathway that is involved in vesicle nucleation and expansion, respectively [44]. In the established C. elegans models having pathologic protein aggregates, such as polyglutamine aggregates or human β-amyloid peptides, bec-1 and atg-7 seem to play key roles in their lysosomal degradation and suppresses the accumulation of abnormal intracellular proteins [45,46]. Another autophagy-related gene, atg-5 protects the pathological feature of Parkinson’s disease and restores the autophagy degradation activity in the zebrafish model [47]. In the autophagy process, atg-5 acts on the autophagosome formation by forming a complex with lgg-3 that is an ortholog of ATG12 of the mammalian gene. The forced expression of these four genes was observed significantly

![Fig. 4. Chemotaxis index of each group. Five independent experiments were performed with at least six petri plates per group in each experiment. Each petri plate contained at least 50 worms. *P < 0.05 compared to the control group, †P < 0.05 compared to the Iso group.](https://doi.org/10.4097/kja.23789)
only when *C. elegans* was pretreated with erythropoietin, suggesting that the autophagosome degradation was enhanced concurrently following the autophagy induction in erythropoietin-treated worms. Although autophagy was activated by repeated isoflurane exposure in the Iso group, the autophagic degradation process seemed to be inadequate compared to that in the erythropoietin-treated animals.

This study had several limitations. First, autophagy was not observed sequentially in the course of the multiple anesthetic exposure. Instead, we compared the final status of autophagosomal accumulation and autophagy-related gene expression in each group. Thus, the autophagy-related markers according to the AIN and erythropoietin treatment were limited. It was further difficult to determine whether this was due to cumulative damage, long-lasting effects, or delayed reactions to repetitive isoflurane exposure. Second, only one inhalation anesthetic gas was applied to the worms and the isoflurane concentration was higher than the clinical concentration. The protective effect of erythropoietin on the AIN was found in this experimental setting; however, it is necessary to elucidate whether the same effect can be drawn in other anesthetic agents. Finally, as experimental research, all experiments were performed in a *C. elegans* model. Although it is good to find the genetic expression and protein levels, the clinical evidence was not certain and that requires further clinical research.

In conclusion, erythropoietin showed neuroprotective effects against AIN and modulated autophagic pathways in *C. elegans*. This experimental evidence of erythropoietin-related neuroprotection against AIN may be associated with the induced autophagic degradation process that was sufficient for handling enhanced autophagy induction.

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**Conflicts of Interest**

Bon-Wook Koo has been an editor for the Korean Journal of Anesthesiology since 2023. However, he was not involved in any process of review for this article, including peer reviewer selection, evaluation, or decision-making. There were no other potential conflicts of interest relevant to this article.

**Data Availability**

The dataset generated during and/or analyzed during the current study is available from the corresponding author on reasonable request. The data will be shared beginning 9 to 36 months following publication provided the investigator who proposes to use the data has approval from an Institutional Review Board (IRB), Independent Ethics Committee (IEC), or Research Ethics Board (REB), as applicable.

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**Supplementary Material**

Supplementary Fig. 1. Chemotaxis index according to the erythropoietin concentration. *P < 0.001 compared to the control group; †P < 0.001 compared to the Iso group.

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Use of the Disposcope endoscope for awake orotracheal intubation in an elderly patient with a large vocal cord polyp
-a case report-

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Background: Vocal cord polyps are commonly encountered in the otorhinolaryngology department. The risk of anesthesia is high in patients with large vocal cord polyps. Awake intubation with appropriate airway tools provides a favorable safety profile.

Case: We present the case of a 60-year-old male patient who had been suffering from a large vocal cord polyp for 16 years. Electronic laryngoscopy revealed that the vocal cord polyp was approximately 1.5 cm in diameter. The polyp had a pedicle and demonstrated synchronous motion with respiratory excursion. It covered almost the entire glottic area during inspiration and moved away from the glottis during expiration. A Disposcope endoscope was used for awake tracheal intubation, and the surgery was completed successfully.

Conclusions: The Disposcope endoscope can be a useful option for awake orotracheal intubation in cases of anticipated difficult intubation and difficult facemask ventilation.

Keywords: Airway management; Airway obstruction; Anesthesia; Patient safety; Tracheal stenosis; Vocal cords.

Vocal cord polyps occur commonly in the otorhinolaryngology department. Hoarseness is the predominant clinical manifestation. As the polyps grow larger, some patients develop symptoms such as dyspnea and even the inability to lie flat. Most vocal cord polyps are diagnosed and treated in the early stage; however, a small percentage of patients do not seek medical treatment until the polyps have caused dyspnea or begun to significantly affect their lives. Patients with large vocal cord polyps have a high risk of general anesthesia due to difficult intubation [1]. Intubation after the administration of potent sedatives or muscle relaxants may aggravate the airway obstruction caused by the polyp, which can lead to an emergency difficult airway [2]. In contrast, awake intubation has a good safety profile as both spontaneous ventilation and intrinsic airway tone are maintained before intubation [3]. In our reported case, awake tracheal intubation in an elderly patient with a large vocal cord polyp was performed using a Disposcope endoscope.

Case Report

Written informed consent was obtained from the patient and his family for the publication of this case report. Institutional review board exemption was obtained.
A 60-year-old male patient weighing 87 kg and 170 cm in height visited the otolaryngology outpatient clinic of our hospital for hoarseness and dyspnea. The patient had presented to our hospital 16 years prior with a chief complaint of hoarseness. At that time, the patient underwent electronic laryngoscopy, which led to the diagnosis of a vocal cord polyp. Consequently, a surgical procedure for vocal cord polyp resection using a self-retaining laryngoscope was scheduled. Due to inadequate airway assessment by the anesthesiologist, the tracheal intubation was difficult. Although the patient was successfully intubated using a traditional direct laryngoscope, the multiple tracheal intubations led to glottic edema, posing an increased surgical challenge and ultimately impeding successful surgical treatment of the vocal cord polyp. After discharge, the patient failed to seek further medical attention at an upper-level hospital. Sixteen years later, he visited the otolaryngology clinic of our hospital again with complaints of being unable to sleep on his back for long periods and worsened dyspnea.

The anesthesia-related physical examination revealed normal mouth opening and head and neck mobility. However, the patient’s thyromental distance was found to be < 6 cm, his airway was Mallampati class III, and he had a poor ability to prognath. Electronic laryngoscopy revealed a vocal cord polyp. The polyp had a pedicle and demonstrated synchronous motion with respiratory excursion. It covered > 90% of the glottic area during inspiration and moved away from the glottis during expiration (Figs. 1A and B).

The patient received oxygen via a facemask at a flow rate of 5 L/min after entering the operating room, followed by intravenous dexmedetomidine at 1 μg/kg/h for 10 min, which was reduced to 0.5 μg/kg/h after the loading dose. Sufentanil (0.15 μg/kg) was also administered. First, the oral cavity, oropharynx, and larynx were anesthetized using 2% lidocaine. With the assistance of the Disposcope endoscope (5.0 mm OD, Disposcope TAIWAN) and epidural catheter (Fig. 2), the "spray-as-you-go" method was used to fully anesthetize the base of the tongue, epiglottis, and glottis with 2% lidocaine, and 3 ml of 2% lidocaine was injected into the trachea through the cricothyroid membrane. The patient

Fig. 1. (A) The polyp covering more than 90% of the glottic area during inspiration and (B) moving away from the glottis during expiration.

Fig. 2. The main body of the Disposcope endoscope and the epidural catheter are tied together tightly with sterile transparent tape. The red arrow indicates the tip of the epidural catheter.

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was asked to open his mouth wide, and endotracheal intubation was performed using the Disposcope endoscope. An endotracheal tube (5.5 mm ID, reinforced, Covidien LLC) was passed through the glottis as the patient exhaled. During intubation, the clinician made sure to prevent the tube tip from touching the vocal cord polyp. The patient received intravenous propofol (100 mg), sufentanil (15 μg), and rocuronium (50 mg) immediately after tracheal intubation. The surgery was completed successfully (Figs. 3A and B), and the postoperative pathological report revealed a vocal cord polyp 1.5 cm in diameter. The patient returned to the hospital for electronic laryngoscopy one month after the operation and complete removal of the vocal cord polyp was confirmed (Fig. 3C).

Discussion

According to an extensive review of the relevant literature worldwide, patients with large vocal cord polyps of this size are relatively rare. Consequently, we conducted a comprehensive evaluation of the patient's airway. The patient's history of difficult tracheal intubation, body mass index, anatomical measurements, and preoperative electronic laryngoscopy results all suggested a difficult airway. The 2022 American Society of Anesthesiologists (ASA) Practice Guidelines for Management of the Difficult Airway recommend awake intubation be performed if the patient is suspected to have a difficult intubation and difficult facemask ventilation is anticipated [5]. If intubation is performed after the induction of general anesthesia, intubation failure may lead to displacement of the vocal cord mass, bleeding, and glottic edema [2]. Therefore, awake intubation was performed in this case to avoid difficult facemask ventilation owing to exacerbated respiratory obstruction. The ASA Difficult Airway Guidelines mention that the literature evaluating the optimal sequence of equipment to use during intubation for anticipated difficult airways and the most effective equipment to be attempted first after failed intubation is limited [5]. In the past, the primary choice for awake intubation in patients with anticipated difficult airways was flexible fiberoptics [6]. However, developing proficiency with fiberoptic intubation requires a rigorous learning process and the technique typically requires a substantial amount of time to perform [7]. With advancements in visualization technology, various types of video laryngoscopes and video stylets are now widely used to manage difficult airways. Compared with conventional direct laryngoscopy, video laryngoscopy has a higher intubation success rate, shorter intubation time, and fewer intubation-related complications. However, video laryngoscopy may not be appropriate for patients with limited mouth opening capacity or cervical spinal injuries. A recent study comparing the efficacy of flexible videoscopes, video laryngoscopes, and video stylets for orotracheal intubation under general anesthesia in patients with difficult airways found that video stylets and flexible videoscopes yielded higher rates of successful first-attempt intubations and better glottic exposure than video laryngoscopes [8]. Additionally, the use of video stylets for endotracheal intubation resulted in a significant

Fig. 3. The surgical treatment of the patient. (A) Video-assisted self-retaining laryngoscope image of the surgical area at the beginning of surgery. The red arrow indicates the glottic mass, and the black arrow indicates the endotracheal tube. (B) The operation is almost complete and most of the glottic mass has been removed; the black arrow indicates the transparent cuff of the endotracheal tube. (C) Electronic laryngoscopy images of the patient one month after surgery.
reduction in intubation time compared with both the video laryngoscope and flexible videoscope. Therefore, we recommend the use of a video stylet as the first choice for difficult airway management. Another previous study found that in patients undergoing oral and maxillofacial surgeries, the required procedural time was reduced when nasotracheal intubation was performed using a Disposcope endoscope (which is a type of video stylet) compared with fiberoptic bronchoscopy [9]. Prolonged awake intubation may increase the risk of loss of airway patency in patients owing to the use of sedative and analgesic drugs. In addition, prolonged intubation may increase patient discomfort and the stress experienced by the anesthesiologist [7]. Although the monitors of most video stylets are connected to the stylet, the Disposcope endoscope transmits images wirelessly to the portable screen. Thus, the screen does not move as a result of maneuvering and advancing the tube during the procedure, facilitating the anesthesiologist’s capacity to observe and manipulate effectively. However, the Disposcope endoscope does have some limitations, such as the lack of a working channel for suctioning secretions, which may compromise visualization if considerable secretions are present. This limitation can be overcome by positioning the lens at the Murphy’s orifice of the tracheal tube without moving the lens over the tip and by improving the operational skill [8]. Although Disposcope endoscopes have recently been used for awake nasotracheal intubation [10], to date, reports on the use of Disposcope endoscope for awake orotracheal intubation are limited.

For this case, the epidural catheter was tightly attached to the Disposcope endoscope. As the special shape of the endoscope is consistent with that of the airway, the tongue base, epiglottis, and glottis can be fully anesthetized. Adequate topical anesthesia of the airway can improve the patient’s tolerance to intubation and minimize the stress response. For this case, we chose an endotracheal tube with an inner diameter of 5.5 mm given the large size of the polyp and our concern that a large tube would not pass smoothly through the glottis or would cause the polyp to fall off. In clinical practice, we have observed that passing the Disposcope endoscope, which is tightly attached to the epidural catheter, through the interior of an endotracheal tube with an inner diameter of 5.5 mm can be difficult, even when it is lubricated with liquid paraffin. In this case, the Disposcope endoscope had to be used twice during intubation: first during adequate topical anesthesia of the airway and again during tracheal intubation. If the inner diameter of the tracheal tube is larger than 5.5 mm, a Disposcope endoscope can be used to simultaneously complete topical anesthesia of the airway and tracheal intubation (Figs. 4A and B). To the best of our knowledge, this is the first study to report the use of a Disposcope endoscope to assist in topical anesthesia of the airway. In the future, we aim to develop removable, disposable consumables mounted on video stylets for topical airway anesthesia.

In conclusion, we suggest that awake orotracheal intubation with the Disposcope endoscope can be a useful option for anticipated difficult intubation and difficult facemask ventilation. Future studies should focus on exploring the value of the Disposcope endoscope in various clinical settings.

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Conflicts of Interest

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

Data Availability

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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References

Intraoperative tourniquet-induced hyperthermia in a pediatric patient: a forgotten association -a case report-

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Background: The intraoperative use of tourniquets is associated with several complications, including hyperthermia. We present the first documented case of tourniquet-induced hyperthermia in a pediatric patient at our institution.

Case: A 5-year-old female with no past medical history underwent tendon release surgery for congenital talipes equinovarus under general anesthesia. Following inflation of a pneumatic tourniquet to a pressure of 250 mmHg on her left thigh, the patient experienced a gradual increase in body temperature. Despite the implementation of cooling measures, the temperature continued to increase until it plateaued. The hyperthermia gradually resolved upon deflation of the tourniquet.

Conclusions: Tourniquet-induced hyperthermia should be considered as a potential cause of intraoperative hyperthermia, particularly in the absence of typical signs of malignant hyperthermia. Early recognition and appropriate management, including deflation of the tourniquet and implementation of cooling measures, are crucial for preventing potential complications associated with hyperthermia.

Keywords: Complications; Hyperthermia; Intraoperative monitoring; Orthopedic procedures; Pediatrics; Sequelae; Tourniquets.

Tourniquet-induced hyperthermia is a rare phenomenon that has not been reported previously at our institution. This case report aims to raise awareness about tourniquet-induced hyperthermia as a possible cause of intraoperative temperature elevation and emphasizes the importance of differentiating it from malignant hyperthermia, particularly in the pediatric population. Although this association has been described previously in the literature, it is often not considered in practice [1–3]. Here, we present a comprehensive case description, including patient demographics, anesthesia induction and surgical procedure details, physiological changes and systemic effects of tourniquet use, along with insights into tourniquet-induced hyperthermia.

Case Report

This case report was approved by the Medical Research Center of Hamad Medical Corporation (ID MRC-04-23-566). Written informed consent was obtained from the patient’s family for publication of this case report.

A previously healthy 5-year-old female weighing 18 kg presented for left foot tendon release surgery for congenital talipes equinovarus. Using standard American Society of
Anesthesiologists monitored vital signs, revealing a blood pressure of 87/57 mmHg, heart rate (HR) of 97 beats/min, and peripheral oxygen saturation (SpO₂) of 100% on room air. General anesthesia was induced at 08:05 with 100 mg of propofol, 10 mg of ketamine, and 10 mg of rocuronium. A size 4.5 endotracheal tube was successfully inserted using direct laryngoscopy on the first attempt. After appropriate positioning, a caudal block with 15 ml of 0.125% levobupivacaine was administered. Anesthesia was maintained using sevoflurane inhalation and remifentanil infusion.

Before tourniquet inflation, the patient received 555 mg cefazolin as prophylaxis. Vital signs recorded immediately before the application of the pneumatic tourniquet on the left thigh at 08:58 showed a blood pressure of 82/59 mmHg, HR of 97 beats/min, and SpO₂ of 100%. The patient’s body temperature measured via an oropharyngeal temperature probe was 36.2°C. The tourniquet was inflated to 250 mmHg by the surgeon at 08:59. The surgical plan included left forefoot deformity correction by open lateral calcaneal osteotomy, tibialis anterior tendon release and transfer, and cuboidal osteotomy.

At 09:10, shortly after the start of the surgery, the patient’s measured body temperature increased to 37.5°C. All active warming devices, including the Bair Hugger and fluid warmer, were immediately stopped. However, the temperature continued to rise, reaching 38.2°C at 09:30. Concerned about the possibility of malignant hyperthermia, anesthesia maintenance was switched from sevoflurane to a propofol infusion although no signs of malignant hyperthermia were present, and end-tidal CO₂ remained within normal limits.

Despite these interventions, the temperature increased to 39.2°C at 09:50. To further facilitate cooling, 20 ml of cold normal saline was administered. The temperature remained elevated at 39.0°C until 10:20 and then plateaued at 38.5°C. At 10:50, the tourniquet on the left thigh was deflated, and the patient’s temperature gradually began to decrease. The surgery was completed at 11:00. By 11:20, the patient’s measured body temperature had decreased to 37.2°C, and anesthesia was discontinued. Once the patient regained full consciousness, she was extubated, and transferred to the post-anesthesia care unit (PACU) for postoperative monitoring and recovery (Fig. 1).

During the postoperative period, the patient’s vital signs and laboratory parameters were monitored regularly to ensure contin-

![Fig. 1. Perioperative temperature change in our patient associated with tourniquet use.](https://doi.org/10.4097/kja.23655)
ued recovery. In the PACU, the patient maintained stable vital signs within normal limits, including a temperature of 36.5°C. Additionally, laboratory findings remained within normal limits, with hemoglobin levels at 13.2 g/dl, platelet counts at 375 x 10⁹/L, urea levels at 1.6 mmol/L, creatinine levels at 24 µmol/L, bicarbonate levels at 20 mmol/L, alanine aminotransferase levels at 0.17 µkat/L, aspartate aminotransferase levels at 0.34 µkat/L, and glucose levels at 5.7 mmol/L. These findings indicated that no significant abnormalities or complications were present.

Following the PACU stay for approximately 90 min, the patient was transferred to the regular pediatric ward for continued monitoring and care. On postoperative day 1 the patient was discharged from the ward with normal vital signs, stable laboratory parameters, and no evidence of complications.

Discussion

Pneumatic tourniquets are commonly used in both upper and lower-limb surgeries to minimize bleeding, optimize the view of the surgical field, and expedite surgical procedures. Despite recent technological advances, using surgical tourniquets can result in tissue damage, ischemia/reperfusion injury, and systemic complications [4,5]. These complications significantly affect patient outcomes, including the length of hospital stay. Therefore, anesthesiologists must recognize these potential complications and manage them in a timely manner.

Complications associated with pneumatic tourniquets vary in severity, ranging from minor and self-limiting to severe and potentially fatal. Systemic effects typically manifest upon deflation of the tourniquet cuff. Local effects and complications may result from direct pressure on the underlying tissues or from ischemia in tissues distal to the tourniquet.

Following 1–2 h of ischemia, anaerobic metabolism occurs in the affected limb. These changes include a moderate increase in PaCO₂, lactic acid, and potassium levels, and a decrease in PaO₂ and pH levels [5–7]. Upon tourniquet deflation, metabolites are released into the circulation, which can result in secondary effects on different-body systems. Tourniquet inflation typically results in a temporary increase in the blood volume by approximately 15% and systemic vascular resistance by up to 20%. Consequently, blood pressure and venous return increase; however, these effects typically diminish within 5 min. The vasodilatory effect of metabolites following tourniquet deflation results in decreased blood pressure and central venous pressure, and increased HR. Some metabolites have a direct effect on the heart as myocardial depressants, leading to reduced cardiac output. Such changes are more pronounced with prolonged use of bilateral tourniquets. The release of metabolites upon tourniquet deflation also affects the respiratory system, resulting in an elevation in the end-tidal carbon dioxide tension by approximately 0.1 to 2.4 kPa. However, this increase typically resolves and returns to baseline levels within 10-13 min. Additionally, a rapid rise in PaCO₂ leads to increased cerebral blood flow and intracranial pressure, particularly in poly-trauma patients with traumatic brain injury. Tourniquet use has also been associated with coagulopathy [6,7].

Edmond Bloch was the first to describe the association between tourniquet use and increased body temperature in pediatric patients [1]. He observed an increase in the body temperature of pediatric patients undergoing orthopedic procedures. In some patients, increase in body temperature was dramatic, raising concerns for malignant hyperthermia. To investigate this phenomenon, a retrospective analysis of 56 pediatric patients who had undergone orthopedic surgery was conducted. The findings provided support for an association between tourniquet use and an increase in body temperature, and subsequent studies further confirmed this association [8,9]. This phenomenon is attributed to reduced metabolic heat transfer between the central and peripheral compartments, as well as decreased heat loss from the limb distal to the tourniquet. This effect is more pronounced in cases involving bilateral tourniquets. The main precipitating factor for the increase in core temperature appears to be the duration of tourniquet inflation. Upon tourniquet deflation, a transient decrease in the core temperature occurs resulting from the redistribution of body heat and the return of hypothermic venous blood from the previously constricted limb to the systemic circulation. The thermoregulatory vasodilation process can thus potentially be arrested, causing a drop in both the central and peripheral temperatures. In general, intraoperative hypo- and hyperthermia are associated with a high risk of adverse events, including coagulopathy. Therefore, maintaining the body temperature is the primary goal. Current evidence on the treatment and management of tourniquet-induced hyperthermia is limited. However, management strategies should employ careful monitoring of the temperature; adjustments in tourniquet inflation times; avoidance of extra layers of drapes, active warming devices or fluid warmers; and a reduction in the surgical time [8–11]. Local complications associated with tourniquet use include tissue damage or edema, rhabdomyolysis, thrombosis, digital ischemia, tourniquet-induced neuropathy, compartment syndrome, and post-tourniquet syndrome [5,7].

Our patient exhibited a gradual increase in temperature after tourniquet inflation. Despite the patient’s hemodynamic stability and isolated temperature increase, malignant hyperthermia was suspected. As a precautionary measure, sevoflurane administra-

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tion was halted and propofol infusion was initiated. The implementation of cooling measures did not significantly decrease the patient's temperature. The patient’s hemodynamic status remained stable, the surgery was continued. Upon tourniquet deflation, the body temperature gradually decreased, raising suspicion that hyperthermia was tourniquet-related. The onset of malignant hyperthermia is not always immediate; sometimes, it is insidious. Thus, malignant hyperthermia must always be considered when the body temperature rises during the course of anesthesia. However, other possibilities should also be considered in such situations, including sepsis, metabolic syndrome, adverse drug reactions, central nervous system disturbances, transfusion-related issues, or heatstroke [12].

In conclusion, although rare, tourniquet-induced hyperthermia should be considered in cases of intraoperative temperature elevation after tourniquet use, particularly in pediatric patients. Aggressive warming methods are not advised in pediatric patients who require intraoperative tourniquets. Anesthesiologists should consider the possibility of tourniquet-induced hyperthermia, particularly in cases involving bilateral tourniquets. Prompt identification and differentiation between tourniquet-induced and malignant hyperthermia is crucial for guiding management decisions and preventing unnecessary interventions.

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Data Availability

All data generated or analyzed during this study are included in this published article.

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References

Sudden ventricular fibrillation due to absence of pericardium in left upper lobectomy
-a case report-

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Case Report

Background: Congenital absence of the pericardium (CAP) is a rare cardiac abnormality. As pericardial defects are usually asymptomatic, most cases are diagnosed during surgery or on autopsy. The patient in this case was found to have CAP during thoracoscope.

Case: We present the unusual case of a 69-year-old patient with CAP who experienced sudden ventricular arrhythmia and developed ventricular fibrillation during left upper lobectomy. Surgical operations, the lateral decubitus position, and other external stimuli may be important risk factors for ventricular fibrillation. The patient regained sinus rhythm soon after intrathoracic cardiac compression and pharmacological treatment, including lidocaine spray (2%, 10 ml) administered to the heart surface. The surgery was then completed without any additional instances of ventricular arrhythmia.

Conclusions: Patients with CAP are more susceptible to cardiac-related adverse events during thoracotomy or thoracoscopy. Treatment of ventricular arrhythmias that occur during lung resection in patients with CAP should be emphasized.

Keywords: Amiodarone; Asymptomatic diseases; Lidocaine; Lung; Pericardium; Ventricular fibrillation.

Congenital absence of the pericardium (CAP) is a rare cardiac abnormality with an estimated incidence ranging from 0.007% to 0.015% on autopsy and 0.044% in a surgical case series [1]. CAP can be classified into entire left- or right-side absence, partial left- or right-side absence, and complete absence of the pericardium, the latter of which is the rarest [2]. Because it is usually asymptomatic and imaging findings are atypical, clinicians may have difficulty diagnosing it [2]. Anatomically, the “bare heart” (absence of pericardium) is susceptible to external stimuli from the lung, pleura, and chest wall, especially when in the lateral decubitus position, during mechanical ventilation, and during thoracoscopic surgery. Many case reports [2,3] have shown a correlation between the absence of the pericardium and adverse cardiac events. A heart without the pericardium is particularly susceptible to external physical stimulation. Here, we present the case of a patient with CAP that experienced frequent premature ventricular contractions and sudden ventricular fibrillation during a left upper lobectomy. We obtained the written informed consent from the patient.

Case Report

A 69-year-old male patient (172 cm, 73.5 kg) with a medical history of hypertension
and coronary artery disease was scheduled to undergo a left upper lobectomy for space-occupying lesions in the lung. A preoperative echocardiography demonstrated trivial tricuspid valve regurgitation and normal ejection fraction (62%). The chest computed tomography (CT) revealed a space-occupying lesion in the left upper lung lobe, chronic inflammation in the right upper lung lobe, bronchitis, and emphysema (Fig. 1A). The coronary CT showed right coronary dominance and a severe lesion in the proximal left anterior descending coronary artery with 70% luminal narrowing. Electrocardiography (ECG) results showed sinus bradycardia and an incomplete bundle branch block. However, the patient did not report any significant discomfort and no significant laboratory abnormalities were noted. The patient was given an American Society of Anesthesiologists grade of III. Perioperative anesthesia was maintained using a nerve block combined with general anesthesia.

After entering the operating room, vital signs including ECG, SpO₂, heart rate, respiratory rate, and invasive blood pressure were continuously monitored. The ECG showed sinus rhythm. Anesthesia was induced with etomidate (0.2 mg/kg), rocuronium (0.6 mg/kg), and sufentanil (0.3 mg/kg). After tracheal surface anesthesia, a double-lumen tracheal tube was inserted using a visual laryngoscope. Correct tracheal positioning of the catheter was confirmed using a fiberoptic bronchoscope. The patient was then placed in the right lateral decubitus position. A thoracic paravertebral block was performed under ultrasound guidance at the T7 level. The patient was mechanically ventilated using volume-controlled ventilation with a breath volume of 6 ml/kg using a mixture of gases in proportion to 50% oxygen and 50% air. Anesthesia was maintained with sevoflurane (2%-2.5%) and rocuronium was administered as needed. An arterial blood gas analysis was performed before surgery, with normal results. The circulatory parameters were also stable.

For the procedure, the seventh intercostal space of the axillary midline was used for the endoscope and the fourth intercostal space of the axillary front line was used for the operation. At this time, the ECG showed occasional premature ventricular beats. As the lens entered the pleural cavity, we discovered a complete absence of the pericardium in the heart (Fig. 1B, Supplementary Video 1). The frequency of premature ventricular contractions gradually increased as the surgery continued. The blood pressure became unstable and began to decrease. Ephedrine (6 mg) was administered to improve the blood pressure. The adhesions were separated, freeing the lung lobes. At this time, his heart rate suddenly increased to 110 mmHg and blood pressure decreased to 90/56 mmHg. ECG revealed paroxysmal ventricular tachycardia. Lidocaine (1 mg/kg) was administered immediately. Continuous lidocaine and norepinephrine were then administered using the micropump, at 80 mg/h and 0.06 µg/kg/min, respectively. The blood pressure increased to 121/78 mmHg. As the patient was in the right lateral decubitus position, his heart experienced significant stimulation during the operation. To obtain a more satisfactory surgical field and complete the operation as soon as possible, the surgeon decided to perform an open thoracotomy. Premature ventricular contractions continued to occur frequently after opening the thoracic cavity. ECG showed polymorphic ventricular tachycardia, accompanied by profound hypotension, which was immediately followed by ventricular fibrillation. The patient’s blood pressure decreased to 45/31 mmHg. Intrathoracic cardiac compression was immediately performed: a single hand was extended straight into the thoracic cavity and the heart was inter-
mittently compressed. A continuous intravenous infusion of amiodarone (30 mg/h) and epinephrine (1 mg) was initiated immediately. Fortunately, the patient quickly regained sinus rhythm. Lidocaine spray (2%, 10 ml) was then administered onto the surface of the heart. No further incidences of ventricular arrhythmia occurred for the remainder of the surgery. The patient was extubated in the postanesthesia care unit and was maintained on continuous monitoring. The patient was then returned safely to the ward and discharged on postoperative day 7. No further cardiac-related adverse events were observed at the 1-month follow-up.

Discussion

The pericardium, which comprises two sacs [4], an outer fibrous membranous sac and an inner serous sac that covers the heart and great blood vessels, serves several physiological and protective functions. The pericardium stabilizes the position of the heart inside the thorax by sternopericardial ligament, conferring cardio-protection from mechanical trauma, and acts as a lubricant. CAP is a rare cardiac malformation. Most patients with CAP are asymptomatic. However, some patients may exhibit atypical symptoms such as chest tightness, chest pain, and palpitations [3,4]. The imaging findings are also atypical, making clinical diagnosis of CAP difficult. As with this case, CAP was not diagnosed preoperatively based on clinical manifestations, laboratory findings, or imaging features. However, we did reanalyze the preoperative examinations retrospectively with the help of radiologists. The chest CT had shown evidence of an absence of the pericardium (Fig. 1A); however, CAP remains difficult to diagnose without surgical outcomes. Additionally, the patient had an incomplete bundle branch block and coronary stenosis, both of which may be associated with CAP. Similarly, some studies have reported [1–5] that patients with CAP may also have sinus bradycardia, ventricular tachycardia, incomplete right bundle branch block, and myocardial infarction. Three cases have been reported [1] with patients who presented with sudden death due to cardiac strangulation across a partial left-sided pericardial defect. Additionally, chest radiography in patients with CAP often shows levoposition of the heart. A tendency toward cardiac levorotation may increase the risk of cardiac torsion in left-sided lobectomies or pneumonectomies [6]. Anesthesiologists should be vigilant about various adverse cardiac events associated with the lack of a pericardium. Ventricular fibrillation associated with CAP has been reported previously [7]. In that case, the presumptive diagnosis was anterior or infarction. However, angiography revealed normal coronary arteries. Steinberg et al. [7] hypothesized that acute torsion of the great vessels secondary to cardiac hypermobility could have led to ventricular fibrillation. That patient received five shocks to restore the pulse. In our case, the coronary CT revealed a severe lesion in the proximal left anterior descending coronary artery. This may have led to insufficient myocardial blood supply and cardiac dysfunction. Additionally, the “bare heart” was compressed due to the surgical operation, consisting of a thoracotomy or thorascopic approach. Indeed, any surgery can affect the cardiac conduction system. Surgical stimuli continued throughout the procedure, which corresponded to frequent ventricular arrhythmias. Ventricular arrhythmia may occur during left upper lobectomies in patients with a normal heart due to hypotension, hypovolemia, hypoxemia, and acidosis. However, the blood gas and circulatory parameters were normal before ventricular arrhythmia occurred. Thus, one could hypothesize that surgical stimuli may trigger ventricular arrhythmias. Early in the treatment course, we focused only on intravenous drugs to correct the ventricular arrhythmias. Amiodarone is an effective antiarrhythmic medication frequently used in the treatment of ventricular and atrial arrhythmias that can block potassium channels, which increases the duration of the cardiac action potential. Lidocaine is a Class IB antiarrhythmic agent that exerts its action by blocking sodium channels. It can reduce arrhythmogenic transient depolarization and twitch tension by decreasing the inward sodium current [8]. However, even though amiodarone and lidocaine were administered in this case, ventricular arrhythmias continued to occur frequently before ventricular fibrillation. We concluded that ventricular arrhythmias would continue as long as the stimuli persisted. After ventricular fibrillation, intrathoracic cardiac compression and pharmacological treatments were administered. Fortunately, the patient quickly regained sinus rhythm. Spraying lidocaine on the heart surface is not commonly performed: Lidocaine is an antiarrhythmic drug and effective local anesthetic. Spraying lidocaine on the larynx and bronchi is well known to inhibit the stress response during endotracheal intubation. We believed that spraying lidocaine on the heart surface could enhance the ability of the heart to respond to external stimuli. Lidocaine reduces the frequency of sodium channel opening and decreases the autorhythmicity of the heart by acting directly on the Purkinje cells and ventricular myocytes. It can also block inward potassium rectifier channels in cardiomyocytes and improve the threshold for ventricular fibrillation. The heart becomes less sensitive to external stimuli after lidocaine spraying. We believe that attenuation of stimulation may contribute to the termination of ventricular fibrillation, as no ventricular fibrillation occurred postoperatively. One could hypothesize that the absence of surgical stimuli, which may have initially triggered ventricular fibrillation, contributed to
its termination. In addition, spraying lidocaine on the heart surface has a prompt onset of action. In this case, this administration method did not result in heart block or any other toxic side effects. However, no relevant studies have reported evidence regarding administering lidocaine spray on the surface of the heart, and thus the concentration, dosage, and mechanisms underlying this treatment need to be investigated.

Patients with CAP are more susceptible to ventricular arrhythmia and fibrillation during thoracotomy or thoracoscopy. Intraoperative ventricular arrhythmia in a patient with CAP is described in this case to increase awareness and provide information on its effective management.

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**Conflicts of Interest**

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

**Data Availability**

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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**Supplementary Material**

Supplementary Video 1. A beating heart without the pericardium.

**References**


Comment on “Comparison of the pericapsular nerve group block with the intra-articular and quadratus lumborum blocks in primary total hip arthroplasty: a randomized controlled trial”

Dear Editor,

We read with great interest the research study comparing the pericapsular nerve group (PENG) block with the quadratus lumborum block (QLB) and intraarticular injection in primary total hip arthroplasty by Et et al. [1] in the recent issue of your esteemed journal. We would like to thank the authors for the quality of their work. However, in the best interest of the readers, we would like to discuss certain aspects in the index study that cannot be overlooked and need to be addressed.

First, the total dose of bupivacaine (30 ml of 0.5% bupivacaine) used in the study might exceed the recommended safe dose (2–2.5 mg/kg) in specific subsets, given that the study did not mention the minimum body weight (exclusion criteria of body mass index > 40 kg/m²) of the patients enrolled in the clinical trial [1]. In addition, the study population included geriatric patients (aged up to 85 years), in whom drug pharmacokinetics could have been significantly affected by age-related organ dysfunction, resulting in an increased predisposition to local anesthetic (LA) toxicity.

Furthermore, the volume and concentration of LA agents affect the duration of analgesia provided by any regional block. In the present study, the drug volumes differed among the groups (30 ml of 0.5% for the QLB group, 20 ml of 0.5% for the PENG block group, and 60 ml of 0.25% in the intraarticular group). Additionally, the concentration was reduced to 0.25% in the intraarticular group, unlike the 0.5% used in the other two groups. The authors also did not compare the mean age or age-wise distribution of patients in the respective groups, which can be a confounding factor, as sensitivity to (LA) agents varies with age.

Ropivacaine is a relatively safe drug, and its plasma concentration has been studied to confirm its safety, even at higher doses [2]. Therefore, ropivacaine would have been a better choice for this study, especially at such high doses. Additionally, the authors could have followed up with their patients for chondrotoxicity, which would have added more evidence regarding this LA associated side effect [3].

Pain scores were higher in the intraarticular group than in the other groups at 3 and 6 h postoperatively. With an intraarticular injection of LA, the joint capsule has a greater surface area for drug absorption, which may explain the poor analgesia provided by this block in the initial hours after surgery [3]. In addition, comparing the effect of an intraarticular block on quadriceps muscle function is futile, as drug deposition is limited to the articular surface, and thus does not affect the nerve supply to any muscle.

The sham procedure followed by the authors for blinding is also unclear [1]. The authors state that the ultrasound probe was held in the same position for both the QLB and PENG block. A sufficient pause was allowed to simulate a blunt needle, then a 20-ml syringe with saline and no other medication was administered. If no injection was performed, the surgeon, attending anesthesiologist, and patient could easily determine the allocated group, and blinding would be inadequate. Intraarticular injections were only performed in the intraarticular group; thus, the surgeon, attending anesthetist, and even the patient, who was awake, would not have been blinded.

Finally, the main advantage of the PENG block is its motor-sparing effect, as it blocks only the articular branches of the femoral and accessory obturator nerve, which are sensory nerve fibers [4]. However, clinical reports of inadvertent quadriceps weakness exist in the literature, even after PENG blocks with 20 ml of LA [5]. Yu et al. [5] hypothesized that LA injection more superficially than intended or needle placement medial to rather than posterior to the psoas tendon may result in superficial spreading of a proportion of the LA, which could inadvertently block the femoral nerve or fascia iliaca. According to Giron-Arango et al., the mechanism of the femoral nerve block, especially with volumes greater than 20 ml, could be LA spread between the pectineus and psoas to target the femoral nerve [4]. Therefore, it should not be surprising that almost 50% of patients in the PENG group had paresis at 3 h. Hence, clinicians should be wary of motor weakness after performing a PENG block and verify correct needle positioning and drug volume.

To conclude, we would like to thank Et et al. [1] for their valuable research. We hope that clarifying the points mentioned above will increase the validity of the manuscript.

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Response to “Comment on Single-shot regional anesthesia for laparoscopic cholecystectomies: a systematic review and network meta-analysis”

Dear Editor,

We would like to extend our gratitude to Dr. Raghuraman for his keen interest and invaluable insights [1] pertaining to our research article [2].

We acknowledge that the sentence in the introduction highlighted by Dr. Raghuraman could be confusing. It would be more accurate to state that numerous meta-analyses have examined different facets of laparoscopic cholecystectomy [3], and a subset of them have placed a specific emphasis on pain management and analgesic needs.

Furthermore, we agree with Dr. Raghuraman’s point regarding the disproportionate representation of groups in our study, which rendered the results inconclusive. Indeed, very few studies were included for certain techniques, such as the paravertebral block (2 studies involving 63 patients) and rectus sheath block (3 studies involving 86 patients). In contrast, a larger population was included for other techniques, such as intraperitoneal instillation (1,490 patients across 37 studies). Additionally, not all studies examined all the outcomes, as noted by Dr. Raghuraman.

Therefore, our study should not be considered the final authority on the subject, but rather an initial analysis of the available literature. Of note, a recent publication [4] has proposed a consensus-based core outcome set for research on regional anesthesia. As this would lead to a greater standardization of outcomes and thus enhance the reliability of future meta-analyses, we hope this framework will be adopted in future studies. However, as stated in the above-cited document, only a core set of outcomes were included, and shoulder pain should be included as it is important in laparoscopic cholecystectomy.

In response to Dr. Raghuraman’s last question, we would like to clarify that the mechanism of action of the transverse abdominis plane block is significantly different from that of the rectus sheath block. However, the most effective interventions in our meta-analysis were regional techniques that addressed visceral pain, such as the paravertebral, quadratus lumborum, and erector spinae plane blocks. This can be clearly observed in Table 2 of the original document, which shows the treatment rankings [2]. Although the paravertebral block did not rank high for most outcomes, this was primarily because of the limited number of studies and participants included in the analysis.

Further research is required to determine the optimal regional techniques for laparoscopic cholecystectomy. However, we advocate for anesthesiologists to adopt a multimodal strategy that addresses somatic, visceral, and shoulder pain, as highlighted by Dr. Raghuraman.

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・ The materials and methods section should include sufficient details of the design, subjects, and methods of the article in order, as well as the data analysis methods and con-

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

7http://www.amamanualofstyle.com/
trol of bias in the study. Sufficient details need to be addressed in the methodology section of an experimental study so that it can be further replicated by others.

- When reporting experiments with human or animal subjects, the authors should indicate whether they received approval from the IRB for the study and the IRB approval number needs to be provided. When reporting experiments with animal subjects, the authors should indicate whether the handling of the animals was supervised by Institutional Board for the Care and Use of Laboratory Animals. "American Society of Anesthesiologists physical status classification" should not be abbreviated. As a rule, subsection titles are not recommended.

- Clearly describe the selection of observational or experimental participants. Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). For additional information, please visit http://www.icmje.org/about-icmje/faqs/icmje-recommendations/.

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

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

- Exceptions
A. The unit for volume is "L", others in "dl, ml, μl".
B. The units for pressure are mmHg or cmH₂O.
C. Use Celsius for temperature
D. Units for concentration are M, mM, μM.
E. When more than 2 items are presented, diagonal slashes are acceptable for simple units. Negative exponents should not be used.
F. Leave 1 space between number and units.

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

- Ions
Ex) Na⁺ [O], Mg²⁺ [O], Mg⁺⁺ [X], Mg⁺⁺ [X]

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

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

- If necessary, the editorial board may request original documents of the references.
- Six authors can be listed. If more than 6 authors are listed, only list 6 names with ‘et al.’
- Provide the start and final page numbers of the cited reference.
- Abstracts of conferences are not allowed to be included in the references. The American Society of Anesthesiologists (ASA) refresher course lecture is not acceptable as a reference.
- Description format
  A. Regular journal
  Author name. Title of journal Name of journal published year; volume: start page-final page.
  B. Monographs
  If reference page is only 1 page, mark ‘p’.
  Mark if it is beyond the 2nd edition.

- C. Chapter

- D. Electronic documents
  E. Online journal article

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

Table
- Type or print each table on a separate sheet of paper.
- Number tables consecutively in the order of their first citation in the text.
- Supply a brief title
  Tables should be more than 4 rows and should not be over 1 page.
- Except for titles and first letters, all of the text in the tables should be written in small alphabetic letters.
- In demographic data, sex would be provided as M/F, and age in yr. Data of year, weight, height, and any other units would be provided with 1 decimal place.
- ‘ ± ’ sign in the upper column of table should be lined up with the lower column.
- Footnotes should be provided consecutively in order of the cited tables or statistics.
- Marks for footnote should be given in order of *, †, ‡, §, ¶, **, ††... When marks are used to explain items of the table, indicate them with superscripts.
- Define all abbreviations except those approved by the International System of Units. Define all abbreviations every
time they are repeated.

③ Legends for figures and photographs
- All of the figures and photographs should be described in the text separately.
- The description order is the same as in the footnotes in tables and should be in recognizable sentences.
- Define all abbreviations every time they are repeated.

(3) Figures and illustrations
① The KJA publishes in full color, and encourages authors to use color to increase the clarity of figures. Please note that color figures are used without charge for online reading. However, since it will be charged upon the publication, authors may choose to use colors only for online reading.
② Standard colors should be used (black, red, green, blue, cyan, magenta, orange, and gray). Avoid colors that are difficult to see on the printed page (e.g., yellow) or are visually distracting (e.g., pink). Figure backgrounds and plot areas should be white, not gray. Axis lines and ticks should be black and thick enough to clearly frame the image. Axis labels should be large enough to be easily readable, and printed in black.
③ Figures should be uploaded as separate tif, jpg, pdf, gif, ppt files. Width of figure should be 84 mm (one column). Contrast of photos or graphs should be at least 600 dpi. Contrast of line drawings should be at least 1,200 dpi. Number figures as “Fig. (Arabic numeral)” in the order of their citation. (ex. Fig. 1).
④ Photographs should be submitted individually. If Figure 1 is divided into A, B, C and D, do not combine it into 1, but submit each of them separately. Authors should submit line drawings in black and white.
⑤ In horizontal and vertical legends, the letter of the first English word should be capitalized.
⑥ Connections between numbers should be denoted by “-“ not “-". Do not space the numbers (ex. 2–4).
⑦ Figures (line drawings) should be clearly printed in black and white.
⑧ Figures should be explained briefly in the footnotes. The format is the same as the table format.
⑨ An individual should not be recognizable in the photographs or X-ray films unless written consent of the subject has been obtained and is provided at the time of submission.
⑩ Pathological samples should be pictured with a measuring stick.

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

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

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

Video clips are uploaded as the last file(s) at the time of manuscript submission and should be marked as supplementary video files.
① The video clip(s) should have simple file names (e.g., Video 1***, Video 2*** ) and include the appropriate extension (e.g., .mov, .mpg).
② The maximum number of video clips is 20.
③ The video clip(s) should be playable on both Windows and MAC computers. The video clip(s) should be tested for playback before submission, preferably on computers not used for their creation, to check for any compatibility issues.
④ Individual video files should be a minimum of 480 x 320 pixels (smaller clips will not be accepted) and a maximum of 2 GB. Files of < 15 MB will be rejected outright unless special arrangements have been made with the editorial board prior to submission. Approval of files of > 2 GB will be made at the end of the review process.
⑤ Supplemental still images that correspond to the respective video clip(s) should be, but are not always required to be, accompanied by legends. The video clip file name(s) should refer to the corresponding figure number(s).

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

Organization of systematic review and meta-analysis: Same as clinical and experimental studies, except,
- All systematic reviews and meta-analyses should be regis-
tered at an appropriate online public registry (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 semicolon (;), and mark a period (.) at the end of the last word.
③ Introduction: Should not be separately divided. Briefly describe the case and background without a title.
④ Case report: Describe only the clinical statement that is directly related to diagnosis and anesthetic management.
⑤ Discussion: Briefly discuss the case, and state conclusions at the end of the case. Do not structure the conclusion section separately.
⑥ References: Do not exceed 15 references. For exceeding the number of references, it should be negotiated with the Editorial Board.
⑦ Tables and figures: Proportional to clinical and experimental studies.

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

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

Cover pages should be formatted as those of clinical research papers. The body text should not exceed 1,000 words and should have no more than 5 references. For exceeding the number of references, it should be negotiated with the Editorial Board. A figure or a table may be used. A maximum of five au-
thors is allowable. Letter may be edited by the Editorial Board and if necessary, responses of the author of the subject paper may be provided.

6) Statistical Round
A Statistical Round is a narrative review of the application of contemporary quantitative sciences to issues of concern to anesthesiology researchers. A Statistical Round involves a focused discussion on one or more unique or interesting statistical analysis methods that has previously been published in this journal or expresses the general policies or opinions of the Statistical Round Board. They are solicited by the Statistical Round Board and reviewed by the Statistical Editor. There are no word limits to or rules regarding the structure of a Statistical Round. They should have an unstructured abstract of no more than 250 words in English. All articles in a Statistical Round will be published in English and translated into Korean for the convenience of Korean readers. The Korean version of the Statistical Round will be published only on the Web page of the Journal (https://ekja.org). The inclusion of sample datasets as Web (Supplemental) content is encouraged.

8. Recently revised instructions for authors are applied from December 2023 submissions.