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

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

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

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Neuromuscular blockade management in patients with COVID-19

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Considerations for crossover design in clinical study

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본 글에서는 동일한 연구대상자 내에서 치료 효과를 비교할 수 있다는 장점과 함께 임상연구에서 자주 사용되는 교차설계를 소개한다. 특히, 임상연구에서 널리 사용되는 2-시기, 2-순서 교차설계(2 × 2 또는 AB/BA 교차설계)의 장단점을 파악하고 분석에 필요한 내용을 소개한다. 또한, 교차설계에서 이월효과, 시기효과, 순서효과 및 시기-치료간 교호작용을 설명하고 데이터 예제와 함께 SAS 코드를 살펴본다. 일반선형모형을 통해 이월효과를 확인한 후 선형 혼합효과모형을 사용하여 치료 효과를 분석한다.

Keywords: Biomedical research; Carryover effect; Crossover design; Linear mixed effect model; Statistics; Washout period.
Effects of etomidate use in ICU patients on ventilator therapy: a study of 12,526 patients in an open database from a single center

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배경: Etomidate 사용의 안전성에 대한 논란이 있어 왔다. 저자들은 단일기관의 중환자실에서 수집된 대단위의 개방 코호트에서 etomidate가 모든 원인의 사망에 미치는 영향을 평가했다.

방법: Medical Information Mart for Intensive Care 3판(MIMIC-III) 데이터베이스를 사용한 후향적 매칭 코호연구의 형식으로 수행하였다. 기계적 인공호흡을 받는 첫날에 etomidate 또는 propofol을 처방 받은 12,526명의 성인 환자 중에서 첫날에 etomidate를 투여 받은 625명의 환자 코호트를 선별한 뒤에 propofol을 투여 받은 나머지 환자들 중에서 6,250명의 환자와 통계적으로 매칭하였다. 일차끝점으로서 모든 원인에 의한 병원내사망률, 48시간 생존율, 심혈관이환율 및 감염성이환율을 코호트 간에 비교하였다. 모든 독립변수들을 단계적으로 제거하는 변수선택법을 사용하는 로지스틱 회귀분석을 통해 etomidate에 의한 용량-사망률 연관을 추정하였다.

결과: 모든 원인에 의한 병원내사망률의 오즈는 etomidate 코호트에서 1.84배 더 높았다 (98.75% CI, 1.42, 2.37). Propofol 코호트와 비교할 때 etomidate 코호트는 48시간 생존의 오즈가 57% 낮았고(0.43 [0.27, 0.73]), 심혈관계환율(0.86 [0.66, 1.12])에서는 차이가 없었고 감염성이환율에서는 1.77배 더 높았다 (1.77 [1.35, 2.31]). 마지막으로, 사망의 오즈는 etomidate 0.1 mg/kg 투여마다 1.36배 증가했다 (1.36 [95% CI: 1.23, 1.49]).

결론: Etomidate는 중환자들의 모든 원인으로 인한 사망을 용량의존적으로 증가시키는 것과 연관되어 있으며, etomidate 투여를 통해 첫 48시간 동안의 생존률을 향상시키지 못하기 때문에 인공호흡 첫날의 수면진정제로 etomidate를 선택하는 것은 바람직하지 않다.

Keywords: Dose-response relationship; Etomidate; Intensive care unit; Mortality; Propofol; Ventilator.

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Previous presentation in conferences:
A preliminary analytic version of this research has been presented by Ha Yeon Park at the Koreanesthesia 2020 (November 6, 2020) in Incheon, Republic of Korea.

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Hemodynamic effects of norepinephrine versus phenylephrine infusion for prophylaxis against spinal anesthesia-induced hypotension in the elderly population undergoing hip fracture surgery: a randomized controlled trial

Maha Mostafa¹, Ahmed Hasanin¹, Mahmoud Mostafa¹, Mai Y Taha¹, Mohamed Elsayad¹, Fatma Alzahraa Haggag¹, Omar Taalab², Ashraf Rady¹, Bassant Abdelhamid¹

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Keywords: Elderly; Hip fracture surgery; Hypotension; Norepinephrine; Phenylephrine; Spinal anesthesia.
Effect of intravenous dexamethasone on the duration of postoperative analgesia for popliteal sciatic nerve block: a randomized, double-blind, placebo-controlled study

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배경: 정맥내(IV) 덱사메타손(dexamethasone)은 말초신경차단 시간을 연장시키지만 아직까지 이러한 효과에 대한 최적의 유효 용량에 대한 연구가 부족하다. 이 연구는 좌골 신경 차단에서 최적의 유효 용량을 결정하기 위해 수술 후 진통 시간에 대한 세 가지 다른 용량의 정맥내 덱사메타손의 효과를 평가하는 것을 목적으로 시행되었다.

방법: 발 및 발목 수술이 예정된 환자에게 생리식염수 또는 IV 덱사메타손(2.5 mg, 5 mg 또는 10 mg)을 투여하도록 무작위로 배정되었다. 전신마취 전에 초음파 유도 하에 슬와 좌골 신경 차단이 0.75% 로피바카인(ropivacaine, 20 ml)을 사용하여 시행되었다. 수술 후 진통시간이 1차 평가 변수이며 통증 점수, 추가 진통제 사용, onset time, 부작용 및 환자 만족도를 2차 평가 변수로 평가하였다.

결과: 대조군과 비교하여 IV 덱사메타손 10 mg (P < 0.001)을 투여 받은 군에서는 좌골 신경 차단의 수술 후 진통기간이 연장되었지만, IV 덱사메타손 2.5 mg 또는 5 mg을 투여 받은 군에서는 유의한 차이가 없었다. 추가 진통제의 사용은 수술 후 24시간 동안만(P = 0.001) 4개군 간에 유의한 차이를 보였으나 그 이후에는 유사하였다. 통증 점수는 수술 후 24시간 동안 4개군 간에 유의한 차이가 없었다. 다른 2차 평가 변수도 4개군 간에 통계적으로 유의한 차이는 없었다.

결론: 본 연구에서 대조군에 비해 IV 덱사메타손 10 mg만이 특별한 부작용 없이 발과 발목 수술에서 좌골 신경 차단에 의한 수술 후 진통 시간을 증가시키는 것으로 나타났다.

Keywords: Analgesia; Ankle; Dexamethasone; Foot; Intravenous injections; Nerve block; Pharmaceutic adjuvants; Sciatic nerve.
Preemptive analgesic efficacy of ultrasound-guided transversalis fascia plane block in children undergoing inguinal herniorrhaphy: a randomized, double-blind, controlled study

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Keywords: Acetaminophen; Analgesia; Child; Fascia; Herniorrhaphy; Postoperative pain.
Prediction of endotracheal tube size using a printed three-dimensional airway model in pediatric patients with congenital heart disease: a prospective, single-center, single-group study

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배경: 소아 환자의 기관내 삽관을 위한 기관내관(endotracheal tube)의 정확한 크기를 결정하기 위해 새로운 방법이 연구되어 왔다. 3차원 프린팅 기술은 수술 분야에서는 성공적이었지만, 마취 분야에 대한 연구는 많지 않다. 이 연구의 목적은 정확한 기관내관 크기를 예측하기 위해 3차원 기도 모델의 정확도를 평가하고, 그 결과를 소아 환자의 기존 연령 기반 공식과 비교하는 것이다.

방법: 선천성 심장 수술이 예정된 6세 미만 소아 환자 35명을 대상으로 하였다. 마취전 기간 동안 3차원 이미지 변환 프로그램을 사용하여 컴퓨터 단층촬영 이미지를 STL (Standard Triangle Language) 파일로 변환하고, FDM (Fused Deposition Modelling) 유형의 3차원 이미지를 사용하여 상부 기관내관까지 이르는 3차원 기도 모델을 인쇄했다. 인쇄된 3차원 기도 모델에 다양한 크기의 기관내관을 삽입하여 기관내관 크기를 선택했다.

결과: 3차원 기도 모델을 사용한 기관내관 크기 예측 방법은 35명의 소아 환자 중 21명(60%)에서 적합한 기관내관 크기를 선택할 수 있었다. 반면 연령 기반 공식은 9명의 환자(26%)에서만 적합한 기관내관 크기를 선택할 수 있었다.

결론: 인쇄된 3차원 기도 모델을 사용하여 기관내관의 적합한 크기를 예측한 결과 연령 기반 공식보다 더 나은 결과를 보였다. 이는 인쇄된 3차원 기도 모델을 사용하여 기관내관의 크기를 선택하는 것이 비정상적인 성장 및 발달 범위를 보이는, 또는 보이지 않는 선천성 심장 질환 환자에서 기관내관의 재삽관 시도 및 합병증을 최소화하는 데 도움이 될 수 있음을 시사한다.

Keywords: Airway management; Computer simulation; Computed tomography; Congenital heart disease; Endotracheal intubation; Three-dimensional printing; Trachea.
Case Report

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Anesthetic management of a parturient with Shone’s syndrome -a case report with review of literature-

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Keywords: Aortic coarctation; Aortic stenosis; Cesarean section; Epidural anesthesia; Mitral valve stenosis; Spinal anesthesia.
Hyper- and hypocoagulability in COVID-19 as assessed by thromboelastometry -two case reports-

혈전탄성측정에 의해 평가된 COVID-19의 과응고성 및 저응고성

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배경: 코로나 바이러스 질환(COVID-19) 관련 응고 병증은 D-dimer, interleukin-6 및 혈장 섬유소원 농도가 높아지고 EXTEM, INTEM 및 FIBTEM 분석에서 응고 경도가 증가하는 혈전탄성측정에서 과응고성이 가장 흔한 특징이다. 임상적으로는 특히 폐 계통에서 혈전증의 발생률이 매우 높은 반면, 출혈 합병증은 드물게 나타난다.

증례: 본 증례보고에서는 서로 다른 혈전탄성측정과 바이오마커 패턴을 보이는 중환자실에 입원한 두 명의 COVID-19 중환자에 대해 설명한다. 혈전탄성측정법에서 한 환자는 과응고성을 보였고, 다른 환자는 저응고 및 섬유소유해 중단을 보였다. 병태 생리학 및 치료 옵션에 대한 잠재적 영향에 대해 논의되었다.

결론: 바이오마커와 혈전탄성측정결과의 조합은 향후 COVID-19에 걸린 중환자에게 가장 적합한 치료 전략을 결정하는 데 도움이 될 수 있다. 이것은 고위험 환자 집단에서 정밀 의학을 확립하는 데 중요한 단계가 될 것이다.

Keywords: Anticoagulants; COVID-19; Fibrinolysis; Hemostasis; Thrombelastography; Thrombosis.
Predicting the proper endotracheal tube size is crucial in pediatric anesthesia. An oversized endotracheal tube may damage the airway. Mucosal edema, ischemia, ulceration, and scar formation may predispose to narrowing of the subglottic airway [1,2]. Conversely, an undersized tube may result in significant leakage of gases, leading to inadequate ventilation, impaired oxygenation, and contamination of the operating room environment. Moreover, insufficient airway sealing can increase the risk of pulmonary aspiration [3].

The age-based formulas (Cole formula: ID [inner diameter] = 4 + age/4 for uncuffed tube; Motoyama formula: ID = 3.5 + 4/age for cuffed tube in children aged 2 or more years; Khine formula: ID = 3.0 + 4/age for cuffed tube in children under 2 years of age) have been adopted as standard practice for several decades. As the physical development and growth of internal organs are not always proportional to age and have substantial individual variation, additional parameters such as weight, height, and finger width have been introduced to improve the prediction of appropriate endotracheal tube size [4,5]. However, the selection of appropriately sized tubes in pediatric patients remains a challenge, and multiple intubation attempts and tube changes are not uncommon. Recently, the measurement of subglottic airway diameter by ultrasonography has emerged for the prediction of pediatric endotracheal tube size [6]. It was shown to better predict the optimal tube size when compared with age- or height-based formulas. However, the use of ultrasound requires training, and an entire picture of the subglottic airway is difficult to obtain.

In the current issue of the Korean Journal of Anesthesiology, Park et al. [7] utilized three-dimensional (3D) printing technology to improve the prediction of proper endotracheal tube size in patients undergoing surgery for congenital heart disease. A 3D airway model was derived from preoperative computed tomography (CT), and the most appropriate endotracheal tube size was determined by inserting tubes of various sizes into the 3D-printed airway model. Adequacy of tube size was evaluated by an air leak test, and the 3D-printed airway model selected the appropriate endotracheal tube in 60% of the patients, whereas the age-based formula accurately predicted tube size in only 26% of the patients.

The application of 3D printing, a rapid manufacturing of prototype objects using a computational model, is expanding widely in the medical industry. 3D-printed models can be used to evaluate complex anatomical structures. They also facilitate the creation of personalized medical devices. Indeed, 3D printing has been used to manage complex airway diseases in pediatric patients [8–10]. As the 3D-printed airway model provides the
entire airway conformation, the advantage of 3D printing may be maximized in patients with difficult airways. Despite its potential advantages, there are also several concerns that may restrict the general application of this technique in pediatric anesthesiology practice. First, 3D printing requires preoperative radiographic imaging, for example, CT. CT for airway evaluation alone cannot be accepted. Second, the efficacy should be compared with traditional formulas or ultrasonic measurements by adequately powered randomized trials. Finally, the method should also be cost-effective. However, advances and refinement in engineering could allow more widespread use of 3D printing technology-mediated personalized airway management.

Conflicts of Interest

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

References

Neuromuscular blockade management in patients with COVID-19

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This narrative review evaluates the evidence for using neuromuscular blocking agents (NMBA) in patients being treated for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). While large prospective randomized-controlled trials (RCTs) are lacking at this point in time, smaller observational studies and case series are reviewed to ascertain the indications and utility of NMBAAs. Additionally, large RCTs that address similar clinical scenarios are reviewed and the authors translate these findings to patients with COVID-19. Specifically, NMBAAs can be helpful during endotracheal intubation to minimize the risk of patient coughing and possibly infecting healthcare personnel. NMBAAs can also be used in patients to promote patient-ventilator synchrony while reducing the driving pressure needed with mechanical ventilation (MV), particularly in patients with the severe clinical presentation (Type H phenotype). Prone positioning has also become a cornerstone in managing refractory hypoxemia in patients with SARS-CoV-2 acute respiratory distress syndrome, and NMBAAs can be useful in facilitating this maneuver. In the perioperative setting, deep levels of neuromuscular blockade can improve patient outcomes during laparoscopic operations and may theoretically reduce the risk of aerosolization as lower insufflation pressures may be utilized. Regardless of the indication, quantitative neuromuscular monitoring remains the only reliable method to confirm adequate recovery following cessation of neuromuscular blockade. Such monitors may serve a unique purpose in patients with COVID-19 as automation of measurements can reduce healthcare personnel-patient contact that would occur during periodic subjective evaluation with a peripheral nerve stimulator.

Keywords: COVID-19; Neuromuscular blockade; Neuromuscular blocking agents; Neuromuscular monitoring; Respiratory distress syndrome; SARS-CoV-2.

Introduction

Coronavirus disease 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) started in December 2019 as an outbreak of pneumonia in Wuhan, Hubei, China [1]. The disease spread rapidly to other areas in China, as well as other countries around the world, becoming a public health problem of international concern [2]. In March 2020, the World Health Organization (WHO) declared the outbreak a pandemic with more than 1,700,000 confirmed cases and 111,600 deaths in more than 210 countries [3].

The Center for Systems Science and Engineering (CSSE) at Johns Hopkins University reported a total global case number of 78,420,543 and deaths of 1,725,057 by December
In the beginning, the experience in Wuhan demonstrated that approximately 3.2% of patients with COVID-19 required intubation and mechanical ventilation (MV) [6]. Since then, frontline health workers face a considerable challenge in providing adequate airway management and preventing the spread of infection due to the high transmission risk of SARS-CoV-2 during aerosol-generating procedures (AGPs) such as endotracheal intubation [7].

Neuromuscular blocking agents (NMBA) are a routinely utilized class of medications in the operating room and intensive care unit (ICU) to facilitate MV, optimize endotracheal intubating conditions, and improve surgical conditions [8–11]. However, prolonged neuromuscular blockade is associated with complications such as patient awareness during paralysis, critical illness myopathy, and residual neuromuscular weakness [11]. The exact efficacy and indications of neuromuscular blockade in patients with COVID-19 remains unclear given the paucity of available literature. The purpose of this review is to summarize the current evidence regarding neuromuscular blockade management in patients with COVID-19 and provide a description of the neuromuscular blockade management strategies available to consider during the global pandemic. In addition, we will review optimal methods for neuromuscular blockade monitoring to aid in determining the level of the blockade and confirm adequate neuromuscular recovery while avoiding complications due to residual neuromuscular blockade.

**Indications and methods**

The use of NMBAs in patients with COVID-19 typically involves optimizing conditions for endotracheal intubation, facilitating MV, and positioning patients with refractory hypoxia in prone. It is important to note that there is no specific guideline regarding the indication for NMBAs in patients with COVID-19. As such, the decision to establish neuromuscular blockade must be individualized by the clinician based on the specific patient and clinical characteristics (Table 1).

The present literature review investigates recent published studies concentrating on the role of NMBAs in patients with COVID-19. The literature search was done in PubMed, Medline, Scopus, and Google Scholar between December 2019 and January 2021. The search used keywords related to the population of interest (SARS-CoV-2, coronavirus, COVID-19 patients) and the intervention of interest (neuromuscular blockade, NMBA, MV, laparoscopy). We also screened references from included studies. Papers that appeared relevant to the topic of interest were retrieved as full texts and were reviewed independently. We included small-scale observational studies and case series as the primary source of information due to the lack of large-scale randomized control trials related to COVID-19.

**Endotracheal intubation**

Although the benefit of establishing an advanced airway is well-recognized in patients with COVID-19, initial respiratory

**Table 1. Indications for NMBA Use in Patients with COVID-19**

<table>
<thead>
<tr>
<th>Indications</th>
<th>Benefits of NMBA use</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endotracheal intubation</td>
<td>Improves intubation conditions and minimizes risk of coughing during airway manipulation.</td>
<td>Consensus guidelines from various societies [12].</td>
</tr>
<tr>
<td>Facilitate MV</td>
<td>Minimization of ventilator dysynchrony, breathing effort, driving pressure, and P-SILI.</td>
<td>Evidence from ARDS and expert opinion [23,57].</td>
</tr>
<tr>
<td>AGPs such as endotracheal suctioning and bronchoscopy</td>
<td>Avoidance of physical movement and coughing during procedure and thus minimizing risk to healthcare providers.</td>
<td>Expert opinion [56].</td>
</tr>
<tr>
<td>Improve oxygenation</td>
<td>Particularly useful in Type H phenotype, improves ventilator synchrony, inhibits inflammatory cytokines.</td>
<td>Meta-analysis from ARDS literature [20].</td>
</tr>
<tr>
<td>Prone positioning</td>
<td>Reduction of complications such as accidental extubation, coughing, endotracheal tube obstruction, main-stem bronchus intubation.</td>
<td>ARDS literature and case reports [30,37].</td>
</tr>
<tr>
<td>Laparoscopic surgery</td>
<td>Deep levels of neuromuscular blockade may facilitate lower pneumoperitoneum insufflating pressures and reduce risk of aerosolization [46,47].</td>
<td>RCTs from surgical literature, expert opinion.</td>
</tr>
</tbody>
</table>

**Notes:**
approach can be directed towards non-invasive therapies [3,6]. This can be accomplished with high-flow nasal cannula, continuous positive airway pressure, or bilevel positive airway pressure (BiPAP). However, respiratory instability can progress rapidly and the need for advanced airway management may be required. While the exact timing remains unclear, patients in respiratory distress showing no improvement, tachypnea with a respiratory rate > 30/min, and poor oxygenation (PaO\textsubscript{2}/FiO\textsubscript{2} < 150 mmHg) after a trial of high-flow oxygen therapy or noninvasive ventilation should be considered for endotracheal intubation and invasive MV [8]. Most experts advocate performing a rapid sequence induction and intubation with rocuronium as this allows for pharmacologic rescue with sugammadex in the catastrophic ‘can’t intubate/can’t ventilate’ scenario. This technique, in conjunction with manual maneuvers to restore airway patency, can facilitate ventilation faster than waiting for succinylcholine-induced neuromuscular blockade to subside [12–14].

Meng et al. [6] described their experience with intubating patients in Wuhan, China. This group stressed that cough suppression in an effort to minimize aerosolization was a top priority to protect clinicians instrumenting the airway. Preoxygenation proved paramount in this vulnerable population and was accomplished with either high-flow nasal cannula or BiPAP [6]. After preoxygenation for at least 3 min, this group proceeded with modified rapid sequence induction using midazolam (1–2 mg) for those extremely anxious patients and lidocaine (> 1.5 mg/kg) to suppress coughing [15]. Etomidate (0.2–0.3 mg/kg) was used for induction for those with hemodynamic instability or propofol (1–1.5 mg/kg) for those with stable hemodynamics. This group then utilized rocuronium (1 mg/kg) or succinylcholine (1 mg/kg) immediately after loss of consciousness. Finally, the airway was secured with video laryngoscopy within 60 s of NMBA administration [6].

On the other hand, in an effort to shorten the time to onset of neuromuscular blockade, a priming dose of rocuronium has been described when intubating patients with COVID-19 [15]. Utilizing 0.03–0.04 mg/kg rocuronium 3 min before intubating, Hoshijima et al. [15] evaluated this technique when intubating patients with COVID-19. Not surprisingly, these patients became hypoxic with oxygen saturations as low as 55% prior to securing the airway as even low levels of neuromuscular blockade proved deleterious to patients with COVID-19 prior to intubation. As such, we discourage the use of a priming dose of a non-depolarizing NMBA in patients with or without COVID-19 as such a practice exposes patients to weakness and its associated complications prior to securing the airway.

In order to avoid patient complications and exposure to health-care workers during endotracheal intubation, most of the current literature suggests the use of fitted respirator masks plus other personal protective equipment [16]. Some experts advocate for 5 min of preoxygenation with a good mask seal and no bag-mask ventilation, a rapid sequence induction under video laryngoscopy by experienced personnel limiting close distance from clinicians to the patient’s oral cavity, and avoiding awake fiberoptic intubation [17]. Finally, adequate neuromuscular blockade can not only lower the risk of viral transmission by avoiding coughing while also providing optimal conditions to instrument the airway [8,18,19].

**Patient self-induced lung injury**

Patient self-induced lung injury (P-SILI) should be considered as a possible complication in SARS-CoV-2-induced acute respiratory distress syndrome (ARDS) [20]. The mechanism of P-SILI is based on three factors: increased lung stress, increased lung perfusion, and patient-ventilator asynchrony [21]. Lung stress is a function of the increase in transpulmonary pressure (barotrauma) and global lung stress resulting in larger tidal volumes (volutrauma). Increases in lung perfusion are associated with an increase in transmural vascular pressure associated with spontaneous effort, as this will cause a more negative pleural pressure and result in increased perfusion to intrathoracic vessels. This phenomenon can cause pulmonary edema, particularly when a vigorous spontaneous effort is made by the patient. Lastly, patient-ventilator asynchrony is associated with significant mortality based on the presence of the reverse triggering effect in which patient effort triggers the ventilator after a ventilator-initiated breath. This dyssynchrony increases the transpulmonary pressures, tidal volumes, and ultimately, lung stress [21].

NMBAs provide a pharmacologic intervention to combat spontaneous effort, lung stress, and ventilator dyssynchrony [22–24]. Therefore, early administration of NMBAs might also play an important role in decreasing devastating pulmonary outcomes. In a cohort of 56 patients with ARDS comparing conventional therapy vs. conventional therapy plus NMBA, Gainnier et al. [22] reported improvement in PaO\textsubscript{2}/FiO\textsubscript{2} ratio at 48, 96, and 120 h after establishing an adequate neuromuscular blockade (P < 0.001). Also, the early administration of NMBA in patients with ARDS with a lung-protective ventilation strategy has brought benefits in terms of inflammatory marker reduction, demonstrating a decrease in IL-8, IL-1beta, IL-6, and IL-8 [23]. Additionally, in those patients with severe ARDS (PaO\textsubscript{2}/FiO\textsubscript{2} < 150 mmHg), the hazard ratio (HR) for death at 90 days using cisatracurium compared with placebo was 0.68 (95% CI, 0.48, 0.98, P = 0.04) [24]. Consequently,
early administration of NMBAs might be a potential therapy utilized to improve survival rate, ventilator-free days, days outside the ICU, and barotrauma [24,25]. While NMBAs have not been comprehensively studied in patients with COVID-19 developing P-SILI, expert opinion, and extrapolating data from similar conditions suggest that this class of medication could be an important option for either prophylactic or supportive therapy in COVID-19 [16].

MV in refractory hypoxia

While the Berlin criteria applies to COVID-19-induced ARDS, the current literature emphasizes there are different COVID-19 clinical presentations (Types L and H) and therapy strategies depend on the severity of lung injury and the MV requirements. Specifically, the severity of infection, host response, physiological reserve, comorbidities, ventilatory responsiveness of the patient to hypoxemia, and the time elapsed between the onset of the disease and clinical deterioration between the two phenotypes. Type L involves a milder presentation and is characterized by low elastance, high compliance, low ventilation-to-perfusion ratio, low lung weight, and low alveoli recruitability. Type H involves high elastance, high right-to-left shunt, high lung weight, and high recruitability due to a larger proportion of non-aerated pulmonary tissue [26]. Authors document an initial non-invasive MV management for Type L, guiding the respiratory support on parameters such as esophageal and central venous pressure swings, while treating Type H in a similar fashion to patients with severe ARDS [26].

While NMBAs can play a valuable role in managing patients with both Type H and L COVID-19 phenotypes, patients with type H may be associated with a better response to neuromuscular blockade given the poorer compliance [26,27]. Traditionally, NMBAs have been used early in the course of ARDS when the PaO2/FiO2 < 150 mmHg in order to improve oxygenation and reduce patient-ventilator dysynchrony with a goal of reducing ventilator-induced lung injuries and inflammatory cytokines [28].

The largest multicenter trial regarding the effectiveness of neuromuscular blockade in ARDS is the ARDS et Curarisation Systematique (ACURASYS) published in 2010. This effort concluded that treatment with cisatracurium for 48 h early in the course of severe ARDS improved the adjusted 90-day survival rate versus placebo (30.8% vs. 44.6%, \( P = 0.04 \), respectively), increased the numbers of ventilator-free days (1–28 days \( P = 0.04 \); 1–90 days \( P = 0.03 \)) and days outside the ICU (1–90 days \( P = 0.03 \)), and decreased the incidence of barotrauma during the first 90 days [24]. Conversely, the Reevaluation of Systematic Early Neuromuscular Blockade (ROSE) trial found the addition of early administration of cisatracurium with concomitant deep sedation did not result in lower mortality than a usual-care approach to MV that included lighter sedation targets demonstrating a mortality rate of 42.5% vs. 42.8% (95% CI, –6.4, 5.9, \( P = 0.93 \), respectively [20]. However, these authors stated possible causes for such results including a higher positive end expiratory pressure strategy in both groups, deeper sedation in the intervention group (higher risk of hypotension, bradycardia, and other cardiovascular effects), and lower prone positioning rate compared to ACURASYS study [20]. As such, the timing of initiating NMBA therapy in patients with hypoxia from SARS-CoV-2-induced ARDS must be individualized.

Prone positioning

Prone positioning has been implemented as part of the non-pharmacological management in cases of moderate and severe ARDS. This technique allows for redistribution of consolidation from dorsal to ventral areas of the lung, removal of the heart’s weight and mediastinum from the lung, improving alveolar ventilation, and minimizing pulmonary inflammatory cytokine production [29]. The Proneing Severe ARDS Patients (PROSEVA) trial described the findings of 466 patients with severe ARDS that underwent prone and supine-positioning sessions for at least 16 h [30]. A total of 237 patients were assigned to the prone group, whereas 229 to the supine group, demonstrating 28-day mortality of 16% and 32.8% (\( P < 0.001 \)), and an unadjusted 90-day mortality rate of 23.6% and 41% (\( P < 0.001 \)), respectively. Most of the complications and causes of mortality were cardiac arrest in the supine group [30]. Additionally, six other randomized trials also concluded that prone positioning had a reduction in mortality (33.7%) compared to non-prone-positioning cases in moderate to severe ARDS for a longer duration of 12 h [30–36]. Proning patients can be safely accomplished with adequate levels of neuromuscular blockade as such agents might help minimize complications including inadvertent extubation, endotracheal-tube obstruction, and main-stem bronchus intubation [30,37]. Although NMBA use is not mandatory in all prone patients, the utilization of adequate neuromuscular blockade during this vulnerable time could facilitate prone positioning in patients with COVID-19 and minimize complications related to this labor-intensive and potentially dangerous technique.

Laparoscopy in COVID-19 patients

Viral studies have detected fragments of SARS-CoV-2 in a vari-
Neuromuscular blockade monitoring

Objective neuromuscular blockade monitoring is not routinely performed in the ICU as subjective evaluation with a peripheral nerve stimulator is the primary assessment method. Nonetheless, a recent international panel of experts released a consensus statement that recommended that quantitative (objective) monitoring should be used whenever NMBAs are administered as such devices are the only means of confirming adequate recovery [49]. Leaving patients with COVID-19 with residual weakness at the time of extubation could have catastrophic consequences given their potentially tenuous clinical status.

While recovery is important, placing objective monitors on the adductor pollicis prior to NMBA administration and endotracheal intubation and waiting for this muscle to reach a train-of-four count of zero can minimize the risk of coughing during airway manipulation. Using monitors in this fashion relies upon an understanding of different muscle sensitivities to neuromuscular blockade. Relying on an objective data that reflects the patient’s current state of neuromuscular blockade has the potential to briefly delay endotracheal intubation as clinicians confirm adequate paralysis rather than relying on expected responses; however, this additional time to ensure adequate neuromuscular blockade could prove to be the difference in a patient with COVID-19 coughing during airway manipulation. Monitoring facial muscles can prove challenging as direct muscle stimulation occurs easily; however, the corrugator supercilii muscle has been reported to have a similar response to NMBA as that of the diaphragm and laryngeal muscles while the orbicularis oculi can respond similarly to the extremities [50]. We agree with other experts [51,52] that monitoring facial muscles should be discouraged as there is a more than five-fold higher risk of residual paralysis when monitoring is performed at the eye muscles than those assessed at the hand muscles [53].

Quantitative monitoring can also be used to confirm adequate paralysis prior to proning a patient. Whether clinicians are utilizing intermittent boluses or continuous infusions of NMBA, the depth of neuromuscular blockade should be assessed and documented during regular intervals with a prone patient. As frequent assessments with a peripheral nerve stimulator can increase direct patient contact, the use of automated quantitative monitors can serve as an innovative method for measuring the level of blockade and reducing the risks to the healthcare team [54]. Such devices also have the ability to be seamlessly incorporated into the electronic medical record — a feature that could improve work-flow efficiency in challenging patients with COVID-19.

We certainly recognize the use of quantitative monitoring is inconsistent in modern anesthesia practices and rarely used in the critical care setting. However, a recent review article has called for objective monitoring in this setting as an innovative approach to critical care medicine [8]. While a comprehensive review of quantitative neuromuscular monitors is beyond the scope of this re-

https://doi.org/10.4097/kja.21106
view, these devices are often categorized by the method they obtain objective data. Acceleromyography measures the acceleration of a muscle, usually the adductor pollicis, to neurostimulation. Similarly, kinemyography measures the degree of bend of a piezoelectric sensor placed between the thumb and index finger following neurostimulation. Electromyography does not rely on an unrestricted, freely-moving thumb as it measures action potentials across the neuromuscular unit and has the advantage of working on ICU patients who may have wrist-restraints to prevent the accidental removal of invasive catheters [54]. These devices allow for automated measurements at a user-defined time interval and can perform various patterns of neurostimulation including train-of-four, single twitch, double burst, and post-tetanic potentiation [55].

Conclusions

NMBAs can prove very useful when caring for patients with COVID-19. This class of medications has particular utility when caring for critically ill patients that require endotracheal intubation, MV, proning, and avoidance of self-induced lung injury. The focus of therapy in these types of patients must integrate multidisciplinary management, including pharmacologic and non-pharmacologic techniques (e.g., MV, AGPs, prone positioning) [56]. Despite the lack of evidence in using NMBAs in COVID-19, some authors have described pragmatic approaches that rely on literature from similar clinical scenarios such as ARDS [57]. Such strategies were designed under duress with the goal of reducing healthcare exposure to SARS-CoV-2 while enhancing patient outcomes. Similarly, NMBAs can play a role in patients with COVID-19 undergoing laparoscopic surgery in an effort to allow for lower pneumoperitoneum insufflating pressures and potentially reducing aerosolization. We also advocate for quantitative monitoring whenever NMBAs are used to avoid complications associated with neuromuscular blockade, independent of whether patients are in the perioperative or critical care setting. Finally, we recognize the need for prospective, RCTs to better elucidate the actual role of NMBAs in this setting.

Conflicts of Interest

JRR has completed Merck-funded research with funds to employer. HCC, VHT, and SK have nothing to disclose.

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Harold Chaves-Cardona (Conceptualization; Writing – original draft; Writing – review & editing)
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Considerations for crossover design in clinical study

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This article introduces a crossover design that is often used in clinical studies, with the advantage of comparing treatment effects within one study subject. In particular, the advantages and disadvantages of the two-period, two-sequence crossover design (2 x 2 or AB/BA crossover design), which is widely used in clinical practice, are identified, and the elements necessary for analysis are introduced. This article explains the carryover effect, period effect, sequence effect, and period-by-treatment interaction in a crossover design and examines the analysis commands of SAS along with example data. After confirming the carryover effect using a general linear model, the treatment effect is analyzed using a linear mixed effect model.

Keywords: Biomedical research; Carryover effect; Crossover design; Linear mixed effect model; Statistics; Washout period.

Introduction

In a crossover study design, two or more treatments (e.g., drugs, procedures) are provided to subjects at different time periods, and the sequence of treatments is randomized for each subject. This design is applied to several fields such as bioequivalence clinical trials, and the simplest study design is a two-period, two-sequence crossover design (AB/BA design)¹. Subjects are randomly allocated to the AB or BA sequence² [1,2]. Subjects in the AB sequence receive treatment A in the first period, and after the effects of treatment A have subsided, they receive treatment B in the second period. The remaining subjects assigned to the BA sequence receive treatment B first and then treatment A (Fig. 1). Therefore, the difference in treatments is derived from a within-subject comparison. On the other hand, in a parallel design, one subject receives only one treatment, therefore, the difference in treatments is derived from a between-subject comparison.

A crossover design has the following advantages. First, the treatment effect is compared within a subject since each subject serves as his or her own control. It removes the inter-subject variability from the comparison between groups and the effect of covariates³.

¹A and B usually refer to test group A and control group B. It was introduced as a crossover design including the four orders AA/AB/BA/BB in consideration of the treatment type and treatment sequence; however, a simplified study design is mainly used in clinical studies, excluding AA and BB, which are the sequences in which the same drug is repeatedly administered.

²Depending on the literature, it is also described as a sequence, a group, or an order. In this article, a group of subjects in the same order of receiving treatment is described as a sequence, and a set of data for subjects receiving the same treatment is described as a group.

³In addition to the independent variables, a variable that the researcher wants to control as a factor that can affect the dependent variable is designated a covariate. Variables such as age and gender are often included.
can be reduced [3]. For this reason, the imbalance of allocation often seen in randomized controlled parallel studies are seldom seen in randomized controlled crossover designs. Second, the crossover design has high power and statistical efficiency. In other words, it is possible to obtain an estimate with the same level of accuracy as a parallel design, even with a smaller number of subjects [1,2,4].

However, there are also limitations in the crossover design. First, the conditions of the subjects must be stable throughout the study. In other words, a case is inappropriate for a study if the disease status changes over time, such as an acute cure, or when symptoms disappear or are cured by treatment in the first period. Second, a washout period may be necessary until the effect of the first treatment subsides. Therefore, if a treatment drug has an extended half-life, it may be difficult to conduct a study with a crossover design. Third, there is a burden that all treatments are carried out on one subject, which often causes ethical problems. Fourth, the processing of dropped or missing data is more problematic than in a parallel design, and the statistical analysis is complex [2,4].

Based on these advantages and disadvantages, it will be helpful in planning and proceeding with an appropriate crossover design to fully understand the various factors encountered in its design and analysis process.

**Standard 2 × 2 crossover design**

The standard 2 × 2 crossover design is used to assess between two groups (test group A and control group B). Each subject is randomly allocated to either an AB sequence or a BA sequence. Subjects in the AB sequence receive treatment A at the first period and treatment B at the second period.

A model can be used to describe the standard 2 × 2 crossover design as follows:

$$Y_{ik} = \mu + S_i + P_j + T_{jk} + C_{jk} + \epsilon_{ik}$$  

Where $Y_{ik}$ is the response of the $i^{th}$ subject in the $k^{th}$ sequence at the $j^{th}$ period, $i = 1, 2, \ldots, n_i$ ($i^{th}$ subject in $k^{th}$ sequence) $j = 1, 2$ (First or second) sequence $k = 1, 2$ (AB or BA)

The subject ($S_i$) and error ($\epsilon_{ik}$) are independent and identically distributed random variables and have a normal distribution with mean 0 and variance $\sigma^2$, and mean 0 and variance $\sigma^2_j$, respectively. This model includes fixed effects such as the period effects ($P_j$), the direct treatment effects ($T_{jk}$), and the carryover effects ($C_{jk}$). For example, $T_{12}$ represents the direct fixed effect of the treatment at period 1 in sequence 2 (Here, at the first period of the BA sequence), and $C_{21}$ is the residual effect carried over from the (2-1)th period to the second period in sequence 1 (Here, the AB sequence). The carryover effect in the standard 2 × 2 crossover design can occur at the second period. The fixed effects at each period in each sequence are summarized as follows.

<table>
<thead>
<tr>
<th>Sequence</th>
<th>First period</th>
<th>Second period</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB sequence</td>
<td>$\mu_{i1} = \mu + P_i + T_{j1}$</td>
<td>$\mu_{i2} = \mu + P_i + T_{j2} + C_{j1}$</td>
</tr>
<tr>
<td>BA sequence</td>
<td>$\mu_{i2} = \mu + P_i + T_{j2}$</td>
<td>$\mu_{i1} = \mu + P_i + T_{j1} + C_{j2}$</td>
</tr>
</tbody>
</table>

Here,

$\mu_{ik} = E(Y_{ik}), P_i = 0, T_{j1} + T_{j2} = 0$, and $C_{j1} + C_{j2} = 0$.

**Treatment emergent effects**

In studies using a crossover design, elements such as carryover effect, period effect, sequence effect, and period-by-treatment interaction should be evaluated before testing the treatment effect. Even if effects other than the treatment effect were carefully considered and excluded in the research planning stage, it is necessary to check the carryover effect or the period effect before analyzing the treatment effect. After checking the above-mentioned effects are not absent, it is common to analyze the treatment effect. It is important in the crossover study planning stage is to design an analysis that does not become complicated and allow effects other than the treatment effect to influence the interpretation of the results [5,6].

---

Subjects are randomly assigned to AB or BA sequence so that the assumption of no sequence effect is established.

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Lim and In · Crossover design in clinical study

Fig. 1. Two-period, two-sequence crossover design.
Treatment effect

This refers to the direct effect of the treatment. In this article, it indicates the effects of A and B and $T_{12}$ in Equation (1).

Period effect

The period effect implies that the effect of the same treatment received at two different periods is different for each period and corresponds to $P_k$ in Equation (1). Since the first and second treatments are inevitably separated in time, an effect may appear depending on the measurement period, not the treatment. Therefore, when comparing the value obtained by subtracting the first period from the second period of the AB sequence with the value obtained by subtracting the value of the first period from the second period of the BA sequence\(^5\), there should be no difference if there is no period effect.

Carryover effect

The carryover effect, which corresponds to $C_{1-2}$ in Equation (1), refers to the effect of the previous treatment or the change caused by the first treatment continues until the next period and alters the effect of the next treatment. Rather than determining that there is no carryover effect by statistical testing, it is better to select a crossover design when the possibility of a carryover effect is medically unlikely or when the effect can be eliminated through a washout period. Analyzing for the period-by-treatment interaction is used to determine whether the two treatment effects are different in the two periods, and it is difficult to distinguish the carryover effect from the period-by-treatment interaction; therefore, the carryover effect and the period-by-treatment interaction are often treated as identical. However, depending on which parameters are included in the crossover design model, the carryover effect may be embedded in parameters other than the period-by-treatment interaction\(^6\). In other words, it is difficult to analyze the carryover effect in the simplified $2 \times 2$ crossover design [5]; therefore, it is important in the study planning stage to design such that the carryover effect does not occur. For example, there is a method to set a sufficient washout period until the treatment effect or change disappears. In the case of drug studies, a washout period is sometimes set at 3–4 times or more of the blood plasma elimination half-life.

\(5\)Both values are the result of treatment B minus the result of treatment A.
\(6\)In the example of this article, the carryover effect is evaluated through sequence effect analysis.

Sequence effect

The fact that subjects are allocated to a particular sequence may affect the results. That is, when comparing the means of the dependent variables in the AB and BA sequences, there should be no difference if there is no sequence effect. This allows the assumption that there is no sequence effect by randomization in the AB/BA sequence. However, it should be noted that this assumption cannot be verified through statistical analysis [6].

Randomization in crossover design

Randomization is performed to eliminate selection bias and to provide statistical evidence for quantitative evaluation. In parallel design, randomization to different treatment groups (A or B) can ensure independence between groups. However, in the crossover design, randomization is performed in sequence, that is, AB or BA sequence, so that virtually no independence between treatment groups is guaranteed. Therefore, as discussed above, it is necessary to test whether the treatment effect shown in the first period remains in the second period. The randomization method may be reviewed in the article of Lim and In [7].

Other considerations

When planning the crossover design, to confirm the treatment effect, the carryover effect should not appear above all. The carryover effect can be found through data analysis, and when this effect is significant, it is difficult to interpret the treatment effect. Therefore, a protocol such as the above-mentioned washout period setting is an appropriate method to eliminate this effect. However, if the washout period is too long, the dropout rate may increase at the second period. In some cases, crossover studies may be impossible. For example, in the case of an acutely curable disease, if it is cured in the first period, there is no reason for the subjects to participate in the second period. Therefore, the crossover design is more suitable for chronic diseases than for acute diseases. These factors should be reflected in crossover design planning.

Statistical model and SAS code

Example

The example used below was published by Senn and Auclair [8]. Thirteen pediatric patients aged 7–14 years were treated sequentially with two distinct bronchodilators, the newer drug formoter-
ol (For, 12 μg) and the control drug salbutamol (Sal, 200 μg). Seven patients were randomized to the For-Sal sequence and six were randomized to the Sal-For sequence. An established washout period of at least 1 d was allowed between administration of the two drugs. Peak expiratory flow (pef, L/min) was measured 8 h after inhalation of each bronchodilator. The SAS code used in the following example was run using SAS 9.4 (SAS Institute Inc., USA) and SAS University Edition installed on a Microsoft Windows 10 (64-bit) operating system.

Data input into SAS

The full data entry is presented in Fig. 1 of the Appendix. The SAS code for printing up to the first five lines (OBS = 5) of all 26 lines of data and the results are as follows:

```
title "PEF data";
PROC PRINT DATA = PEF (OBS = 5);
RUN;
```

<table>
<thead>
<tr>
<th>OBS</th>
<th>sequence</th>
<th>subject</th>
<th>period</th>
<th>treat</th>
<th>pef</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>For-Sal</td>
<td>1</td>
<td>1</td>
<td>For</td>
<td>310</td>
</tr>
<tr>
<td>2</td>
<td>For-Sal</td>
<td>1</td>
<td>2</td>
<td>Sal</td>
<td>270</td>
</tr>
<tr>
<td>3</td>
<td>For-Sal</td>
<td>4</td>
<td>1</td>
<td>For</td>
<td>310</td>
</tr>
<tr>
<td>4</td>
<td>For-Sal</td>
<td>4</td>
<td>2</td>
<td>Sal</td>
<td>260</td>
</tr>
<tr>
<td>5</td>
<td>For-Sal</td>
<td>6</td>
<td>1</td>
<td>For</td>
<td>370</td>
</tr>
</tbody>
</table>

Analysis of variance table to test other effects

Determining whether various effects other than the treatment effect appearing in this data can be easily accomplished through the analysis of variance table. The following code is used for the construction and execution of a general linear model to which analysis of variance is applied. Here, *sequence* represents For→Sal or Sal→For, the *subject* is a pediatric patient, and *period* represents the first period (1) or the second period (2). *treat* means cure using For or Sal. *CLASS* defines the variables to be used in the model, and *MODEL* is a code that specifies the independent and dependent variables.

```
PROC GLM DATA = PEF;
    CLASS sequence subject period treat;
    MODEL pef = sequence subject (sequence) period treat;
RUN;
```

Fig. 2 shows the execution result of the above SAS code, and Table 1 summarizes this result in an analysis of variance table. As mentioned above, it is not possible to separately confirm all effects or interactions because of the limitations of the simplified crossover design; hence, the carryover effect is inherent in other effects or interactions. In this crossover design model, the carryover effect is inherent in the *sequence*. Therefore, the result for the *sequence* is shown as carryover in Table 1.

In the table of the sum of squares in Fig. 2, the total sum of squares is divided into the between-subject sum of squares and the within-subject sum of squares. The between-subject sum of squares is again divided into the sum of squares for the carryover effect and the sum of squares for the residual. The within-subject sum of squares is divided into the sum of squares for the treatment effect, the sum of squares for the period effect, and the sum of squares for the residual. Neither the carryover effect ([F(1,11) = 4.84 > 0.45], P = 0.5177) nor the period effect ([F(1,11) = 4.84 > 2.17], P = 0.1683) is statistically significant.

<table>
<thead>
<tr>
<th>Source</th>
<th>DF</th>
<th>Sum of Squares</th>
<th>Mean Square</th>
<th>F Value</th>
<th>Pr &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>14</td>
<td>130233.9973</td>
<td>9302.4284</td>
<td>12.40</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Error</td>
<td>11</td>
<td>8254.4643</td>
<td>750.4058</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corrected Total</td>
<td>25</td>
<td>138488.4615</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Source</th>
<th>DF</th>
<th>Type III SS</th>
<th>Mean Square</th>
<th>F Value</th>
<th>Pr &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>sequence</td>
<td>1</td>
<td>335.1877</td>
<td>335.1877</td>
<td>0.45</td>
<td>0.5177</td>
</tr>
<tr>
<td>subject (sequence)</td>
<td>11</td>
<td>114878.2738</td>
<td>10443.4794</td>
<td>13.92</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>period</td>
<td>1</td>
<td>1632.0742</td>
<td>1632.0742</td>
<td>2.17</td>
<td>0.1683</td>
</tr>
<tr>
<td>treat</td>
<td>1</td>
<td>14035.9203</td>
<td>14035.9203</td>
<td>18.70</td>
<td>0.0012</td>
</tr>
</tbody>
</table>

Fig. 2. Part of the output of SAS PROC GLM (General linear model procedure). DF: degrees of freedom, SS: sum of squares.
Table 1. Analysis of Variance Table for a Standard 2 × 2 Crossover Design (Example Data)

<table>
<thead>
<tr>
<th>Source of variation</th>
<th>d.f.</th>
<th>Type III sum of squares</th>
<th>Mean square</th>
<th>F</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carryover</td>
<td>1</td>
<td>335</td>
<td>335</td>
<td>0.45</td>
<td>0.518</td>
</tr>
<tr>
<td>Residual</td>
<td>11</td>
<td>114878</td>
<td>10443</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within-subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>1</td>
<td>14036</td>
<td>14036</td>
<td>18.70</td>
<td>0.001</td>
</tr>
<tr>
<td>Period</td>
<td>1</td>
<td>1632</td>
<td>1632</td>
<td>2.17</td>
<td>0.168</td>
</tr>
<tr>
<td>Residual</td>
<td>11</td>
<td>8254</td>
<td>750</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>138488</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Due to the limitation of the simplified 2 × 2 crossover design, all effects or interactions cannot be estimated separately. Therefore, depending on the model to be designed, the carryover effect is inherent in other effects or interactions. Here, the carryover effect is confirmed through the sequence. That is, in this crossover design model, the carryover effect is inherent in the sequence effect. Therefore, the result for the sequence is displayed as Carryover. d.f.: degrees of freedom.

**Type 3 Tests of Fixed Effects**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Num DF</th>
<th>Den DF</th>
<th>F Value</th>
<th>Pr &gt; F</th>
</tr>
</thead>
<tbody>
<tr>
<td>sequence</td>
<td>1</td>
<td>11</td>
<td>0.03</td>
<td>0.8611</td>
</tr>
<tr>
<td>period</td>
<td>1</td>
<td>11</td>
<td>2.17</td>
<td>0.1683</td>
</tr>
<tr>
<td>treat</td>
<td>1</td>
<td>11</td>
<td>18.70</td>
<td>0.0012</td>
</tr>
</tbody>
</table>

**Estimates**

<table>
<thead>
<tr>
<th>Label</th>
<th>Estimate</th>
<th>Standard Error</th>
<th>DF</th>
<th>t Value</th>
<th>Pr &gt;</th>
<th>Alpha</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>46.6071</td>
<td>10.7766</td>
<td>11</td>
<td>4.32</td>
<td>0.0012</td>
<td>0.05</td>
<td>22.8881</td>
<td>70.3262</td>
</tr>
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</table>

**Least Squares Means**

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<th>Estimate</th>
<th>Standard Error</th>
<th>DF</th>
<th>t Value</th>
<th>Pr &gt;</th>
<th>&lt;.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>treat</td>
<td>For</td>
<td>341.49</td>
<td>20.8110</td>
<td>11</td>
<td>16.41</td>
<td>&lt;.0001</td>
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<tr>
<td>treat</td>
<td>Sal</td>
<td>294.88</td>
<td>20.8110</td>
<td>11</td>
<td>14.17</td>
<td>&lt;.0001</td>
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**Differences of Least Squares Means**

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<th>Estimate</th>
<th>Standard Error</th>
<th>DF</th>
<th>t Value</th>
<th>Pr &gt;</th>
<th>&lt;.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>treat</td>
<td>For</td>
<td>Sal</td>
<td>46.6071</td>
<td>10.7766</td>
<td>11</td>
<td>4.32</td>
<td>0.0012</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 3. Part of the output of SAS PROC MIXED (Mixed effect model procedure). DF: degrees of freedom, Den DF: DF for the denominator, Num DF: DF for the numerator.

**Analysis of treatment effect**

```plaintext
PROC MIXED DATA = PEF;
   CLASS sequence subject period treat;
   MODEL pef = sequence period treat;
   RANDOM subject;(sequence);
   LSMEANS treat/PDIFF;
   ESTIMATE 'Treatment' treat 1 -1 /CL ALPHA = 0.05;
RUN;
```

The subject is included as a random effect through RANDOM subject (sequence). LSMEANS treat/PDIFF is a code that describes the P value for the difference between two treatments, and ESTIMATE ‘Treatment’ treat 1 -1 /CL ALPHA = 0.05 represents the estimate of the treatment effect and 95% confidence interval.

After confirming that other effects do not appear through the analysis of variance table, the treatment effect can be analyzed using a linear mixed effect model (Fig. 3). In pef, the average was 341.5 ml after inhalation of For and 294.9 ml after inhalation of Sal, and the pef was as high as 46.6 ml after inhalation of For (95% CI: 22.9 – 70.3 ml, P = 0.012).

**Conclusion**

The AB/BA design is a simplified form of the AA/AB/BA/BB crossover design introduced in clinical practice. It has many ad-
vantages, such as the ability of subjects themselves to reduce the influence of covariates by acting as a control group, and the higher power and statistical efficiency compared to those of the parallel design. However, there are also several limitations such as the difficulty in studying drugs with long half-lives, the requirement for subject stability even at different periods, administration of all treatments to one subject, and complicated processing of dropped or missing data. Therefore, it is necessary to understand the strengths and weaknesses of this study design and to apply an appropriate analysis method. It should also be noted that if a carry-over effect occurs when using a crossover design, only the results of the first period can be explored.

Conflicts of Interest

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

Author Contributions

Chi-Yeon Lim (Conceptualization; Resources; Supervision; Writing – review & editing)
Junyong In (Conceptualization; Software; Writing – original draft)

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References

Appendix

Fig. 1. Data Input in SAS

```
DATA PEF;
  INPUT sequence $ subject period treat $ pef;
DATALINES;
For-Sal 1 1 For 310
For-Sal 1 2 Sal 270
For-Sal 4 1 For 310
For-Sal 4 2 Sal 260
For-Sal 6 1 For 370
For-Sal 6 2 Sal 300
For-Sal 7 1 For 410
For-Sal 7 2 Sal 390
For-Sal 10 1 For 250
For-Sal 10 2 Sal 210
For-Sal 11 1 For 380
For-Sal 11 2 Sal 350
For-Sal 14 1 For 330
For-Sal 14 2 Sal 365
Sal-For 2 1 Sal 370
Sal-For 2 2 For 385
Sal-For 3 1 Sal 310
Sal-For 3 2 For 400
Sal-For 5 1 Sal 380
Sal-For 5 2 For 410
Sal-For 9 1 Sal 290
Sal-For 9 2 For 320
Sal-For 12 1 Sal 260
Sal-For 12 2 For 340
Sal-For 13 1 Sal 90
Sal-For 13 2 For 220
;
RUN;
```

Spaces are used to separate free formatted data. Data reported by Senn SJ and Auclair P (Statistics in Medicine 1990; 9: 1287-302) were permitted to reuse from the Wiley Publisher.
Effects of etomidate use in ICU patients on ventilator therapy: a study of 12,526 patients in an open database from a single center

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Background: There is a debate regarding the safety of etomidate. We evaluated the effects of etomidate on mortality in a large cohort of critical care patients.

Methods: This retrospective matched-cohort study was performed using the Medical Information Mart for Intensive Care version 3 (MIMIC-III) database. Among 12,526 adult patients who were prescribed etomidate or propofol on the first day of mechanical ventilation, 625 patients administered etomidate were statistically matched with 6,250 patients administered propofol. The primary outcome measures were all-cause in-hospital mortality, 48-hour survival, cardiovascular morbidity, and infectious morbidity. Logistic regression analysis with stepwise selection of variables was performed to examine the dose-mortality relationship of etomidate.

Results: All-cause in-hospital mortality was 1.84 times higher in the etomidate cohort (OR: 1.84, 98.75% CI: 1.42, 2.37). Compared to the propofol cohort, the etomidate cohort showed 57% lower odds of 48-hour survival (0.43 [0.27, 0.73]), no difference in odds of cardiovascular morbidity (0.86 [0.66, 1.12]), and 1.77 times higher odds of infectious morbidity (1.77 [1.35, 2.31]). Additionally, the odds of mortality increased by 1.36 times per 0.1 mg/kg of etomidate (1.36 [95% CI: 1.23, 1.49]).

Conclusions: Etomidate is a poor choice as a hypnotic drug on the first day of mechanical ventilation, as it is associated with a dose-dependent increase in all-cause mortality, and does not improve survival for the first 48 h.

Keywords: Dose-response relationship; Etomidate; Intensive care unit; Mortality; Propofol; Ventilator.

Introduction

The use of etomidate for tracheal intubation in septic patients has been reported to show no association with an increased mortality rate [1]. However, some meta-analyses indicated a strong association between mortality and the use of etomidate for tracheal intubation in patients with sepsis [2]. Further, a higher mortality rate has been reported in critically ill patients administered etomidate in comparison to other anesthetic induction agents [3]. Etomidate has also been reported to be associated with increased 30-day mortality when administered during anesthesia in patients undergoing non-cardiac surgery [4]. Conversely, Wagner et al. [5] reported no association between etomidate exposure and poor outcomes, including mortality, in patients undergoing cardiac surgery. The rea-
sons for these discrepancies regarding the safety of etomidate are unclear.

This retrospective study was performed to determine the dose-response relationship between etomidate exposure and mortality using the vast amount of data from the Medical Information Mart for Intensive Care version 3 (MIMIC-III), a database of combined real-world health records, prescriptions, dictionaries, diagnostic information (including disease-related groups), and complete survival and mortality information for patients admitted to the intensive care unit (ICU) of a large tertiary care hospital located in Boston, MA, USA.

Materials and Methods

Construction of cohorts

MIMIC-III is an open database of electronic health records of 38,597 adult critical care patients (>16 years) at the Beth Israel Deaconess Medical Center, a tertiary care hospital in Boston, MA, USA, from 2001 to 2012 [6]. The use of de-identified MIMIC-III data in the present study was not deemed research in human subjects by the Institutional Review Board (IRB) of the University of Massachusetts Medical School, which waived the requirement for informed consent. After completing the required training, all co-authors were granted access to MIMIC-III for free use of the data without additional IRB approval. The selection of patients in the etomidate and propofol cohorts was based on the following criteria.

- Common inclusion criteria: adult patients treated with a mechanical ventilator for at least 1 h.
- Etomidate cohort: patients prescribed etomidate (≤20 mg) on the first day of mechanical ventilation (cohort start date).
- Propofol cohort: patients prescribed propofol instead of etomidate on the first day of mechanical ventilation. These patients were never prescribed etomidate during admission.

Patients with a history of previous hospitalization within 7 days and body weight or height above or below the respective upper and lower 0.1 percentile were excluded. A total of 12,526 patients were enrolled in the study before matching cohorts (etomidate, n = 6,250; propofol, n = 6,250) (Supplementary Table 1).

Matching

The patients were matched based on the propensity to use etomidate. By preparing statistically matched cohorts, we minimized the heterogeneity of the patients due to the retrospective design. The matching procedure used a total of 43 variables consisting of 9 physical characteristics, 4 clinical features, and 30 disease components of the Elixhauser comorbidity index [7,8] as covariates for calculating the propensity scores. The nine physical characteristics were sex, three age groups (younger than 65, 65–86, and older than 86), four BMI groups (body mass index, <18.5, 18.5–25.0, 25.0–30.0, and >30 kg/m²), and ethnicity (white vs. non-white). The four clinical features were hypothalamic adrenal insufficiency as a primary diagnosis, previous history of treatment with adrenal suppressants (ketoconazole, metyrapone, suramin, aminoglutethimide, carbamazepine, phenobarbital, phenytoin, rifampin, and mitotane), admission before mid-2008, and a sequential organ failure assessment (SOFA) score >5.0. Adopting the nearest neighbor matching method, a 1:10 matching ratio, and targeting absolute values of standardized differences <0.1, a total of 6,875 patients were assigned after matching to the etomidate cohort (n = 625) or the propofol cohort (n = 6,250) (Supplementary Table 1).

Primary outcome measures

The four primary outcome variables were all-cause in-hospital mortality, survival for the first 48 h, cardiovascular morbidity, and infectious morbidity. Unless otherwise noted, in this manuscript mortality refers to all mortalities except those occurring within 48 h since sedative administration. Cardiovascular morbidity and infectious morbidity were judged using the ICD-9 code for diagnosis; the numbers in parentheses indicate the dotless version of the ICD-9 code. Cardiovascular morbidity was related to hypovolemia (27652), dialysis hypotension (45821), other iatrogenic hypotension (45829), atypical shock (78550), cardiogenic shock (78551), shock unrelated to trauma (78559), and cardiac and peripheral complications, unclassified (9971/9972). Infectious morbidity was due to ventilator-associated pneumonia (99731); infection of the central catheter (99931), bladder, or urological organs (99664 and 99665); infection of the stoma (tracheostomy, 51901; esophagostomy, 53086; gastrostomy, 53641; and colostomy or enterostomy, 56961); infection of the implanted prosthesis (99660, 99661, 99662, 99663, 99666, 99667, 99668, and 99669); and other post-operative infections (99859).

After the finding by Vinclair et al. [9] that adrenal inhibition was full-blown in 48-hour, we adopted a 48-hour interval after the day of etomidate administration as the guarantee period. Acute deaths after etomidate administration were excluded because they would generally have causes other than etomidate administration. Therefore, deaths that occurred within the initial 48 h after the
cohort start date were excluded when counting all-cause in-hospital mortality.

Secondary outcome measures including dose–mortality relationship with the exploration of other factors

The secondary outcomes were supplementation with corticosteroids (n), vasopressor therapy (n), cortisol blood concentration measured in the morning after the cohort start date (μg/dl), accumulated time of vasopressor therapy (h) summed after the cohort start date, duration of ICU stay (days), total duration of hospitalization (days), and dose–mortality relationship of etomidate.

To check the dose-mortality relationship that may exist in the etomidate cohort, factors that may influence mortality were explored in the post-matching cohorts. We removed all variables that contributed little to the overall regression model. Variables were selected by the Akaike's Information Criterion (AIC)-based stepwise selection method in pursuit of the most parsimonious model. All variables used for calculating the propensity score were used again in the logistic regression analysis, and a stepwise selection of the variables was performed. In the regression model using only the selected variables, a relationship was established between the administered dose (every 0.1 mg/kg) of etomidate and all-cause in-hospital mortality. In the dataset, neither LD<sub>50</sub> nor LD<sub>95</sub> was extrapolated as the observed dose ranges were not far beyond 0.5 mg/kg.

Blood pressure profile on the cohort start date

Systolic blood pressure (SBP) and mean blood pressure (MBP) on the cohort start date were compared between the two cohorts.

Data manipulation and analytical tools

After obtaining the rights to handle MIMIC-III, the entire dataset was imported and rebuilt as a copy of the SQL database on a personal computer having a 64-bit Darwin operating system. The codes for MIMIC-III shared by The Laboratory of Computational Physiology of the Massachusetts Institute of Technology (https://github.com/MIT-LCP/mimic-code/tree/main/mimic-iii/concepts), that included patients' comorbidities, vasopressor use, ventilator days, body weight, and height were utilized. Temporary tables were created using SQL and batch-queried into R version 3.5.5 (R: A language and environment for statistical computing, R Foundation for Statistical Computing, Austria. 2019). We employed the R software for all subsequent manipulations and analyses. We applied all statistical inferences, focusing on the size of the effect (odds ratio [OR] or Cohen’s d) and its associated uncertainty (CI), which complied with the American Statistical Association’s 2016 Statement on P values [10]. ORs were calculated using the conditional maximum likelihood method in the primary outcome and secondary measures, except the dose–response estimation from the log-odds in logistic regression analysis. To calculate the intervals, the alpha was adjusted to 98.75% (= (1 − [0.05/4]) × 100) for the four primary outcome measures, or 95% for other measures. To address the size of the effect, the OR was adopted for incidence data and Cohen’s d was used for interval data.

Results

The top 20 diagnoses for the admitted patients were obtained and are listed according to the after-matching cohorts in Supplementary Table 2. The maximum blood pressure was higher, while the minimum blood pressure was lower in the etomidate cohort than in the propofol cohort (Table 1).

Primary outcome measures

Overall, 6,690 of the 6,875 patients survived for the first 48 h after administration of the study drug. The patients receiving etomidate showed 1.84 times higher odds of hospital mortality (OR: 1.84 [98.75% CI: 1.42, 2.37]), 57% lower odds of survival for the first 48 h (0.43 [0.27, 0.73]), no significant difference in the odds of cardiovascular morbidity (0.86 [0.66, 1.12]), and 1.77 times higher odds of infectious morbidity (1.77 [1.35, 2.31]) than the propofol cohort (Fig. 1).

Secondary outcome measures

The frequencies of corticosteroid replacement and vasopressor therapy were 1.82 times and 1.39 times higher in the etomidate cohort than in the propofol cohort, respectively. A total of 3,399 cortisol measurements were made in 1,341 patients (195 and 1,146 patients in the etomidate and propofol cohorts, respectively). Etomidate was associated with a trivial decrease in the morning blood cortisol level (95% CI, Cohen's d = −0.30 μg/dl). In comparison to the propofol cohort, the etomidate cohort showed a longer cumulative vasopressor duration (42.7 vs. 68.1 h), total ICU stay (8.9 vs. 14.9 days), and number of hospital days (16.7 vs. 23.1 days) (Table 2). The administered dose of etomidate ranged from 0.02 to 0.50 mg/kg, with a mean of 0.19 mg/kg and median of 0.19 mg/kg, and Q1 and Q3 of 0.14 and 0.24, respectively. The estimated odds of mortality increased by 1.36 times per 0.1 mg/kg of etomidate (1.36 [95% CI: 1.23, 1.49]). These estimated OR of
**Table 1.** Blood Pressure Profiles of the Cohorts on the First Day of Mechanical Ventilation

<table>
<thead>
<tr>
<th></th>
<th>Etomidate (n = 625)</th>
<th>Propofol (n = 6,250)</th>
<th>Cohen's d</th>
<th>95% CI</th>
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<tbody>
<tr>
<td></td>
<td></td>
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<td></td>
<td>Lower</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>117.8</td>
<td>118.9</td>
<td>−0.1</td>
<td>−0.2</td>
</tr>
<tr>
<td>Minimum</td>
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<td>86.1</td>
<td>−0.3</td>
<td>−0.3</td>
</tr>
<tr>
<td>Maximum</td>
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<td>153.9</td>
<td>0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>77.7</td>
<td>78.8</td>
<td>−0.1</td>
<td>−0.1</td>
</tr>
<tr>
<td>Minimum</td>
<td>51.4</td>
<td>57.0</td>
<td>−0.4</td>
<td>−0.4</td>
</tr>
<tr>
<td>Maximum</td>
<td>116.9</td>
<td>109.1</td>
<td>0.2</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Cohen's d = (etomidate mean − propofol mean)/SD. SBP: systolic blood pressure, MBP: mean blood pressure.

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---

**Table 2.** Additional Outcome Measures

<table>
<thead>
<tr>
<th></th>
<th>Etomidate (n = 625)</th>
<th>Propofol (n = 6,250)</th>
<th>OR</th>
<th>Cohen's d*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>Steroid replacement (n)</td>
<td>41</td>
<td>232</td>
<td>1.82</td>
<td>-</td>
<td>1.26</td>
</tr>
<tr>
<td>Vasopressor (n)</td>
<td>436</td>
<td>3901</td>
<td>1.39</td>
<td>-</td>
<td>1.16</td>
</tr>
<tr>
<td>Cortisol level (μg/dl)*</td>
<td>24.2</td>
<td>26.3</td>
<td>-</td>
<td>−0.12</td>
<td>−0.30</td>
</tr>
<tr>
<td>Vasopressor duration (h)</td>
<td>68.1</td>
<td>42.7</td>
<td>-</td>
<td>0.26</td>
<td>0.17</td>
</tr>
<tr>
<td>ICU stay (days)</td>
<td>14.9</td>
<td>8.9</td>
<td>-</td>
<td>0.60</td>
<td>0.51</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>23.1</td>
<td>16.7</td>
<td>-</td>
<td>0.42</td>
<td>0.34</td>
</tr>
</tbody>
</table>

*Cohen's d = (etomidate mean − propofol mean)/SD. *A total of 3,399 cortisol measurements in 1,341 patients (195 and 1,146 patients in the etomidate and propofol cohorts, respectively). OR: odds ratio, ICU: intensive care unit.
The dose-mortality relationship did not change before and after the removal of other variables using the AIC-based stepwise selection method (Figs. 2 and 3). Male sex, age < 86 years, BMI > 18.5, SOFA score < 5.0, and absence of pre-existing adrenal insufficiency were associated with a better in-hospital survival rate. Non-elective admission and admission before mid-2008 were associated with poor in-hospital survival. The effects of all other potential factors are shown in Fig. 3.

Discussion

We found a relation between the dose of etomidate administered and mortality in ICU patients on ventilator support. Although we observed that an increase in etomidate dose was associated with a higher mortality rate, it was difficult to determine the presence of a causal link; randomized controlled trials are required to infer such a relation.

Etomidate seemed to be used selectively in patients with wide blood pressure fluctuations. However, the use of etomidate did not rescue patients in the first 48 h after its administration. Cardiovascular morbidity was not diminished despite the use of etomidate. Moreover, the etomidate cohort received vasopressor therapy more frequently and had a longer cumulative vasopressor duration. Further, the use of etomidate was associated with a higher rate of infectious morbidity and a higher incidence of subsequent corticosteroid replacement, which in turn was associated with a higher mortality rate.

The Bradford Hill criteria of causation indicate that when greater exposure leads to a greater incidence of the effect or an inverse proportion is observed, it can be taken to suggest a causal relationship. However, it should be noted that most previous studies examining the relationship between etomidate and a high mortality rate ignored the dose-mortality relationship. In this study, in addition to the application of a propensity score matching procedure, we calculated the dose-mortality relationship rather than using randomization. We established a relationship between etomidate dose and mortality, but our results by themselves cannot confirm the existence of a causal relationship. However, this is an important finding considering the miscellaneous and multifactorial characteristics of deaths of patients undergoing respiratory therapy. Moreover, our results may be useful as a basis for future research regarding mortality in ICU patients administered etomidate.

There were two additional notable aspects of the dose-mortality relationship indicated in this study. First, the estimates of the calculated OR of dose-mortality relationship remained consistent up to two decimal places in a vigorous stepwise selection of the variables (1.36 [1.23, 1.49] vs. 1.36 [1.23, 1.49] for before and after the variable-selection), thereby indicating that the dose-effect of etomidate on mortality was independent of other factors. Second, the calculated OR of dose-mortality relationship is 1.85 for the well-accepted dose regimen of the etomidate (0.2 mg/kg), which comes from the squared OR 1.36 of dose-mortality relationship for every 0.1 mg/kg etomidate dose. It indicates that the odds of death will be increased by 1.85 times for every 0.2 mg/kg increment in dose of etomidate. It is very cautious to compare the calculated OR 1.85 of dose-mortality relationship with the OR 1.84 for mortality of the etomidate cohort presented in Fig. 1, as the dose range of etomidate in current study was very wide from 0.02 to 0.5 mg/kg. Considering the fact that other variables had little influences on the derivation of the OR 1.36 of dose-mortality relationship for etomidate use, however, it would be worth studying further sensitivity analysis.

This study had some limitations due to its retrospective nature. First, the MIMIC-III dataset does not clearly mention the reason for prescribing the sedatives. We only gathered information on the prescription of etomidate and propofol and selected patients who were prescribed sedatives on the first day of mechanical ventilation. It was unclear whether the sedatives were used to facilitate intubation or for other purposes. We just assumed that the intensivists used sedatives in patients who required mechanical ventilation.

Second, the MIMIC-III dataset does not explain the physicians’ intentions in choosing etomidate over other drugs. We assumed that the intensivists utilized etomidate because of the benefit that it provides hemodynamic stability in patients in an unfavorable condition. Blood pressure fluctuations were not included in the initial list of variables for the matching procedure. This significant factor is emphasized by the fact that, as presented in Table 1, the average SBP and average MBP of the two cohorts were almost the same. However, fluctuations were observed in SBP, which were wider in the etomidate cohort than in the propofol cohort (82 vs. 68 mmHg, respectively). Although the etomidate cohort showed more severe SBP fluctuations, the MBP was almost the same in the two cohorts, and the difference in the extent of fluctuation between the two groups was 14 mmHg. This greater blood pressure fluctuation indicates an unstable hemodynamic state, which may have affected the decisions of the intensivists in selecting the etomidate which has minimal effect on vital signs.

In conclusion, etomidate usage showed a significant dose-dependent relationship with mortality in ICU patients undergoing mechanical ventilation for a variety of diagnoses. Etomidate was not helpful in improving the initial survival of ICU patients showing unstable vital signs; the etomidate cohort showed 57% lower...
Fig. 2. Etomidate dose-effect on mortality before the variable selection. All variables were included tentatively to explain the mortality with the dose of etomidate. BMI: body mass index, SOFA: sequential organ failure assessment, AIDS: acquired immune deficiency syndrome.
odds of survival in the first 48 h than the propofol cohort. Although etomidate provides favorable hemodynamics, it failed to improve survival in the first 48 h after administration, and showed a dose-dependent association with increased overall mortality rate (Supplementary Digital Content 3)

Fig. 3. Dose-mortality relationships with the selection of factors. The effects of the dose of etomidate on mortality were adjusted after a stepwise selection of variables. BMI: body mass index, SOFA: sequential organ failure assessment, AIDS: acquired immune deficiency syndrome.

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**Conflicts of Interest**

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

**Author Contributions**

Ha Yeon Park (Conceptualization; Data curation; Investigation; Resources; Writing – original draft; Writing – review & editing)

Younsk Lee (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Visualization)

Chi-Yeon Lim (Data curation; Formal analysis; Software)

Mina Kim (Data curation; Resources; Software)

Jieun Park (Data curation; Investigation; Resources)

Teakseon Lee (Data curation; Formal analysis; Software)

**Supplementary Materials**

Supplementary Table 1. Patient characteristics and pre-existing conditions before and after propensity score matching

Supplementary Table 2. Top 20 Admission Diagnoses in After-Matching Cohorts

Supplementary Digital Content 3. The full analytical code was developed by the authors and is freely available at https://github.com/ylee03/etomidate_kja

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**References**


Hemodynamic effects of norepinephrine versus phenylephrine infusion for prophylaxis against spinal anesthesia-induced hypotension in the elderly population undergoing hip fracture surgery: a randomized controlled trial

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Departments of ¹Anesthesia and Critical Care Medicine, ²Orthopedic Surgery, Cairo University, Cairo, Egypt

Background: Elderly population are at increased risk of spinal anesthesia-induced hypotension increasing their risk for postoperative morbidity and mortality. This study aimed to compare the hemodynamic effects of prophylactic infusion of norepinephrine (NE) versus phenylephrine (PE) in elderly patients undergoing hip fracture surgery under spinal anesthesia.

Methods: Elderly patients scheduled for hip fracture surgery were randomized to receive either NE infusion (8 µg/min) (NE group, n = 31) or PE infusion (100 µg/min) (PE group, n = 31) after spinal anesthesia. Outcomes included mean heart rate, mean blood pressure, cardiac output, incidence of spinal anesthesia-induced hypotension, incidence of bradycardia, and incidence of hypertension.

Results: Sixty-two patients with a mean age of 71 ± 6 years were included in the final analysis (31 patients in each group). The NE group showed a higher mean heart rate and cardiac output than the PE group. The NE group had a lower incidence of reactive bradycardia (10% vs. 36%, P = 0.031) and hypertension (3% vs. 36%, P = 0.003) than the PE group. No study participant developed hypotension, and the mean blood pressure was comparable between the two groups.

Conclusions: Both NE and PE infusions effectively prevented spinal anesthesia-induced hypotension in elderly patients undergoing hip fracture surgery. However, NE provided more hemodynamic stability than PE; maintaining the heart rate, higher cardiac output, less reactive bradycardia, and hypertension.

Keywords: Elderly; Hip fracture surgery; Hypotension; Norepinephrine; Phenylephrine; Spinal anesthesia.

Introduction

In the elderly, the incidence of spinal anesthesia-induced hypotension can be as high as 73% [1], exposing this vulnerable group to reduced organ perfusion and increasing the risk of perioperative morbidity and mortality [2,3].
Sympathetic blockade after spinal anesthesia results in venodilation, which reduces venous return and hence cardiac output and results in hypotension [4]. Therefore, the use of alpha-adrenergic agonist drugs induces constriction of compliant veins, effectively reverses the vasodilatory effect of spinal anesthesia, and reduces the need for unnecessary fluid loading [5]. In the elderly population, the mechanism of hypotension differs from that in young adults, as it is mainly caused by a reduced stroke volume rather than systemic vascular resistance [6].

The prophylactic use of vasopressor agents for preventing spinal anesthesia-induced hypotension is warranted in high-risk populations and is currently recommended in obstetric anesthesia [7]. In the elderly population, although the use of vasopressor prophylaxis makes sense, the available data for drug groups and doses are sparse. Phentylephrine (PE) is a synthetic α-agonist vasoconstrictor that has been evaluated (in maintaining hemodynamic parameters) during spinal anesthesia in the elderly population [1]. However, PE (being a pure α agonist) was reported to decrease the heart rate and cardiac output [8], which limits its use in patients with reduced cardiac contractility; this fact makes the use of PE in elderly patients questionable. Furthermore, Jakobsson et al. [9] reported that spinal anesthesia-induced hypotension in the elderly could be a sign of impaired cardiac performance; therefore, PE might not be the ideal vasopressor for use in this population.

Norepinephrine (NE) has a agonistic and weak β agonistic activity; thus, in addition to its vasoconstriction properties, NE has modest cardio-stimulatory function compared to PE [10]. NE has been successfully evaluated for prophylaxis against spinal anesthesia-induced hypotension in obstetric anesthesia [8,11,12]. In this study, we aimed to compare the hemodynamic effect of prophylactic NE versus PE infusion in elderly patients undergoing hip fracture surgery under spinal anesthesia.

### Materials and Methods

This randomized controlled trial was conducted in the orthopedic surgical theater at Cairo University Hospital from January to March 2020 after the Institution Research Ethics Committee approval (No: D-7-2019) and clinical trial registration (NCT 04195321). Written informed consent was obtained from all patients before their enrollment in the study. The study was conducted in accordance with the Helsinki Declaration-2013.

Elderly patients (> 60 years), American Society of Anesthesiologists physical status I–II, scheduled for hip fracture surgery under spinal anesthesia, were included. Patients with known cardiac abnormalities (left ventricular ejection fraction < 50% or decompen-sated heart failure, heart block, arrhythmia), uncontrolled hypertension, hyperthyroidism, and monoamine oxidase inhibitor use were excluded from the study. Patients with a history of allergy to any of the study drugs and patients who had contraindications for spinal anesthesia were excluded.

Patients were randomly allocated at a 1 : 1 ratio to either the NE group or the PE group, using a computer-generated random sequence and concealed envelopes that contained the drug preparation instruction.

Preoperative fasting instructions were 6 hours for solid food, and clear fluid was allowed up to 2 hours preoperatively. Upon arrival to the operating room, routine monitors (electrocardiogram, pulse oximetry, and non-invasive blood pressure monitor) were applied; an intravenous line was secured, and routine pre-medications (ranitidine 50 mg slow IV) were administered. Baseline preoperative blood pressure was recorded in the supine position with an average of 3 readings, with a difference of less than 5 mmHg.

Before the initiation of spinal anesthesia for all study patients, an electrical cardiometry device ICON™ (Osypka Cordiotonic, German) was applied to the patient through 4 electrodes at the following sites: below the left ear, above the midpoint of the left clavicle, left mid-axillary line at the level of the xiphoid process, and 5 cm inferior to the third electrode. Stroke volume variability (SVV) was measured while the patient maintained standard calm breathing at 8 breaths/min for 1 min before the intrathecal injection. The patient with SVV ≥ 13% was considered a fluid responder [13] and received a fluid bolus of 8 ml/kg Ringer’s acetate (FIBCO, Egypt) over 10 min. The fluid bolus was repeated until the SVV became less than 13%, and spinal anesthesia was then performed.

After the induction of spinal anesthesia, maintenance fluid at 2 ml/kg/h of Ringer acetate was initiated.

Spinal anesthesia was performed in the sitting position at the level of L2–3 or L3–4 interspaces with a 25-gauge spinal needle. After confirming cerebrospinal fluid flow, 10 mg of 0.5% hyperbaric bupivacaine plus 25 µg fentanyl were injected. The degree of sensory block (cold test by alcohol gauze) was assessed in the following sites: below the left ear, at the level of T6–8 dermatomal level. If spinal anesthesia failed, the patient was excluded from the study and was managed according to the attending anesthetist’s discretion, local expertise, and clinical practice.

Vasopressor infusion according to the randomization was initiated after obtaining cerebrospinal fluid, through the same line as IV fluids aided by a three-way stopcock, after the induction of spinal anesthesia.

Patients in the NE group received NE infusion (8 mg norepinephrine bitartrate/4 ml, equivalent to 4 mg norepinephrine
base/4 ml, Alexandria Co., Egypt) at a starting rate of 1 ml/min of 8 µg/ml solution (prepared by diluting 4 µg NE in 500 ml saline).

Patients in the PE group received PE infusion (10 mg/1 ml ampoule, Sterop Co., Belgium) at a starting rate of 1 ml/min of 100 µg/ml solution (prepared by diluting 10 µg of PE in 100 ml saline).

All drug preparations were performed by a research assistant who was also responsible for opening the envelope and group assignment with no further involvement in the study. After diluting the drug as instructed, the diluted drug was then withdrawn into a 50 ml syringe to be given to the attending anesthetist.

If any episode of spinal anesthesia-induced hypotension occurred (defined as mean blood pressure < 80% of the baseline reading during 45 min after the spinal block), the protocol was set to be managed by 5 µg NE, and the infusion rate was increased by 20%. If the hypotensive episode persisted for 2 min, another bolus of norepinephrine was administered.

If bradycardia (defined as heart rate ≤ 50 beats/min) with hypotension occurred, it was managed with 0.5 mg of atropine IV. If bradycardia occurred with hypertension (mean blood pressure > 125% of baseline), the vasopressor infusion was stopped.

Hypertension was defined as an increased mean blood pressure of > 125% of the baseline reading. Hypertensive episodes that persisted for 2 consecutive readings were managed by reducing the infusion by 50%. If hypertension persisted after the reduction of the infusion rate, the vasopressor infusion was stopped. The vasopressor resumed at 50% of the starting dose if there was a further decline in blood pressure.

Vasopressor infusion was continued for 45 min after spinal anesthesia. If the patient develops hypotension after discontinuation of the infusion, blood pressure management will depend on the fluid status of the patient. If hypotension occurred because of blood loss, 3 : 1 Ringer’s acetate was infused as a replacement until transfusion threshold is met; thereafter, the packed red blood cell is given with a target hemoglobin level of ≥ 9 g/dl. In case hypotension was unrelated to blood loss, the vasopressor was re-initiated at the last dose before discontinuation.

The primary outcome was mean heart rate during vasopressor infusion.

For secondary outcomes heart rate, cardiac output, and mean blood pressure (baseline, then every 2 min after spinal anesthesia for 20 min, then every 5 min until the end of the operation) were analyzed. Other outcomes included the incidence of bradycardia, tachycardia (heart rate > 100 beats/min), spinal anesthesia-induced hypotension, and reactive hypertension. Pre- and intraoperative fluid volume, blood loss, and the need for blood transfusion were recorded.

Statistical analysis

The mean heart rate during the first 45 min after spinal anesthesia under PE infusion was 68 ± 9 beats/min, as calculated from a pilot study. We calculated our sample size to detect a mean difference of 10 beats/min between both groups. Using MedCalc Software version 14 (MedCalc Software bvba, Belgium), a minimum of 28 patients were required to have a study power of 80% and an alpha error of 0.05. We performed a more conservative calculation by increasing the study power to 99%, which increased the sample size to 62 patients (31 patients per group). To compensate for any dropouts, the final number of envelopes was 68 (34 per group).

Data analysis was performed using Statistical Package for Social Science (SPSS) software, version 21 for Microsoft Windows (SPSS Inc., USA). Categorical data are reported as numbers and percentages and were analyzed using the chi-square test. Continuous data were checked for normality using the Shapiro-Wilk test. Normally distributed data are presented as mean ± SD and were analyzed using the Mann-Whitney U test. For repeated measures, a two-way repeated measure analysis of variance (ANOVA) was used to evaluate drug (between-group factor) and time (repeated measures). We analyzed the hemodynamic data for 60-min (shortest intervention time). The Bonferroni test was used to adjust for multiple comparisons. A P value of 0.05 or less was considered significant.

Results

Seventy patients were screened for eligibility, and two patients were excluded because they did not satisfy the study’s inclusion criteria. The 68 included patients were randomized into either NE (n = 34) or PE (n = 34) groups. Six patients (three from each group) were not included in the final analysis. Sixty-two patients were available for the final analysis (31 patients in each group) (Fig. 1).

The mean age of the included patients was 71 ± 6 years, and 33 (53%) were men. Demographic data and baseline hemodynamic characteristics were comparable between the study groups (Table 1).

The mean heart rate during vasopressor infusion was higher in the NE group than in the PE group (79 ± 8.4 and 68 ± 4.4 beats/min, respectively, P < 0.001) (Table 2, Fig. 2). The heart rate was generally maintained during NE infusion in relation to the baseline readings. During PE infusion, the heart rate decreased in relation to the baseline reading (Fig. 2). Furthermore, the incidence
Assessed for eligibility (n = 70)
  Randomized (n = 68)
    Excluded (n = 2)
      • Not meeting inclusion criteria (n = 2)
      • Declined to participate (n = 0)
      • Other reasons (n = 0)
    • Other reasons (n = 0)
  • Other reasons (n = 0)

Allocated to intervention (n = 34)
  • Received allocated intervention (n = 31)
  • Did not receive allocated intervention (failed spinal anesthesia) (n = 3)

Allocated to intervention (n = 34)
  • Received allocated intervention (n = 32)
  • Did not receive allocated intervention (failed spinal anesthesia) (n = 2)

Lost to follow-up (poor cardiometry signal) (n = 1)
  • Discontinued intervention (n = 0)

Lost to follow-up (n = 0)
  • Discontinued intervention (n = 0)

Analyzed (n = 31)
  • Excluded from analysis (n = 0)

Analyzed (n = 31)
  • Excluded from analysis (n = 0)

Fig. 1. CONSORT flow diagram for patient enrollment.

Table 1. Demographic Data and Baseline Hemodynamic Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>NE group (n = 31)</th>
<th>PE group (n = 31)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>71 ± 6.4</td>
<td>71 ± 5.8</td>
<td>0.869</td>
</tr>
<tr>
<td>Sex (M)</td>
<td>18 (58)</td>
<td>15 (48)</td>
<td>0.611</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>81 ± 12</td>
<td>79 ± 13</td>
<td>0.641</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>170 ± 8.6</td>
<td>167 ± 8.8</td>
<td>0.153</td>
</tr>
<tr>
<td>ASA PS</td>
<td></td>
<td></td>
<td>0.791</td>
</tr>
<tr>
<td>I</td>
<td>10 (32)</td>
<td>12 (39)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>21 (68)</td>
<td>19 (61)</td>
<td></td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td>0.732</td>
</tr>
<tr>
<td>Bipolar hemiarthroplasty</td>
<td>17 (55)</td>
<td>14 (45)</td>
<td></td>
</tr>
<tr>
<td>Total hip replacement</td>
<td>2 (7)</td>
<td>2 (7)</td>
<td></td>
</tr>
<tr>
<td>Dynamic hip screw</td>
<td>12 (39)</td>
<td>15 (48)</td>
<td></td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>70 (60, 80)</td>
<td>60 (60, 80)</td>
<td>0.665</td>
</tr>
<tr>
<td>Level of spinal anesthesia</td>
<td>T8 (8, 10)</td>
<td>T8 (6, 10)</td>
<td>0.380</td>
</tr>
<tr>
<td>Preoperative fluid volume (ml)</td>
<td>536 (480, 616)</td>
<td>520 (488, 616)</td>
<td>0.756</td>
</tr>
<tr>
<td>Baseline heart rate (beats/min)</td>
<td>78 ± 10</td>
<td>82 ± 6</td>
<td>0.061</td>
</tr>
<tr>
<td>Baseline mean blood pressure (mmHg)</td>
<td>81 ± 12</td>
<td>80 ± 7</td>
<td>0.710</td>
</tr>
<tr>
<td>Baseline cardiac output (L/min)</td>
<td>6.6 ± 1.2</td>
<td>7 ± 0.8</td>
<td>0.175</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, number of patients (%) or median (Q1, Q3). ASA PS: American Society of Anesthesiologist physical status. NE group: norepinephrine group, PE group: phenylephrine group.

of bradycardia was lower in the NE group than in the PE group (3/31 [10%] and 11/31 [36%], respectively, P = 0.031) (Table 2). None of the included patients developed tachycardia or hypotension. There was no statistically significant difference in mean blood pressure readings between both groups during drug infusion. The mean blood pressure was higher than the baseline value starting at the eighth and second min after the onset of NE and PE infusion, respectively, until the end of the infusion (Fig. 3). One (3%) patient in the NE group and eleven (36%) patients in the PE group developed reactive hypertension (P = 0.003). (Table 2) The episode of reactive hypertension in the NE group occurred just before the time to terminating the infusion as per the study.
The episodes of reactive hypertension in PE usually occurred 2 or 4 min after the onset of PE infusion and lasted for ≤ 2 min and did not require a reduction of the infusion rate.

Cardiac output was higher in the NE group than in the PE group. Furthermore, the cardiac output increased in the NE group in relation to the baseline reading, while it decreased in relation to the baseline in the PE group (Table 2, Fig. 4).

Immediately after termination of the NE infusion, the heart rate, mean blood pressure, and cardiac output were comparable to the baseline readings. In the PE group, the heart rate and cardiac output continued to be lower in relation to the baseline 15 min after the discontinuation of the infusion (Figs. 2–4).

Other intraoperative outcomes, namely intraoperative fluid volume, blood loss, and the need for blood transfusion, were comparable between the two groups (Table 2).

### Discussion

We report that both NE and PE successfully prevented spinal anesthesia-induced hypotension in the elderly. However, NE infusion maintained the heart rate and cardiac output better than PE infusion. The incidence of reactive bradycardia and hypertension was lower, and the mean heart rate was higher in the NE group than in the PE group. These findings are similar to those of previous reports that compared the two drugs in the obstetric population [8,14].

Both NE and PE exert their vascular action through the activation of α-receptors, resulting in vasoconstriction in the arterial and venous sides, increasing systemic vascular resistance and venous return. Owing to its pure α-stimulation activity, PE infusion causes a reflex reduction in the heart rate and cardiac output [15] in addition to a direct effect on the left ventricular contractility.
In contrast, NE has a modest β-receptor agonist activity, which maintains blood pressure without reducing cardiac output. It has been reported that lower doses of PE could reduce the incidence of reactive hypertension but do not lower the incidence of bradycardia [17, 18].

The blood pressure values were comparable between the two study groups. This is probably because we used equipotent doses of the two study drugs. We selected the dose of PE according to Ferré et al. [1], in the same population in which the authors used 100 µg/min to maintain blood pressure. For a fair comparison, we aimed to use an equipotent dose of NE in the other group. Ngan Kee [19] estimated that the relative potency between PE and NE was 1:13; therefore, we hypothesized that an NE dose of 8 µg would be equipotent to a PE dose of 100 µg.

Intraoperative hypotension is an independent risk factor for postoperative 5- and 30-day mortality in patients undergoing hip surgery [2]. Spinal anesthesia, the most common route of anesthesia in hip surgery, is usually associated with hypotension, whose risk is increased in elderly patients. This increased risk is due to age-related cardiovascular changes, such as increased basal sympathetic activity and reduced baroreceptor sensitivity [9]. Furthermore, spinal anesthesia-induced hypotension can occur even
in pre-hydrated elderly patients [20,21]. Thus, the use of prophy-
lactic vasopressors for preventing hypotension is increasingly
used in vulnerable populations and is already recommended in
obstetric practice [22]. PE is the most commonly used drug for
prophylaxis and management of postspinal hypotension. Howev-
er, PE infusion is frequently associated with bradycardia; this was
reported in obstetric [8,14] and general surgical patients [16] and
was present in 36% of our patients. With advanced age, there is
progressive stiffness of the myocardium; hence, the cardiac output
is more dependent on active filling from atrial contraction [23].
Therefore, reduction of heart rate in the elderly is associated with
reduced cardiac output, which in turn would affect organ oxygen
delivery [9]. In the elderly, the main mechanism of spinal anesthe-
sia-induced hypotension is reduced stroke volume [6] and the in-
ability to increase cardiac output [9] rather than a reduction in
systemic vascular resistance. In addition to bradycardia, PE has
been reported to reduce global left ventricular function [16].
Therefore, it is necessary to use a drug with the least depressing
effect on heart rate and, subsequently, the cardiac output.

The heart rate and cardiac output began to increase after dis-
continuation of the PE infusion but remained lower than the
baseline levels until the end of the analysis, while the mean blood
pressure returned to baseline level 5 min after terminating the in-
fusion. This delayed return of the heart rate and the cardiac out-
put to the baseline level might be explained by the age-related de-
crease in baroreceptor sensitivity to changes in blood pressure
[24].

The current study introduces, for the first time, NE infusion in
the elderly population during spinal anesthesia. By comparing
equipotent doses of NE and PE, NE was able to maintain the
blood pressure without reducing the heart rate or cardiac output.
Since cardiac output is a major determinant of oxygen delivery
[25], NE would be able to preserve oxygen delivery in the elderly.
By maintaining hemodynamic stability, NE might be beneficial in
elderly patients with a high prevalence of impaired myocardial
contractility [24,26].

The current study has some limitations. First, it is a single-cen-
ter study. Second, we did not include patients with cardiac comor-
bidities. Future research could evaluate the efficacy of both drugs
in these patients. Third, we used the available evidence for choos-
ing the equipotent dose of NE to PE, depending on the data ob-
tained from the obstetric population. Future dose-response stud-
ies are needed to identify equipotent doses of the two drugs and
optimum dosing in the elderly population. Lastly, the cardiac out-
put was assessed noninvasively using electric cardiometry. Electric
cardiometry-derived absolute cardiac output values were reported
as not interchangeable with the thermodilution method [27];
however, electric cardiometry had acceptable trending ability [28];
thus, it was used to follow-up the changes in the cardiac output in
various populations [29,30].

In conclusion, both NE and PE infusions effectively prevented
spinal anesthesia-induced hypotension in elderly patients under-
going hip fracture surgery. However, NE provided more hemody-
namic stability than PE in the form of maintaining the heart rate,
higher cardiac output, less reactive bradycardia, and hypertension.
Future dose-response studies are needed to identify the equipo-
tent doses of the two drugs and optimum dosing in the elderly
population.

Conflicts of Interest

No potential conflict of interest relevant to this article was re-
ported.

Author Contributions

Maha Mostafa Ahmad (Conceptualization; Data curation; Formal
analysis; Investigation; Methodology; Supervision; Validation;
Writing – original draft)

Ahmed Hasanin (Conceptualization; Data curation; Formal
analysis; Investigation; Methodology; Project administration; Re-
sources; Supervision; Validation; Visualization; Writing – original
draft; Writing – review & editing)

Mai Y Taha (Data curation; Investigation; Methodology;
Resources; Validation; Writing – original draft; Writing – review & edit-
ing)

Mohamed Elsayad (Data curation; Investigation; Methodology;
Resources; Validation; Visualization; Writing – original draft;
Writing – review & editing)

Omar Taalab (Conceptualization; Data curation; Investigation;
Methodology; Resources; Validation; Visualization; Writing – original
draft; Writing – review & editing)

Maha Mostafa Ahmad (Conceptualization; Data curation; Formal
analysis; Investigation; Methodology; Resources; Writing – original draft; Writing – review & editing)

Ashraf Rady (Conceptualization; Investigation; Methodology;
Project administration; Resources; Supervision; Validation; Visu-
alization; Writing – original draft; Writing – review & editing)

Bassant Abdelhamid (Conceptualization; Data curation; Investi-
gation; Methodology; Project administration; Supervision; Vali-
dation; Visualization; Writing – original draft; Writing – review & editing)

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Effect of intravenous dexamethasone on the duration of postoperative analgesia for popliteal sciatic nerve block: a randomized, double-blind, placebo-controlled study

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Background: Intravenous (IV) dexamethasone prolongs the duration of a peripheral nerve block; however, there is little available information about its optimal effective dose. This study aimed to evaluate the effects of three different doses of IV dexamethasone on the duration of postoperative analgesia to determine the optimal effective dose for a sciatic nerve block.

Methods: Patients scheduled for foot and ankle surgery were randomly assigned to receive normal saline or IV dexamethasone (2.5 mg, 5 mg, or 10 mg). An ultrasound-guided popliteal sciatic nerve block was performed using 0.75% ropivacaine (20 ml) before general anesthesia. The duration of postoperative analgesia was the primary outcome, and pain scores, use of rescue analgesia, onset time, adverse effects, and patient satisfaction were assessed as secondary outcomes.

Results: Compared with the control group, the postoperative analgesic duration of the sciatic nerve block was prolonged in groups receiving IV dexamethasone 10 mg (P < 0.001), but not in the groups receiving IV dexamethasone 2.5 mg or 5 mg. The use of rescue analgesics was significantly different among the four groups 24 h postoperatively (P = 0.001) and similar thereafter. However, pain scores were not significantly different among the four groups 24 h postoperatively. There were no statistically significant differences in the other secondary outcomes among the four groups.

Conclusions: This study demonstrated that compared to the controls, only IV dexamethasone 10 mg increased the duration of postoperative analgesia following a sciatic nerve block for foot and ankle surgery without the occurrence of adverse events.

Keywords: Analgesia; Ankle; Dexamethasone; Foot; Intravenous injections; Nerve block; Pharmaceutic adjuvants; Sciatic nerve.
account of its potential neurotoxicity [5]. In addition, there is concern about the potential hazard of precipitation when LA is mixed with dexamethasone [6]. Thus, intravenous (IV) administration of dexamethasone can be an alternative option, although perineural dexamethasone is superior to IV dexamethasone in prolonging postoperative analgesia as seen in a previous study [7]. In contrast to perineural dexamethasone, dose-finding studies investigating IV dexamethasone, especially for lower extremity blocks, remain scarce.

Therefore, we compared the effect of three different IV dexamethasone doses on postoperative analgesic duration after an ultrasound-guided popliteal sciatic nerve block to determine the optimal effective dose of dexamethasone as an adjuvant. We hypothesized that 2.5 mg, 5 mg, and 10 mg of IV dexamethasone would increase the postoperative analgesic duration of sciatic nerve block by at least 25% when compared with the control group.

Materials and Methods

This trial was approved by the Institutional Review Board of Inha University Hospital (Incheon, South Korea; #2016-050-014) and registered with the Clinical Trial Registry of Korea (https://cris.nih.go.kr/cris/index.jsp; identifier: KCT0002486; principal investigator: Jang Ho Song; date of registration: 04.04.2017) before patient enrollment. This prospective randomized study was undertaken at Inha University Hospital in accordance with the Helsinki Declaration. Adult inpatients with an American Society of Anesthesiologists physical status classification I–III scheduled to undergo foot and ankle surgery, with surgical incision expected to be outside of the saphenous nerve territory, were enrolled between April 2017 and December 2018. In case of ankle fracture, we excluded patients who were expected to undergo surgical procedures with medial ankle incision and open reduction and internal fixation with plate fixation. Patients with contraindications to regional anesthesia, body mass index > 35 kg/m², pre-existing neuropathy, diabetes, chronic steroid or opioid use, allergy to study medications, or pregnancy were also excluded. Written informed consent was obtained from all the patients.

Using a computer-generated random assignment and concealment method with sealed envelopes, patients were randomly allocated to receive IV saline 0.9% (control [group C]) or a dexamethasone (5 mg/ml) dose of 2.5 mg (group D2.5), 5 mg (group D5), or 10 mg (group D10) [8]. Sciatic nerve block was performed under ultrasound guidance using 20 ml of ropivacaine 0.75%. We chose ropivacaine to hasten the onset time of the block and prolong its duration [9–11]. Sealed envelopes with the study group allocation were opened before the block placement, and study solutions were prepared with syringes containing 2 ml by one of the authors who was not involved in performing the blocks, patient care, or outcome assessment. The study drug was administered before the block placement. The anesthesiologist performing the blocks, surgeons, and outcome assessors were blinded to the group allocation.

Block technique

Standard monitoring techniques, including electrocardiography, noninvasive blood pressure monitoring, and pulse oximetry, were applied to all patients along with supplemental oxygen on arrival to the induction room and used throughout the procedure. All patients were administered IV midazolam (0.03 mg/kg) and fentanyl (1 µg/kg) for sedation and anxiolysis before the block. All the blocks were performed by the same anesthesiologist. Patients received the sciatic nerve block via a popliteal approach, with a portable ultrasound unit equipped with a 6–13 MHz linear probe (Vivid q, GE Healthcare, USA) and an 80 mm 22-gauge needle (UniPlex NanoLine, Pajunk, Germany). The nerve stimulator was set at 0.5 mA, 0.1 ms, and 1 Hz. Patients were placed in the lateral decubitus position, with the operative leg in a non-dependent position. The tibial nerve was first identified in popliteal crease. Subsequently, probe was moved proximally until it merges with the common peroneal nerve. After disinfection and skin infiltration with 2% lidocaine (2 ml), the needle was advanced using an out-of-plane technique until its tip was positioned between the tibial and peroneal nerves inside the paraneurale sheath [12]. A small volume (<1 ml) of saline was initially injected to ensure that the needle tip was correctly positioned. After the negative aspiration, 20 ml of ropivacaine 0.75% was injected incrementally. Any adverse events (such as vascular puncture, LA toxicity, or unintentional paresthesia) during the block administration were noted accordingly.

Block assessment

Following the LA administration, two investigators evaluated sensory and motor block onset every 5 min for 30 min. Sensory block was assessed in the tibial (plantar surface of the foot) and peroneal (dorsum of the foot) nerves using a cold test and as per the following scale: 0 = normal sensation; 1 = less cold; and 2 = not cold, when compared with the contralateral extremity. Motor block (plantar flexion of the tibial nerve and dorsiflexion of the peroneal nerve) was assessed using the following scale: 0 = no block; 1 = paresis; and 2 = paralysis. The onset times to sensory
(time after completion of LA injection to loss of cold sensation in all nerve territories) and motor (time after completion of LA injection to paralysis of the tibial and peroneal nerve) blocks were recorded. Success of block was defined as analgesia in the tibial and peroneal nerves dermatomes and a lack of requirement for supplementary analgesia for pain in the surgical wound in the post-anesthesia care unit (PACU). Only patients with successful blocks were included in this study.

**Perioperative management**

Due to the relatively long duration of tourniquet compression and assessment of the exact cause of postoperative pain (sciatic or saphenous nerve territory), patients underwent standard general anesthesia by a blinded attending anesthesiologist after the 30 min evaluation. Anesthesia was induced using propofol with endotracheal intubation facilitated by cisatracurium. Anesthesia was maintained using 40% oxygen in air mixture and 2–3% sevoflurane. Muscle relaxation was antagonized using pyridostigmine and glycopyrrolate. After the surgical procedure, patients were transferred to the PACU and they stayed there until they met the PACU discharge criteria.

In the PACU, pain scores were assessed using a numerical rating scale (NRS) for pain (0 = no pain; 10 = worst possible pain) at 30 min after PACU arrival. Patients reporting an NRS score > 3 were administered IV fentanyl 25 µg every 10 min until they were comfortable. Patients who reported medial ankle pain were excluded from the study.

Standardization of postoperative analgesia was carried out. All patients received 1 g of IV paracetamol every 6 h, irrespective of pain status. For rescue analgesia, patients were instructed to request analgesics (diclofenac 75 mg via intramuscular route) when an NRS of > 3 was reported on the operated foot or ankle. Persistent pain was treated with 50 mg IV tramadol. Further, meperidine 25 mg IV was administered to the patient in case of persistent pain, despite the use of diclofenac and tramadol.

**Outcome measurement**

The primary outcome was the duration of postoperative analgesia, which was defined as the time between the end of the LA injection and the first request for rescue analgesia for surgical pain in the operative extremity. For data analysis, patients who did not request any analgesics within the first 36 h had their duration of analgesia recorded as 36 h. The primary outcome was determined from their medical records. Secondary outcomes included pain scores, use of rescue analgesia, onset time to sensory and motor block, incidence of PONV, adverse effects, and patient satisfaction, respectively. An investigator blinded to group allocation assessed the following parameters 24 h after surgery: pain scores, incidence of PONV, adverse event(s), and patient satisfaction. The use of supplemental analgesics during the first 36 h after surgery was also recorded. The incidence of PONV was noted during the first 24 h after surgery. Any adverse events (e.g., paresthesia, numbness, or motor weakness) were also noted. Patient satisfaction was evaluated using an NRS (0 = very dissatisfied; 10 = very satisfied) [13]. Each patient was followed up with an attendant surgeon for 8 weeks to identify any neurological deficits or wound infection in the operative limb.

**Statistical analysis**

Sample size calculation was performed using data from a previous study that reported a postoperative analgesic duration of 15.4 h following a sciatic nerve block [14]. In the present study, a 4 h difference was considered clinically relevant. Assuming a standard deviation of 4 h, a calculated sample size of 18 patients was required for each group with a type I error of 0.05 and a power of 0.80. To allow for block failure and possible dropouts, 25 patients were included in each group.

Data are summarized as mean (standard deviation [SD]), median (Q1, Q3), or number (proportion [%]), as appropriate. Continuous variables were assessed for normality using the Kolmogorov-Smirnov test. The primary outcome was analyzed using the Kruskal-Wallis test, and differences between groups were analyzed using the Mann-Whitney U test with Bonferroni correction for multiple comparisons. The log-rank test was used to analyze the Kaplan-Meier plots for the block duration. Secondary outcomes were analyzed using the Kruskal-Wallis test or Pearson χ² test (or Fisher’s exact test) when appropriate. Differences were considered statistically significant at P < 0.05. For Bonferroni correction of multiple comparisons, P < 0.008 (0.05/6) was considered statistically significant. SPSS version 19.0 (IBM Corp., USA) for Windows (Microsoft Corp., USA) was used for statistical analysis.

**Results**

A total of 100 patients were recruited in this study. Eight patients were excluded after randomization due to block failure (n = 6) and/or unanticipated extensive surgery (two patients receiving autologous iliac crest bone grafting). Ten patients (one in group C, five in group D2.5, and two in groups D5 and D10) reported persistent ankle pain and were hence excluded. The patient
flow throughout the study is illustrated in Fig. 1. There were no significant differences among the four groups in terms of demographic or surgical data (Table 1). No significant differences in the onset time to sensory (P = 0.710) and motor block (P = 0.848) were observed among the four groups (Table 2). No adverse events during the block performance were observed in any of the groups.

The median duration of analgesia was as follows: group C—20.0 h (18.0–25.5 h); group D2.5—24.5 h (18.4–27.8 h); group D5—25.4 h (22.0–31.5 h); and group D10—29.1 h (25.7–36.0 h). There were significant differences among the groups (Kruskal-Wallis chi-squared = 17.392; df = 3; P < 0.001). Compared with group C, the postoperative analgesic duration of sciatic nerve block was prolonged in group D10 (P < 0.001), but not in group D2.5 (P = 1.000) or D5 (P = 0.106). The Kaplan-Meier survival analysis of the primary outcome also suggested prolongation of analgesic duration in group D10 compared to group C and no detectable difference between groups D2.5 and D5 and group C (Fig. 2). For comparison of the survival distributions between the four groups, the log-rank chi-squared statistic was 13.2, with df = 3 (P = 0.004).

Differences in pain scores in the PACU and 24 h after surgery were not statistically significant among the groups (Table 2). In addition, there were no significant differences in the worst possible pain scores. However, there was a significant difference in the number of patients who requested rescue analgesics among the 4 groups at 24 h (Deviance = 15.85; df = 3; P = 0.001, Table 2), but not 24–36 h after surgery. There were three, four, four, and seven patients in groups C, D2.5, D5, and D10, respectively, who did not request any rescue analgesics during the first 36 h after the block placement.

The four groups demonstrated a similar incidence of PONV (P = 0.723). In addition, no significant differences in adverse effects were observed among the four groups. Patient satisfaction was similar in all groups (P = 0.476) (Table 3). No neurological deficits or wound infections were observed in the patients on a follow-up visit performed by the surgeon 2–4 weeks postoperatively.

**Discussion**

We evaluated the effects of three different doses of IV dexamethasone on the postoperative analgesic duration of the sciatic nerve block. When compared with the control, only 10 mg of IV dexamethasone increased the duration of postoperative analgesia in the sciatic nerve block. Although the use of rescue analgesics was statistically different among the four groups 24 h after surgery, other secondary outcomes were similar among all the groups.

In this study, we observed a prolonged duration of sciatic nerve block following IV dexamethasone (10 mg). Although the precise mechanism was not clearly elucidated, this might be associated with the systemic anti-inflammatory effects of dexamethasone [15]. Several doses of dexamethasone have been used to prolong
the duration of postoperative pain management. In the case of the perineural route, doses between 1 mg and 4 mg can increase the block duration in a dose-dependent manner [16]. A recent meta-analysis reported that 4 mg of perineural dexamethasone had a ceiling effect [17].

There was a tendency of prolonged postoperative analgesia with increasing dosage of IV dexamethasone in the present study. However, only 10 mg of IV dexamethasone resulted in a statistically significant prolongation of postoperative analgesia for a sciatic nerve block. A previous study compared three different doses of IV dexamethasone with saline for an interscalene block [8]. The authors reported that IV dexamethasone 2.5 mg and 10 mg increased the duration of interscalene analgesia after shoulder surgery. The discrepancy between previous and current study may be described by the differences in the type of surgery. In con-

### Table 1. Demographic and Surgical Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group C (n = 23)</th>
<th>Dexamethasone</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group D2.5 (n = 18)</td>
<td>Group D5 (n = 21)</td>
<td>Group D10 (n = 20)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>53 ± 14</td>
<td>52 ± 14</td>
<td>54 ± 15</td>
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<tr>
<td>Weight (kg)</td>
<td>66 ± 14</td>
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<td>61 ± 12</td>
</tr>
<tr>
<td>Height (cm)</td>
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<td>161 ± 10</td>
<td>160 ± 8</td>
</tr>
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<td>Sex (M/F)</td>
<td>7/16</td>
<td>6/12</td>
<td>7/14</td>
</tr>
<tr>
<td>ASA PS (I/II/III)</td>
<td>14/8/1</td>
<td>12/5/1</td>
<td>12/9/0</td>
</tr>
<tr>
<td>Tourniquet time (min)</td>
<td>100 ± 32</td>
<td>94 ± 30</td>
<td>93 ± 22</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>111 ± 43</td>
<td>104 ± 38</td>
<td>104 ± 43</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ankle fracture osteosynthesis</td>
<td>8</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Hallux valgus correction</td>
<td>13</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Ankle arthrodesis</td>
<td>2</td>
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<td>3</td>
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</table>

Values are presented as mean ± SD or number of patients. ASA PS: American Society of Anesthesiologists physical status. Group C: control group, Group D2.5: dexamethasone 2.5 mg, Group D5: dexamethasone 5 mg, Group D10: dexamethasone 10 mg.

### Table 2. Secondary Outcomes of Onset Time to Sensory and Motor Block, Pain Scores, and Rescue Analgesics

<table>
<thead>
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<th>Dexamethasone</th>
<th>P value</th>
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<tbody>
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<td></td>
<td>Group D2.5 (n = 18)</td>
<td>Group D5 (n = 21)</td>
<td>Group D10 (n = 20)</td>
</tr>
<tr>
<td>Onset time (min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensory block</td>
<td>10 (10, 15)</td>
<td>15 (6, 25)</td>
<td>15 (8, 20)</td>
</tr>
<tr>
<td>Motor block</td>
<td>20 (15, 30)</td>
<td>25 (11, 30)</td>
<td>25 (20, 30)</td>
</tr>
<tr>
<td>Pain score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In PACU</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
</tr>
<tr>
<td>At 24 h</td>
<td>3 (0, 5)</td>
<td>5 (3, 6)</td>
<td>4 (2, 5)</td>
</tr>
<tr>
<td>Worst possible pain</td>
<td>7 (4, 8)</td>
<td>8 (4, 9)</td>
<td>6 (3, 9)</td>
</tr>
<tr>
<td>Rescue analgesics*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–24 h after surgery</td>
<td>20 (87)/7 (30)</td>
<td>12 (67)/3 (17)</td>
<td>11 (52)/5 (24)</td>
</tr>
<tr>
<td>24–36 h after surgery</td>
<td>10 (43)/2 (9)</td>
<td>6 (33)/0 (0)</td>
<td>11 (52)/2 (10)</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3) or number (%). *Rescue analgesics was presented as number of patients (%) using non-opioid/opioid analgesics. PACU: post-anesthesia care unit. Group C: control group, Group D2.5: dexamethasone 2.5 mg, Group D5: dexamethasone 5 mg, Group D10: dexamethasone 10 mg.

Fig. 2. Kaplan-Meier survival plot illustrating the duration of postoperative analgesia in the study groups. Group C: control group, Group D2.5: dexamethasone 2.5 mg, Group D5: dexamethasone 5 mg, Group D10: dexamethasone 10 mg. *P = 0.004 (log-rank test) compared to control group.

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Intravenous dexamethasone

Table 3. Secondary Outcomes of Incidence of PONV, Adverse Effects, and Patient Satisfaction

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group C (n = 23)</th>
<th>Dexamethasone</th>
<th>Group D2.5 (n = 18)</th>
<th>Group D5 (n = 21)</th>
<th>Group D10 (n = 20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PONV</td>
<td>4 (17.4)</td>
<td>1 (5.6)</td>
<td>3 (14.3)</td>
<td>3 (15.0)</td>
<td>0.723</td>
<td></td>
</tr>
<tr>
<td>Paresthesia</td>
<td>16 (69.6)</td>
<td>11 (61.1)</td>
<td>13 (61.9)</td>
<td>13 (65.0)</td>
<td>0.938</td>
<td></td>
</tr>
<tr>
<td>Motor weakness</td>
<td>7 (30.4)</td>
<td>6 (33.3)</td>
<td>7 (33.3)</td>
<td>9 (40.9)</td>
<td>0.771</td>
<td></td>
</tr>
<tr>
<td>Satisfaction</td>
<td>10 (9, 10)</td>
<td>10 (9, 10)</td>
<td>9 (8, 10)</td>
<td>10 (9, 10)</td>
<td>0.476</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%) or median (Q1, Q3). PONV: postoperative nausea and vomiting. Group C: control group, Group D2.5: dexamethasone 2.5 mg, Group D5: dexamethasone 5 mg, Group D10: dexamethasone 10 mg.

In conclusion, the results of the present study demonstrated that compared to the control group, only IV dexamethasone 10 mg increased the duration of postoperative analgesia following a sciatic nerve block for foot and ankle surgery without the occurrence of adverse events.

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Conflicts of Interest

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

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References


Preemptive analgesic efficacy of ultrasound-guided transversalis fascia plane block in children undergoing inguinal herniorrhaphy: a randomized, double-blind, controlled study

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Background: Surgical repair of congenital inguinal hernia results in significant postoperative discomfort and pain. The aim of the current study was to evaluate the pre-emptive analgesic efficacy of a transversalis fascia plane (TFP) block after pediatric inguinal herniorrhaphy.

Methods: Forty-four patients aged 12 to 60 months who underwent unilateral inguinal herniorrhaphy were enrolled. Four patients were excluded, and the remaining were allocated to the control group and the TFP block group. In the TFP block group, 0.4 ml/kg bupivacaine 0.25% was instilled in the plane between the transversus abdominis and transversalis fascia, while in the control group 0.9% saline was used instead of bupivacaine. The collected data were the total dose of paracetamol consumed during the first 12 h postoperatively, the postoperative Face, Leg, Activity, Cry, Consolability (FLACC) pain score, time to first use of rescue analgesia, number of patients required additional postoperative analgesics, and parents’ satisfaction.

Results: The median paracetamol consumption was significantly lower in the TFP block group than in the control group, and FLACC pain scores were significantly lower for all study times in the TFP block group with higher parental satisfaction scores than those for the control group. The number of patients who required additional analgesics was significantly lower in the TFP block group than in the control group.

Conclusions: The use of a TFP block decreases postoperative analgesic consumption and postoperative pain intensity after pediatric inguinal herniorrhaphy. Future studies with larger sample size are required to evaluate the actual complications rate of TFP block.

Keywords: Acetaminophen; Analgesia; Child; Fascia; Herniorrhaphy; Postoperative pain.

Introduction

Surgical repair of congenital inguinal hernia is a common day-case procedure during childhood that results in significant postoperative discomfort and pain [1]. Preemptive analgesia relieves pain prior to the surgical incision and during the perioperative period, and prevents the occurrence of central sensitization by interfering with the transmission of peripheral nociceptive signals to the spinal cord [2].

Ultrasound-guided transversus abdominis plane block (TAP) and ilio-inguinal/ilio-hypogastric (II/IH) nerve block are the most commonly and effectively used peripheral
nerve block techniques to alleviate postoperative pain after surgical repair of inguinal hernia in children [3].

The transversalis fascia plane (TFP) block is a peripheral ultrasound-guided nerve block in which the local anesthetic is instilled between the transversus abdominis muscle and its enclosing transversalis fascia at the level of the posterior axillary line targeting the T12 and L1 nerves that convey the nociception from the antero-lateral abdominal wall [4].

The analgesic efficacy of TFP block has been demonstrated in adult surgery, including iliac crest bone graft harvesting [5], inguinal herniorrhaphy [6], and cesarean section [7,8]. In pediatric surgery, the only report of the TFP block was provided by Ahiskalioglu et al. [9] in two children, one of them underwent unilateral open inguinal herniorrhaphy and the other was scheduled for re-implantation of the ureter into urinary bladder via pfannenstiel incision.

This prospective, controlled, randomized study was conducted to evaluate the effect of performing TFP block before skin incision in children undergoing unilateral inguinal herniorrhaphy on postoperative pain and analgesic requirements. We hypothesized that the TFP block would reduce postoperative non-opioid analgesic requirements. The primary endpoint was postoperative non-opioid analgesic consumption, and the secondary endpoints were pain score, time to first rescue analgesia use, and parental satisfaction.

Materials and Methods

This prospective, randomized, double-blinded, controlled, superiority study was conducted in our institutional university hospital from June to November 2020 after receiving approval from our Faculty of Medicine institutional research board (IRB Code Number, R.20.06.870) on 10th June 2020, and was registered at the Pan-African Clinical Trial Registry (PACTR202006532101847) prior to patient enrollment. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

After obtaining informed written consent from the patient’s parents or their legal guardians, 44 consecutive eligible patients were enrolled. Children aged between 12 and 60 months with American Society of Anesthesiologists physical status I or II undergoing scheduled elective unilateral inguinal herniorrhaphy were included in the study.

Exclusion criteria included previous inguinal surgery; history of clinically significant cardiac, hepatic, renal, or neurological dysfunction; coagulopathy; known allergy to amide local anesthetics; and systemic or local infection at the puncture site.

Randomization was performed using computer-generated random numbers prior to surgery. An opaque sealed envelope was used and opened in the operative theater by an anesthesiologist who was not involved in the study and who prepared the study drugs. The anesthesiologist who was responsible for the patient and the nurse who recorded the patient data were unaware of the patient’s group allocation. Patients were randomly allocated to the TFP block group or control group according to the patient randomization chart (Fig. 1).

The patient received no premedication before anesthesia induction. On arrival in the operating room, standard monitoring including pulse oximetry, non-invasive blood pressure, and three lead electrocardiography and capnography (after induction) were applied to the patient. General anesthesia was induced using 8% sevoflurane in 100% oxygen. After achieving an adequate depth of anesthesia, a 22-gauge peripheral venous catheter was inserted in the forearm, and an appropriately sized i-gel (i-gel™, Intersurgical Ltd., UK) supraglottic airway based on the child’s weight was properly placed by the attending anesthesiologist. Anesthesia was maintained under controlled pressure support ventilation using 1–2% sevoflurane in a mixture of 50% oxygen/air, fentanyl 1 μg/kg, and atracurium 0.5 mg/kg. The patient received standardized fluid therapy in the form of 3–5 ml/kg/h crystalloid. The skin incision was performed 15 minutes after the block induction. Any increase in the heart rate and mean arterial blood pressure that was 20% above the preoperative value in response to skin incision was managed using fentanyl 0.5 μg/kg, repeated at 3-min intervals. At the end of surgery, the muscle relaxant was reversed, and the i-gel

![Fig. 1. CONSORT flow diagram. TFP: transversalis fascia plane.](https://doi.org/10.4097/kja.20601)
airway was removed after full recovery of consciousness.

Ultrasound-guided TFP block was performed immediately after induction of anesthesia by an experienced single operator under aseptic conditions. The patient was placed supine, and the skin at the site of needle puncture was sterilized with 2% chlorhexidine and isolated with sterile drapes. A high frequency (8–14 MHz), linear ultrasound pediatric probe (Mindray® 10L24EA, China) wrapped in a sterile sheath was placed over the lateral abdominal wall between the iliac crest and subcostal margin at the midaxillary line in an oblique direction with the ultrasound probe mark directed upward.

The probe was manipulated to obtain an image showing the muscles of the abdominal wall and transversalis fascia at its junction with the anterior layer of the thoraco-abdominal fascia at the lateral end of the quadratus lumbrorum muscle (Fig. 2A). A 22-gauge, 50-mm short bevel needle was advanced using an in-plane technique, from the anterior to the posterior wall traversing the skin, external and internal oblique muscles, and posterior tail of the transversus abdominis muscle and its enclosing fascia. Immediately after piercing the fascia of the transversus abdominis muscle, 0.4 ml/kg bupivacaine 0.25% was instilled (Fig. 2B) in TFP block group. A placebo (0.4 ml/kg 0.9% saline) was used instead of bupivacaine in the control group.

At the end of surgery, patients were transferred to a post-anesthesia care unit (PACU) where they received 1 mg/kg rectal diclofenac suppository as a part of postoperative multimodal analgesia. The patients were discharged 30 minutes after from the PACU to the ward when they were completely awake and thermodynamically stable with tolerable pain.

Postoperative pain was assessed by an experienced pediatric nurse who was blinded to the patient’s group allocation using the 10-point behavioral face, leg, activity, cry, consolability (FLACC) pain scale, with a minimum score of 0 and a maximum of 10 [10]. If the FLACC score was 4 or more, 10 mg/kg paracetamol was administered intravenously as rescue analgesia, which could be repeated every 6 hours with a maximum total dose of 30 mg/kg in the first 12 h postoperatively. Fentanyl 1 µg/kg was administered if the FLACC score did not fall below 4 despite the use of paracetamol as rescue analgesia. Following standard day case surgery protocol, the patients were discharged from the hospital after 12 h.

The primary outcome measure was the total dose of paracetamol consumed during the first 12 h postoperatively. The secondary outcome measures were increase in heart rate and mean arterial pressure of more than 20% in response to skin incision; intraoperative fentanyl consumption; postoperative FLACC pain score after 0.5 h in PACU, and 2, 4, 6, 9, and 12 h in the ward; time to first rescue analgesia use; number of patients who required additional postoperative analgesics; fentanyl consumption during the first 12 h postoperatively, and parental satisfaction evaluated using a five-point Likert scale (very satisfied: 5, satisfied: 4, neutral: 3, dissatisfied: 2, and very dissatisfied: 1) [11]. Block-related complications, including local anesthetic toxicity, lower limb motor weakness, and vascular or abdominal organ puncture, were reported.

**Fig. 2.** (A) Ultrasound images of transversalis fascia plane before local anesthetic injection. (B) Ultrasound images of transversalis fascia plane after local anesthetic injection. EO: external oblique muscle, IO: internal oblique muscle, TA: transversus abdominis muscle, QL: quadratus lumbrorum muscle, LA: local anesthetic.
Sample size and statistical analyses

The sample size was calculated using G*Power software (G*Power version 3.1.9.2, Kiel University, Germany). The primary outcome was the total dose of paracetamol consumed in the first 12 h postoperatively. As there were no previous similar studies at the time of designing the study protocol, an external pilot study with five patients in each group was performed (the results were not included in the full-scale-study). From this pilot, paracetamol consumption in the first 12 h postoperatively was found to be 15.8 ± 4.7 mg/kg in the TFP block group and 20.8 ± 6.9 mg/kg in the control group. Assuming that a mean postoperative paracetamol consumption of less than 5 mg/kg would indicate a significant difference between the two study groups; a total sample of 36 patients (18 in each group) was required to achieve a power (1−β) of 80% and type I α error of 0.05. Four patients were included in each group to compensate for any dropouts. Thus, the final sample consisted of 22 patients in each group.

Statistical testing was performed using IBM SPSS Statistics for Windows, Version 21.0 (SPSS®, IBM Corp., USA). Data were tested for normality using the Shapiro-Wilk test. The distribution of data was represented as mean ± standard deviation (SD) for quantitative parametric data; frequency, number, and proportion for categorical data; and median (Q1, Q3), minimum and maximum, for non-parametric data. Data analysis was performed to display the statistically significant differences between the two groups. The Mann-Whitney U test was used to analyze non-parametric data. For quantitative data, the unpaired Student’s t-test was used to compare the means of the two groups. Fisher’s exact test was used to analyze categorical data. P < 0.05 was considered statistically significant.

Results

Forty-four patients were recruited for this randomized, controlled, double-blind, superiority study. Four patients were excluded because they did not meet the inclusion criteria or their legal guardians refused to consent to participation. The remaining 40 patients were allocated into two equal groups: the TFP block and control group (Fig. 1). There were no significant differences in patient characteristics (age, sex, weight, or height) or duration of surgery between the studied groups (Table 1).

The median (Q1, Q3) paracetamol consumption (mg/kg) in the first 12 h postoperatively was significantly lower (P < 0.001) in the TFP block group (n = 2) than in the control group (n = 10) (Table 2). The intraoperative mean fentanyl consumption (μg/kg) was significantly lower (P = 0.005) in the TFP block group (1.10 ± 0.08) than in the control group (1.50 ± 0.51) (Table 2). The number of patients who required postoperative rescue analgesia was significantly greater (P < 0.001) in the control group (n = 20) than in the TFP block group (n = 3). The median (Q1, Q3) time to first rescue analgesia in the control group was 4.5 (1.5, 6) hours, and for the three patients who required rescue analgesia in the TFP block group was 9, 1, 6 hours respectively (Table 2).

Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>TFP block group (n = 20)</th>
<th>Control group (n = 20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (month)</td>
<td>24 (12, 54)</td>
<td>18.5 (12, 60)</td>
<td>0.198</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>12.5 (10, 19)</td>
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<td>0.199</td>
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<tr>
<td>Height (cm)</td>
<td>90.4 ± 12.5</td>
<td>86.9 ± 14.1</td>
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<td>Sex (M/F)</td>
<td>18/2</td>
<td>18/2</td>
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<tr>
<td>Surgery duration (min)</td>
<td>40.9 ± 8.0</td>
<td>42.3 ± 6.7</td>
<td>0.567</td>
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</tbody>
</table>

Discussion

This prospective, randomized, superiority controlled study was conducted to evaluate the efficacy of the TFP block performed before skin incision in reducing postoperative pain scores and analgesic requirements in children undergoing elective unilateral inguinal herniorrhaphy. The results of the current study showed that, performing a TFP block before skin incision was associated with lower postoperative analgesic requirements (paracetamol and fentanyl), lower postoperative pain scores, lesser need for rescue analgesia, and better parental satisfaction than the control treatment. The above results demonstrate the analgesic efficacy of...
the TFP block for pediatric inguinal herniorrhaphy.

The inguinal region is supplied by highly variable and complex sensory neuronal innervations from the II, IH, and genitofemoral nerves (GFN). The II and IH nerves originate from the first lumbar (L1) spinal nerve root with occasional contributions from the 12th thoracic nerve root, while the GFN is formed by contributions from L1 and L2 nerve roots [12].

In pediatric surgeries, the use of ultrasound (US) guidance for fascial muscle plane blocks has been associated with increased success rate and reduced volume of local anesthetics needed for the block [13].

The most commonly used ultrasound-guided fascial muscle plane blocks to provide effective postoperative analgesia after inguinal herniorrhaphy are II/IH nerve block and TAP block [3]. Few studies have compared the efficacy of TAP and II/IH nerve block for providing postoperative analgesia after inguinal surgery with conflicting results [14,15]. Recently, quadratus lumborum block [16,17] and erector spinae block [18,19] have been reported to be effective in reducing postoperative pain and analgesic consumption after pediatric inguinal herniorrhaphy.

To the best of our knowledge, no prior study has been conducted to evaluate the efficacy of TFP block in reducing postoperative pain scores and analgesic consumption in children undergoing inguinal herniorrhaphy. The only case report of TFP block in

### Table 2. Intraoperative and Postoperative Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>TFP block group (n = 20)</th>
<th>Control group (n = 20)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of patients with 20% increase in HR and MAP after incision</td>
<td>2 (10)</td>
<td>10 (50)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Intraoperative fentanyl consumption (µg/kg)</td>
<td>1.10 ± 0.08</td>
<td>1.50 ± 0.51</td>
<td>0.005</td>
</tr>
<tr>
<td>Number (%) of patients requiring rescue analgesia</td>
<td>3 (15)</td>
<td>20 (100)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Time to first rescue analgesia (h)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First patient</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second patient</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third patient</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative paracetamol consumption (mg/kg)</td>
<td>0 (0, 0)</td>
<td>20 (10, 30)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Incidence of postoperative fentanyl administration (%)</td>
<td>5</td>
<td>35</td>
<td>0.019</td>
</tr>
<tr>
<td>Block related complications (%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number of patient (%), mean ± SD or median (Q1, Q3). TFP: transversalis fascia plane, HR: heart rate, MAP: mean arterial blood pressure. *P < 0.05, statistically significantly different from the control group.

### Table 3. Postoperative FLACC Pain Score

<table>
<thead>
<tr>
<th>Elapsed time after PACU admission</th>
<th>TFP block group (n = 20)</th>
<th>Control group (n = 20)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 h</td>
<td>1.5 (1, 2)</td>
<td>3 (2, 3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2 h</td>
<td>1 (1, 2)</td>
<td>3 (2, 3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>4 h</td>
<td>1 (1, 2)</td>
<td>3 (3, 4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>6 h</td>
<td>1.5 (1, 2)</td>
<td>4 (3.5, 5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>9 h</td>
<td>1.5 (0.5, 2.5)</td>
<td>3 (2.5, 4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>12 h</td>
<td>1.5 (0, 3)</td>
<td>3 (3, 4)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3). FLACC: face, leg, activity, cry, consolability, TFP: transversalis fascia plane. *P < 0.05, statistically significantly different from the control group.

---

Fig. 3. Five-point Likert scale for evaluating parental satisfaction. Values are presented as median (Q1, Q3). *P < 0.05, statistically significantly different from the control group.
children was described by Ahiskalioglu et al. [9] who performed TFP block in two children leading to similar results to those of our study. One of the patients was a 5-year-old girl scheduled for uretero-cystostomy via Pfannenstiel incision and the other child was a 4-year-old boy scheduled for unilateral inguinal herniorrhaphy; they reported improved postoperative analgesia in both cases.

Tulgar et al. [20] performed a combination of ultrasound-guided TFP block and TAP block and reported adequate and effective intraoperative anesthesia and analgesia under propofol infusion at a sedative dose with effective postoperative analgesia in an adult patient undergoing inguinal hernia repair.

López-González et al. [6] compared the postoperative analgesic effect of both ultrasound-guided TFP block and TAP block after adult inguinal herniorrhaphy and found that both blocks provided good postoperative analgesia and a higher sensory level was associated with TFP block.

Several clinical trials have demonstrated that the TFP block is associated with good postoperative analgesia with reduced analgesic consumption after iliac crest bone graft harvesting [5] and cesarean section [7,8].

The TFP block influences the II and IH nerves in the plane between the investing fascia of the transversus abdominis and transversalis fascia. The II and IH nerves vary in their position at the level of the iliac crest as both nerves penetrate the transversus abdominis muscle at the level of the dorsal segment of the iliac crest in 61% of the population, and in 34.2% they combine to form a common trunk [12]. Therefore, more proximal blocks, e.g., TFP block, are more effective than TAP and II/IH nerve blocks.

The inguinal hernial sac is partially innervated by the genital branch of the GFN, which is not covered by II and IH nerve blocks, potentially leading to visceral pain as a result of traction on the hernial sac. Sasaoka et al. [21] found that the only benefit of performing GFN block in addition to II and IH nerve blockade was intraoperative attenuation of the hemodynamic stress response to surgical manipulation of the inguinal hernal sac without any postoperative analgesic effect.

The TFP block involves injection of local anesthetics superficial to the transversalis fascia and deep to the tapering aponeurosis of the transversus abdominis muscle, just lateral to the quadratus lumborum muscle. At this point, the transversalis fascia combines with the anterior layer of the thoracolumbar fascia. This may explain the spread of local anesthetic to the paravertebral space blocking both the rami of the thoracic spinal nerves (dorsal and ventral) and rami communicantes, which supply the sympathetic chain [22].

Two patients in the TFP block group had an increase in heart rate and mean arterial pressure of more than 20% of the preoperative value immediately after skin incision, which may be attributed to block failure.

TFP block was associated with good parental satisfaction with postoperative pain management, as their children were almost pain free with minimal need for postoperative analgesics. Pain control allows children to remain calm, sleep, and eat well, avoiding irritability and insomnia.

There were no reported complications related to the ultrasound-guided TFP block, including local anesthetic toxicity, lower limb weakness, and vascular or abdominal organ needle puncture. This indicates that the safety of TFP block with needle visualization using ultrasound is very good in children.

The current study has a few limitations. First, we could not monitor intraoperative nociception to evaluate the efficacy of TFP block in controlling painful intraoperative events, such as skin incision, as these monitors are not available in our hospital. Intraoperative nociception can be measured using the anesthesia analgesia index using a CE-certified PhysioDoloris monitor (MetroDoloris Medical Systems, France) and nociception level index measurement using a PMD-200™ (Medasense Biometrics Ltd., Israel) monitor [23]. Second, patient follow-up was limited to the first 12 h postoperatively as inguinal hernia repair is a day-case surgery and early discharge is recommended by our hospital policy. Third, we did not assess the effect of TFP block on the incidence of chronic pain after inguinal herniorrhaphy in pediatric patients as this requires several months of follow-up.

From the findings in our study, we concluded that performing a TFP block before surgical incision in children undergoing unilateral inguinal herniorrhaphy results in reduction of postoperative analgesic requirements, adequate postoperative pain control, and good parent’s satisfaction. Ultrasound guidance makes the TFP block an easy and effective peripheral nerve block. Future studies with larger sample size are required to evaluate the actual complication rate of TFP block.

**Conflicts of Interest**

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

**Author Contributions**

Ibrahim Abdelbaser (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing)

Nabil A. Mageed (Supervision; Writing – review & editing)

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References  


Prediction of endotracheal tube size using a printed three-dimensional airway model in pediatric patients with congenital heart disease: a prospective, single-center, single-group study

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Departments of ¹Anesthesia and Pain Medicine, ²Biomedical Engineering, ³Radiology, Pusan National University Yangsan Hospital, Pusan National University School of Medicine and Medical Research Institute, Yangsan, Korea

Background: To determine the correct size of endotracheal tubes (ETTs) for endotracheal intubation of pediatric patients, new methods have been investigated. Although the three-dimensional (3D) printing technology has been successful in the field of surgery, there are not many studies in the field of anesthesia. The purpose of this study was to evaluate the accuracy of a 3D airway model for prediction of the correct ETT size, and compare the results with a conventional age-based formula in pediatric patients.

Methods: Thirty-five pediatric patients under six years of age who were scheduled for congenital heart surgery were enrolled. In the pre-anesthetic period, the patient’s computed tomography (CT) images were converted to Standard Triangle Language (STL) files using the 3D conversion program. A Fused Deposition Modelling (FDM) type 3D printer was used to print 3D airway models from the sub-glottis to the upper carina. ETT size was selected by inserting various sized cuffed-ETTs to a printed 3D airway model.

Results: The 3D method selected the correct ETT size in 21 out of 35 pediatric patients (60%), whereas the age-based formula selected the correct ETT size in 9 patients (26%).

Conclusions: Prediction of the correct size of ETTS using a printed 3D airway model demonstrated better results than the age-based formula. This suggests that the selection of ETT size using a printed 3D airway model may be feasible for helping minimize re-intubation attempts and complications in patients with congenital heart disease and/or those with an abnormal range of growth and development.

Keywords: Airway management; Computer simulation; Computed tomography; Congenital heart disease; Endotracheal intubation; Three-dimensional printing; Trachea.

Introduction

To determine the correct size of endotracheal tubes (ETTs) for endotracheal intubation of pediatric patients is no menial task. The conventional method of determining ETT size is based on children’s ages with the presumption of normal growth and development; therefore, applying the same method to children who do not follow this pattern due to disease makes this method hardly applicable [1]. In the past, the use of uncuffed ETTS was recommended due to concerns about possible complications after endotracheal intu-
bation under six years of age [2]. Recent studies showed that cuffed ETT does not increase the risk of post-extubation stridor compared with uncuffed ETT [3,4]. However, it is important to select the correct size of cuffed ETT, so as not to tightly seal the trachea, and increase the risk of reintubation.

In particular, in pediatric patients undergoing cardiac surgery due to congenital heart disease, there may be accompanying airway anomalies. Furthermore, most patients need to maintain the ETT after surgeries for a certain period of time. In addition, pediatric patients with congenital heart disease may have impaired growth and development [5,6]. For this reason, it may be difficult to find an appropriate size ETT using an age-based formula; several studies have suggested their own modified formula [7–9]. Determining the correct ETT size is highly important, because endotracheal intubation with an improperly sized ETT can lead to complications such as airway injury, mucosal ischemia or edema, post-extubation wheezing, subglottic stenosis, improper ventilation, and pulmonary aspiration [10].

Currently, the importance of personalized treatment is increasing and conventional methods need to evolve based on the development of science and technology. Printed three-dimensional (3D) airway modeling is one of these techniques, which is used for airway evaluation and surgical treatment, and its usefulness has been reported [11–13]. As a pre-anesthetic plan to predict the correct ETT size, we considered intubating various ETT sizes on a printed 3D airway model of each pediatric patient. The purpose of this study was to evaluate the accuracy of a 3D airway model for prediction of the correct ETT size in pediatric patients, and to compare the results with a conventional age-based formula.

Materials and Methods

This study involved 35 pediatric patients. Written informed consent was obtained by the legal guardians. Ethical approval was provided by the Institutional Review Board of the Pusan National University Yangsan Hospital, Yangsan, Korea (Ref: 05-2019-116). The clinical research was registered at ClinicalTrials.gov (Ref: NCT04814888), and conducted in accordance with the Helsinki Declaration 2013. We required a sample size of 35 to achieve 80% power, and a significance level (alpha) of 0.05, using a two-sided paired t-test with reference to Schramm et al’s study [14]. We enrolled children under 6 years of age (range 4 days to 61 months) scheduled for surgery for congenital heart disease from September 3, 2019 to March 16, 2020 with chest computed tomography (CT) images including upper airways even if the patient had a high level of the American Society of Anesthesiologists (ASA) physical status. Pediatric patients with congenital heart disease were chosen because they usually keep their ETT with mechanical ventilation in the intensive care unit for longer lengths of time. In addition, these children have a relatively high risk of complications associated with ETT compared to healthy patients. Exclusion criteria were as follows: pediatric patients with intubation or tracheostomy before general anesthesia due to underlying disease, small sized airway with inner diameter < 3.0 mm because of preterm or low birth weight, unstable vital signs during induction, history of difficult intubation, or emergency surgery where printing a 3D airway model in advance was not possible (Fig. 1).

In the pre-anesthetic plan, Digital Imaging and Communications in Medicine files of pediatric patients’ CT images were con-

Fig. 1. CONSORT flow diagram.
verted to Standard Triangle Language (STL) files using the 3D conversion software open-source program InVersalius (InVersalius 3.0, Renato Archer Information Technology Center, Brazil) (Fig. 2A). The STL files were converted to G-Code files for 3D printing using CreatWare 6.4.6 (CreatWare 6.4.6, Henan Suwei Electronic Technology Co., Ltd., China) (Fig. 2B). A Fused Deposition Modelling (FDM) type 3D printer CreatBot (CreatBot F430, Henan Suwei Electronic Technology Co., Ltd., China) was used to print 3D airway models from the sub-glottis to the upper carina (Fig. 3A). We also considered the interval between the date of the preoperative CT scan and the date of surgery for avoidance of bias. Fortunately, preoperative CT scan for congenital heart surgery is usually performed one to seven days before surgery in our hospital.

Two anesthesiologists unaware of patient’s demographic data such as height, weight, and age, predicted and recorded the ETT size by inserting various sized cuffed-ETTs (MallinckrodtTM Hi-Lo tracheal tube, Covidien, Ireland) (Table 1) to a printed 3D airway model (Figs. 3B and 3C). If the diameter of the trachea is undersized, air leak around the ETT can occur. In that case, we can use that ETT after inflating the pilot balloon with a small amount of air. We used cuffed ETT because we think that this is more beneficial to patients than another trial of intubation. For the conventional method, an age-based formula (ID [mm] = [age in

Fig. 2. The methods for conversion of image from CT. (A) DICOM files of pediatric patients CT images were converted to STL files using the 3D conversion software-open source program InVersalius (InVersalius 3.0, Renato Archer Information Technology Center, Brazil). (B) The STL files were converted to G-Code files for 3D printing using CreatWare 6.4.6 (CreatWare 6.4.6, Henan Suwei Electronic Technology Co., Ltd., China). CT: computed tomography, DICOM: Digital Imaging and Communications in Medicine, STL: Standard Triangle Language, 3D: three-dimensional.
years/4] + 3.5, ID; internal diameter) (in case of a cuffed ETT, 3.5 instead of 4 is used because the cuff increases the outer tube diameter by approximately 0.5 mm) was employed; next, we calculated and recorded the ETT size [2,15]. The nearest commercially available ETT size within 0.3 mm by age-based formula was determined with reference to Schramm et al. [14].

Standard monitoring (non-invasive blood pressure measurement, electrocardiogram, and pulse oximetry) was applied to pediatric patients in the operating room. General anesthesia was induced with ketamine 1 mg/kg and rocuronium 0.6 mg/kg and maintained with sevoflurane. After intubation with a cuffed ETT by a printed 3D airway model was finished, an air leak test was performed by one of three anesthesiologists dedicated to pediatric cardiac anesthesia.

To evaluate the conformity of ETT size, the patient was laid supine in a neutral position, and airway pressure was gradually increased to ≥ 20 cmH₂O; then audible air leak was checked by a stethoscope in the patient’s mouth or throat by three anesthesiologists who were in charge of anesthesia for pediatric cardiac surgery. If there was audible leakage under 10 cmH₂O or no audible leakage over 20 cmH₂O, the anesthesiologists considered that the ETT size was not optimal. According to studies by Shibasaki et al. [10] and Weiss et al. [4], we used 20 cmH₂O as a higher limit for the air leakage test. The pilot balloon was inflated if there was an audible leakage under 10 cmH₂O, and the cuffed ETT was kept in the patient’s trachea if there was no audible leakage over 20 cmH₂O. The duration of mechanical ventilation in the intensive care unit is usually several hours, and we feel that avoidance of reintubation is preferable to the patient. The reliability of the ETT size prediction by the printed 3D airway model was compared with the results of the age-based formula. Intubation-related complications were evaluated by the anesthesiologist and the surgeon from the end of anesthesia until hospital discharge.

Table 1. Recommendations for Age-based Cuffed ETT Size Selection and External Diameter of Cuffed ETT (Mallinckrodt)

<table>
<thead>
<tr>
<th>Age group</th>
<th>Recommended ETT size</th>
<th>Inner diameter (mm)</th>
<th>Outer diameter (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term</td>
<td>3.0–3.5</td>
<td>3.0</td>
<td>4.3</td>
</tr>
<tr>
<td>1–6 months</td>
<td>3.5</td>
<td>3.5</td>
<td>4.9</td>
</tr>
<tr>
<td>7–12 months</td>
<td>3.5–4.0</td>
<td>4.0</td>
<td>5.6</td>
</tr>
<tr>
<td>1–2 years</td>
<td>4.0–4.5</td>
<td>4.5</td>
<td>6.2</td>
</tr>
<tr>
<td>3–4 years</td>
<td>4.5</td>
<td>5.0</td>
<td>6.9</td>
</tr>
<tr>
<td>5–6 years</td>
<td>4.5–5.0</td>
<td>5.5</td>
<td>7.5</td>
</tr>
</tbody>
</table>

ETT: endotracheal tube.
**Results**

Demographic data is shown in Table 2. Non-normal continuous variables were expressed as median (Q1, Q3). Our method selected the correct ETT size in 21 out of 35 pediatric patients (60%), whereas the age-based formula selected the correct ETT size in 9 patients (26%) (Table 3). Our method over-estimated the ETT size in 11 of 14 patients and under-estimated size in 3 patients, whereas the age-based formula over-estimated the ETT size in 13 out of 26 patients and under-estimated size in 13 patients (Tables 3 and 4, Fig. 4). The nine successful intubations using age-based formula included five cases (cases 11, 17, 22, 28, 33) matched with the 3D airway model, and four other cases (cases 6, 8, 26, 29) unmatched with the 3D airway model. Actually, two other cases (cases 12, 23) also looked successful when using the age-based formula instead of the 3D airway model. However, those two cases were simulated by using uncuffed ETT with the 3D airway model because we tried to find the best fit ETT. We also compared the result of two cases (cases 12, 23) with age-based formula, and they were not matched to each other. Finally, the unsuccessful 26 cases using age-based formula were considered as under- or over-estimated cases compared with the successful 3D airway model. There was no reintubation, and the estimated ETT size by the 3D print airway model seen in Table 4 is the finally inserted ETT size by age-based formula in the cases of success and failure.

The correct ETT size was predicted as 67% in 6 patients (cases 10, 13, 17, 24, 30, 31) of 9 neonates < 1 month by the 3D airway model and as 11% (1 of 9, case 17) by the age-based formula. Air leakage was found in 2 out of 9 patients under a pressure of 10 cmH₂O and no air leakage was observed in 1 patient over 20 cmH₂O. Even in the age group in the range from 2 to 6 years old, generally used for the age-based formula, the 3D airway model predicted the correct ETT size in 3 (cases 3, 16, 33) out of 4 patients (75%). However, the age-based formula predicted the correct ETT size for only 1 patient (case 33) (25%) in 2- to 6-year-old patients. No complications occurred after extubation in any patients (Table 4).

**Discussion**

In general anesthesia for pediatric patients, the age-based formula is commonly used to select an accurate ETT size [15,16], but conflicting results have been reported [10]. Due to scientific and technological innovations, new methods, such as those using ultrasound, have been investigated to determine the ETT size [17]. The 3D printing technology has been successful in the field of surgery, but there are not many studies in the field of anesthesia, since it is mainly used as an educational tool rather than for clinical use [18]. We performed this study to predict the correct ETT size by means of a printed 3D airway model based on two-dimensional radiologic images for pediatric patients with potentially unusual airway sizes and shapes. As a result, we found that the prediction of a correctly sized ETT in pediatric patients with congenital heart disease by the 3D airway model (60%) was better than the age-based formula (26%).

**Table 2. Patient Characteristics**

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>35</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>19/16</td>
</tr>
<tr>
<td>Age (months)*</td>
<td>4 (1, 9)</td>
</tr>
<tr>
<td>Number of patients (%) ≥ 24 months</td>
<td>4 (11.4)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>6.2 (3.7, 8.1)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>62.0 (50.0, 71.3)</td>
</tr>
</tbody>
</table>

Values are presented as number or median (Q1, Q3). *Due to some patients being below one year of age, the age has been provided in months.

**Table 3. Comparison between the 3D Airway Model and Age-based Formula for the Selection of Correct Size of the ETT**

<table>
<thead>
<tr>
<th>Formula or model used to determine the correct ETT size</th>
<th>Age-based formula</th>
<th>Incorrect</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Correct</td>
<td>5</td>
<td>21 (60)</td>
</tr>
<tr>
<td></td>
<td>-Underestimated</td>
<td>4</td>
<td>14 (40)</td>
</tr>
<tr>
<td>3D airway model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-Overestimated</td>
<td>4</td>
<td>11 (31.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-3 (8.6)</td>
</tr>
<tr>
<td></td>
<td>Total (%)</td>
<td>9 (26)</td>
<td>35 (100)</td>
</tr>
<tr>
<td></td>
<td>-Underestimated</td>
<td>13 (37)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-Overestimated</td>
<td>13 (37)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number or number (%). ETT: endotracheal tube, 3D: three-dimensional.
<table>
<thead>
<tr>
<th>No</th>
<th>Age* (months)</th>
<th>Calculated ETT size by age-based formula</th>
<th>Actual ETT size by age-based formula</th>
<th>Estimated ETT size by 3D print airway model</th>
<th>Air leakage &lt; 10 cmH₂O</th>
<th>Air leakage ≥ 20 cmH₂O</th>
<th>Success</th>
<th>Complication</th>
<th>Matched with calculated ETT size by age-based formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>3.59</td>
<td>3.5</td>
<td>4</td>
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<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>3.597</td>
<td>3.5</td>
<td>4</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>3</td>
<td>61</td>
<td>4.783</td>
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<td>5.5</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
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<td>3.537</td>
<td>3.5</td>
<td>3</td>
<td>N</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>3.67</td>
<td>3.5</td>
<td>4.5</td>
<td>N</td>
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<td>N</td>
<td>N</td>
</tr>
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<td>4</td>
<td>3.598</td>
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<td>Y</td>
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<td>N</td>
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<td>4</td>
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<td>Y</td>
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<td>N</td>
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ETT: endotracheal tube, 3D: three-dimensional, N: no, Y: yes. *Due to some patients being below one year of age, the age has been provided in months.
In comparison with studies on ETT selection by ultrasound, our results (60%) were better than the 48% of Schramm et al. [14], similar to 60% of Bae et al. [19], and lower than 98% of Shibasaki et al. [10]. These differences in results may be due to the following reasons. While ultrasound studies improved the accuracy by measuring the transverse diameter of the airway using neuromuscular blockers and the respiratory cycle, our study could not apply these factors to CT scans, which are the basis for the 3D airway model [14]. In addition, the age range of patients in the ultrasound studies was older, and a pressure of 25 cmH\(_2\)O or 30 cmH\(_2\)O defined as the air leak test was higher than the 20 cmH\(_2\)O used in our study [20].

The age-based formula predicted the correct ETT size in 9 of 35 pediatric patients (26%); the formula over-estimated size in 13 of 26 patients and under-estimated in 13 patients. The result of the age-based formula was not accurate, because our pediatric patients had congenital heart disease and most were < 1 year old. In fact, several studies have questioned the accuracy of the age-based formula [14,20].

In order to reduce re-intubation, even if the air leak test was not successful, the ETTs were retained unless ventilation was not maintained with ETT cuff inflation or if there was resistance to the ETT going through the airway. The conformity evaluation criterion was set to a pressure of 20 cmH\(_2\)O in our study, but there were also studies reporting a pressure of 25 cmH\(_2\)O or 30 cmH\(_2\)O or more. This is because it is advantageous for the management of respiratory secretions through the ETT and mechanical ventilation to have the appropriate airway pressure after surgery; the air leak test is not a perfect method to predict conformity of the ETT size, and inter-observer variation exists [21]. Unlike other studies, this study included pediatric patients of a wide range of ages from 4 days to 5 years, and those with a high level of ASA physical status with potential airway anomaly. This suggests that this method might be useful for airway assessments in this type of patient.

A 3D airway model is safe for patients, easy to learn, and requires little time, while ultrasound methods require apnea during measurements and staff training [19]. Because the 3D airway model dose not present two-dimensional image in the specific lesion, but reflects the actual airway shape, it may help anesthesiologists understand the anatomy of the airways and may be useful for making a better pre-anesthetic plan via simulation of intubation. Furthermore, using this model can reduce the number of intubation attempts and has the advantage of decreasing the risk of

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complications.

However, this study has some limitations. First, 3D implementation of medical imaging data requires high-quality imaging, and applying 3D conversion software programs to airway images is more difficult than applying the programs to images of solid organs because of the air layer. In addition, 3D printed airway models may differ from the actual airway they are derived from due to flexibility. Second, since the selection of a correctly sized ETT by a 3D airway model lacks an objective numerical indicator measuring the circumference of the narrowest part of the 3D airway model, there may be human errors from the blinded-tester. Third, in consideration of patient safety and ethical aspects of working with pediatric patients, we only used a cuffed ETT for reducing the risk of multiple intubation attempts and maintaining proper ventilation by inflating the cuff if needed. The inconsistent wrinkles of the deflated cuff can also affect the resistance of the ETT surface and the air leak test. Hence, if both cuffed and uncuffed were used as in Shibasaki et al. [10], or if inflation was applied to the cuffed ETT as in Altun et al. [17] to evaluate the adequacy of ETT size, the success rate may have been higher in our study. Fourth, although this study did not present the results of the best fit ETTs because of minimization of re-intubation, there is a possibility that the replaced 0.5 mm smaller or larger ETT also would not pass the air leak test. This is because even ETTs of the same inner diameter have different outer diameters depending on the manufacturer. Cuffed and uncuffed ETTs with 0.5 mm difference in inner diameter, which are clinically considered the same size ETTs, did not lead to the same results in the air leak test in clinical practice [22]. Fifth, we do not have a compliant material similar to the patients’ airway, and the printed 3D airway model is less compliant after printing and fixing in room temperature. This might influence finding the proper size of ETT, and especially result in underestimating the size of ETT. Finally, clinical application of the results from this study would be limited because a printed 3D airway model can only be obtained when there are recent preoperative CT images.

Despite these limitations, prediction of the correctly sized ETT and simulation of intubation using a 3D printing technique may have clinical significance for the following reasons. Recent airway images using newer modalities including bronchoscopic examination or radiologic imaging have had researchers questioning the tenet of the conical shaped airway, and it has been clearly demonstrated that the airway is elliptical rather than circular with the anterior-posterior diameter being greater than the transverse diameter [1]. The 3D airway model also showed the same results, since each pediatric patient had an airway with individual characteristics. Indeed, it was observed that ready-made ETTs did not properly fit the airway size and shape of individual pediatric patients. Since the image quality is affected by the patients’ respiration during CT scan, it is difficult to find the narrowest part, and even if the diameter is measured, the accuracy might be degraded. In a printed 3D airway model, it is possible to check the indentation due to the relationship with the surrounding structures along with the entire airway shape, so even if the image is blurred, enough airway information can be obtained from the printed 3D airway model. The 3D airway model might also present the information of tracheal anatomy in the patient who has an anomaly of the trachea or possibility of difficult intubation.

In conclusion, prediction of the correct size of the ETTs using a printed 3D airway model has demonstrated better results than the age-based formula. In particular, our study included patients with congenital heart disease and an abnormal range of growth and development; thus the selection of the ETT size using a printed 3D airway model in such a group may be feasible for helping minimize re-intubation attempts and complications. However, routine use in all pediatric patients needs to be further investigated. In the future, the 3D printer technique used in this study might be further developed in collaboration with a department of materials engineering, and used to create novel ETTs with individual size and shape.

**Conflicts of Interest**

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

**Author Contributions**

Syeon Park (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Validation; Visualization; Writing – original draft; Writing – review & editing)
Jisoo Ahn (Data curation; Writing – review & editing)
Sung Uk Yoon (Software; Writing – review & editing)
Ki Seok Choo (Software; Writing – review & editing)
Hye-Jin Kim (Writing – review & editing)
Minwoo Chung (Writing – review & editing)
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References


Heart disease remains one of the most common causes of maternal mortality. Shone’s syndrome (SS) was first described in 1963 by John Shone [1]. It is characterized by:

1) Left ventricular (LV) inflow tract obstruction in the form of a supra-valvular mitral valve (MV) ring or a parachute MV
2) LV outflow tract obstruction in the form of aortic stenosis (AS), which may be supra-valvar, valvular with a bicuspid aortic valve (BAV), or sub-valvar
3) Aortic abnormalities in the form of hypoplasia of the aortic arch or coarctation of aorta (Co-A). The lesions encountered in SS are represented in Fig. 1.

It has an incidence of 0.67% in adults with congenital heart disease and the most common lesions seen in this syndrome are congenital MV stenosis (93%), Co-A (75%), and AS (71%) [2]. It can exist in a complete form (all lesions present), or more frequently in a partial or incomplete form (LV inflow obstruction and any one of the other abnormalities) [2]. The syndrome is extremely rare in pregnancy. We describe our anesthetic management for a parturient with repaired but with residual SS who underwent an uneventful Cesarean section (C-section).

**Background:** Shone’s syndrome is a rare complex congenital cardiac condition, characterized by a supra-valvular mitral ring, parachute deformity of the mitral valve, aortic stenosis, and coarctation of the aorta.

**Case:** A 26-year-old parturient with partial Shone’s syndrome presented to our delivery unit in pulmonary edema. She underwent a scheduled cesarean section performed under a combined spinal-epidural anesthetic at 33 weeks. She had multidisciplinary input from the cardiac, obstetric, and anesthetic teams, which led to a good outcome. A review of the five published case reports of Shone’s syndrome in pregnancy is presented along with key findings.

**Conclusions:** Our case report and the review highlight the successful use of combined spinal-epidural anesthetic and provides guidance to the multidisciplinary team on the varied presentation and the optimum management of women with Shone’s syndrome during the peripartum period.

**Keywords:** Aortic coarctation; Aortic stenosis; Cesarean section; Epidural anesthesia; Mitral valve stenosis; Spinal anesthesia.
Case Report

Written informed consent was obtained from the patient. A 26-year-old primigravida with a body mass index (BMI) of 25.71 kg/m² (weight 70 kg, height 165 cm) presented to our delivery suite in Manchester at 32-weeks with a 2-week history of dyspnea on exertion, orthopnea, and palpitations. She was known to have SS. Her syndrome consisted of a subaortic valve, parachute MV, mild LV outflow tract obstruction with Co-A, and a BAV. The mitral ring, LV outflow tract obstruction, and the Co-A were repaired at the age of three by open heart surgery, which was followed by a dual chamber pacemaker insertion for complete heart block. The BAV and the parachute MV were not repaired. This was followed by balloon dilatation of the aorta for recoarctation at the age of 12. She remained asymptomatic following this till the end of the second trimester of pregnancy.

On presentation to our unit, she had a heart rate (HR) of 100 beats/min, blood pressure (BP) of 136/88 mmHg, respiratory rate (RR) of 28 breaths/min with oxygen saturations (SpO₂) 90–92% on room air. Auscultation revealed bilateral crepitations along with a mid-diastolic murmur and a diagnosis of acute pulmonary edema was made. Arterial blood gas (ABG) revealed a pH – 7.48, partial pressure of carbon dioxide (pCO₂) – 23.5 mmHg, partial pressure of oxygen (pO₂) – 90.76 mmHg, base excess of 4 mmol/L and a lactate of 3 mmol/L. Her hemoglobin was 12.2 g/dl, serum potassium (K⁺) was 3.6 mmol/L, and serum magnesium (Mg²⁺) was 0.65 mmol/L. Her N-terminal pro-B-type natriuretic peptide (NT-pro BNP) levels were 1,020 pg/ml. Her chest X-ray was suggestive of pulmonary edema and electrocardiogram (ECG) showed a sinus tachycardia with P mitrale.

She was transferred to the coronary care unit and the treatment instituted included oxygen, intravenous (IV) furosemide 20 mg, 5 mg of IV dexamphetamine, and oral bisoprolol 2.5 mg. Fluid balance was monitored using strict input and output monitoring with a urinary catheter, and oral potassium chloride and IV magnesium were supplemented to maintain K⁺ > 4 mmol/L and Mg²⁺ > 0.7 mmol/L.

Pacemaker check revealed an appropriately functioning dual chamber DDD device. Cardiotocography as part of fetal monitoring revealed a normal trace. A trans-thoracic echocardiogram (TTE) revealed:

1) A BAV with mild AS with a velocity of 2.5 m/s across the valve and a mean gradient of 25 mmHg
2) A normal LV size (LV diastolic diameter of 4.4 cm), with an ejection fraction of 48%, with mildly impaired systolic function
3) Parachute MV with chordal attachment to single papillary muscle, MV area of 1.12 m², mean gradient of 8 mmHg across MV, moderate MV stenosis with mild-moderate regurgitation
4) Severely dilated left atrium (LA-volume/body surface area of 49 ml/m²)
5) A normal aortic root, with a normally functioning repair (velocity across the aorta was 2.4 m/s) with no diastolic tail
6) A mildly dilated well-functioning right ventricle (base RV of 4.3 cm and mid RV of 3.8 cm with preserved RV fractional area of change > 40%), mild tricuspid regurgitation (vena contracta width of 3 mm, max velocity of 3.4 m/s) with estimated mean pulmonary artery (PA) pressure of 56 mmHg with a moderately dilated right atrial volume of 67 ml.

Her case was discussed at the multi-disciplinary cardiology, obstetric, anesthetic team meeting. In view of her on-going symptoms, limited mobility, and detection of a severely dilated LA and raised PA pressure on TTE, the team decided to administer tinzaparin 4500 IU subcutaneously for thromboprophylaxis.

Despite medical management for the next 72 h, she complained of dyspnea on minimal exertion. She required 2 L of oxygen to maintain saturations of 97% (94% on air) but was able to lie almost flat without significant difficulty. A repeat ABG on oxygen, revealed a pH – 7.42, pCO₂ – 30.5 mmHg, pO₂ – 93.33 mmHg, base excess of 2 mmol/L with a lactate of 1.6 mmol/L. As thromboembolism remains one of the most common direct causes of death in pregnancy in the United Kingdom (UK), on a risk-benefit basis, based on her symptoms and dependence on oxygen, the team decided to rule out pulmonary embolism (PE) with a com-

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puterized tomography with pulmonary angiography (CTPA), which was reported back as normal.

In view of her symptoms and significant pulmonary hypertension, a decision was made to deliver her by category (Cat) 3 C-section in accordance with The Royal College of Obstetricians and Gynaecologists’ guidelines for classification of urgency of C-section (Cat 1: Immediate threat to life of woman or fetus, Cat 2: Maternal or fetal compromise, which is not immediately life-threatening, Cat 3: Needing early delivery but no maternal or fetal compromise, Cat 4: At a time to suit the woman and maternity team). Maternal steroids were administered to accelerate fetal lung maturity. After discussion with the patient of the potential risks and benefits of general anesthesia (GA) compared with neuraxial anesthesia, it was decided to perform the surgery under combined spinal-epidural (CSE) anesthesia. The decision process incorporated the patient’s preference to stay awake and witness the delivery of her baby along with partner in the operating theatre.

In theatre, a 16 gauge (G) peripheral cannula was inserted and the patient had ECG, 

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and invasive BP monitoring was established in theatre via a radial artery catheter. Baseline HR was 86 beats/min and BP was 100/58 mmHg. A 12-h interval between the last dose of prophylactic tinzaparin and administration of CSE anesthetic was followed in accordance with The European Society of Anesthesiology guidance [3]. CTG was monitored during and after the CSE insertion and was normal at all times.

With the patient in the sitting position, using an aseptic technique, the epidural space initially was detected with a 16 G Tuohy needle using a loss-of-resistance to saline technique at the L3–4 intervertebral space and an epidural catheter threaded into the epidural space. A test dose of 5 ml of 0.1% bupivacaine was given to rule out intrathecal catheter placement. This was followed by a subarachnoid injection at L4–5 interspace of 7.5 mg of hyperbaric bupivacaine and 300 μg diamorphine with a 25 G pencil point needle. The patient was positioned supine with left uterine displacement and 500 ml of compound sodium lactate (CSL) solution commenced along with a phenylephrine infusion 100 μg/ml at the rate of 30 ml/h. Within 12 min, a bilateral block to cold up to T8 to S5 dermatomes was established. To augment the block height, 5 ml of 0.75% ropivacaine was administered via the epidural catheter. Once the block height to T4 dermatome with cold spray was confirmed, C-section was commenced, and a female infant weighing 2.3 kg was delivered. APGAR scores of 5 at 1 min and 8 at 5 min were recorded. Oxytocin 5 IU was given as an IV infusion over 20 min to avoid tachycardia and hypotension. Pacemaker was kept on throughout the C-section. Patient was hemodynamically stable throughout, blood loss recorded during the C-section was 700 ml, and the procedure was completed uneventfully in 45 min. The phenylephrine infusion was weaned off gradually. Her epidural was removed at the end of the surgery to facilitate thromboprophylaxis following C-section. Tinzaparin 4,500 IU was administered subcutaneously 4 h after removal of epidural and continued for 10 days post-operatively. She stayed in our cardiac intensive care unit for 24 h, then stepped down to our obstetric high dependency unit over the next 48 h, and was discharged uneventfully from the hospital on the 7th post-operative day.

Discussion

To our knowledge, this is one of the first case report, highlighting the successful use of CSE in a parturient with SS.

Considering that SS is a fixed cardiac output lesion, the physiological changes of pregnancy, including a 25% increase in HR, a 25% drop in systemic vascular resistance (SVR), a 40% increase in cardiac output, anemia, and a 25% increase in oxygen demand are poorly tolerated [4]. Dyspnea on exertion, orthopnea, palpitations, and pulmonary edema are common presentations in SS when the MV stenosis is prominent, suggestive of heart failure or new onset arrhythmia. These were seen at 32 weeks in our parturient when the cardiac output peaks in pregnancy. On echocardiography, our patient had moderate MV stenosis, mild AS with a BAV, pulmonary hypertension, and a normal aorta. Appropriate medical therapy was instituted, and we ruled out PE with a CTPA in view of our patient’s persistent dyspnea.

The obstetric, cardiology, anesthetic as well as the neonatal teams were involved early in our case so as to plan the mode of delivery, analgesia, anesthesia, and post-partum care in accordance with the National Institute of Health Care and Excellence and the European Society of Cardiology guidelines [5,6]. Our team made the decision of delivering our patient with a C-section at 33 weeks in view of her persistent dyspnea, oxygen requirements, and significant pulmonary hypertension.

The optimal choice of analgesic and anesthetic technique for delivery in a patient with SS where MV stenosis as well as AS is predominant lesion should encompass the following goals:

1) Optimum analgesia
2) A slow HR to decrease oxygen demand and increase diastolic filling time
3) Maintain sinus rhythm
4) Avoiding fall in SVR and maintaining contractility
5) Avoiding any increase in pulmonary vascular resistance (PVR) (hypoxia, hypercarbia, acidosis, hypothermia, high
positive end-expiratory pressure)
6) Avoidance of Valsalva maneuver and shortening the second stage of labor
7) Avoiding fluid overload, aortocaval compression, and maintaining euolemic status and if coarctation exists, avoid swings in BP and hypertension.

Neuraxial anesthesia for C-section in fixed cardiac output lesions though may result in a drop in SVR, but when titrated appropriately with a suitable vasopressor, might be a technique of choice in these cases and has been reported in AS and MV stenosis [7,8]. We opted for a CSE technique as it allowed us to place a small intrathecal dose of local anesthetic along with an opioid to initiate the block, the final height of which could then be titrated using the epidural top up. The low dose of local anesthetic in CSE provided us with a good quality of block, avoided the sudden hypotension, and the intrathecal diamorphine added to the local anesthetic contributed to good post-operative pain relief. A CSE technique with separate needle and separate interspaces was utilized in our case as it allowed us to test the epidural catheter before placement of intrathecal drug. After intrathecal local anesthetic with opioid achieved a block of T8, we topped up our epidural catheter with ropivacaine to augment block height to T4 dermatome, which allowed the surgery to be carried out uneventfully. BP was maintained in our case by using phenylephrine infusion, which is the vasopressor of choice in obstetric anesthesia. It also avoids tachycardia and maintains SVR, which was advantageous in SS.

Other options for neuraxial anesthesia include using:
1) A de novo spinal anesthetic (SA), which could lead to a dramatic drop in SVR with an unpredictable spread
2) A continuous SA using an intrathecal catheter, which we were unfamiliar with
3) A de novo epidural technique, which is associated with incomplete sensory and motor block, and conversion to GA.

We avoided a GA as our patient was keen to stay awake during the C-section. GA has the advantage of secure airway and the ability to perform a real time transesophageal echocardiography but also has the disadvantages of sympathetic stimulation associated with laryngoscopy, positive pressure ventilation, and increasing PVR thus decreasing venous return, as well as the known obstetric risks of difficult intubation, aspiration, and awareness.

We chose IBP monitoring in our case using an arterial line to facilitate beat-to-beat BP monitoring and blood gas analysis as our patient was dependent on oxygen. Central venous access was not thought to be necessary as we were mindful of the possible risk of inducing an arrhythmia. Oxytocin was given as a slow infusion to avoid tachycardia and hypotension and fluid neutral balance was maintained replacing blood loss with CSL. Though our neonate was premature, a good neonatal outcome was reported in our case.

We present a systematic review of all the published case reports of SS over the last two decades. Using the NICE Healthcare Databases' advanced search engine, a search of the Medline, CINAHL, and EMBASE databases from January 1, 2000 to December 31, 2019 was conducted in January 2020. The following search terms were used in the search strategy: Shone's syndrome OR Shone's complex OR Shone's anomaly AND Obstetric OR Pregnant OR Labor OR Cesarean. The search was limited to humans, and to reports written and published in English. All articles generated had their reference lists and citations hand-checked by the authors and any additional articles were scrutinized. Full text articles were included in the analysis if they confirmed the diagnosis of SS and described the mode of delivery. Information extracted from the case reports included age, parity, BMI, mode of delivery, weeks of gestation, clinical presentation, echocardiographic findings, anesthesia details, and neonatal outcomes.

Results

We found five published case reports of SS in pregnancy since the year 2000 [9–13]. Their demographics, initial presentation to the delivery unit, echocardiogram findings, maternal, and neonatal outcomes along with their anesthetic management are presented in Table 1.

Mean age of women in the literature review was 22.6 years, mean BMI was 26.3 kg/m², and three of the five women (60%) were primiparous [10,11,13]. All the published case reports in our review had a partial or incomplete form of SS (100%) with two of the five women (40%) having some form of surgical correction in childhood [12,13].

Clinical presentation

Dyspnea on exertion, orthopnea, palpitations, and pulmonary edema were the presenting symptoms in three case reports (60%) [10,11,13]. Beta blockers and diuretics were commonly utilized in these cases.

Women can also present with systemic hypertension where Co-A features in SS prominently. In three of the case reports (60%), the reported BP on presentation was greater than 140/90 mmHg [9,10,13]. These patients may be mistakenly diagnosed
<table>
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<td>Baseline BP mmHg</td>
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<td>152/98</td>
<td>103/51</td>
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<td>140/96</td>
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<tr>
<td>Aortic valve</td>
<td>Bicuspid mean ΔP 35 mmHg</td>
<td>Normal</td>
<td>Bicuspid mild AS</td>
<td>Normal previous resection of subaortic membrane</td>
<td>Bicuspid peak ΔP 80 mmHg, previous resection of subaortic membrane</td>
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<tr>
<td>Mitral valve</td>
<td>Dysplastic thickened leaflets</td>
<td>Supra-valvular mitral ring ΔP 22 mmHg then decreased to 14 mmHg</td>
<td>Mild MS</td>
<td>Parachute MV valve area 1.2 cm²</td>
<td>ΔP 21 mmHg</td>
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<td>Aortic aneurysm</td>
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<td>Repaired Co-A</td>
<td>Re-Co-A descending aorta ΔP 37 mmHg</td>
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with pre-eclampsia but absence of proteinuria, a normal urinary-protein creatinine ratio, and use of biomarkers such as the ratio of sFlt-1 (soluble FMS-like tyrosine kinase-1; an anti-angiogenic factor)/PIGF (placental growth factor; an angiogenic factor) might provide clues to the obstetric team in ruling out pre-eclampsia [14].

Echocardiography findings

In the five case reports described in our review:

1) MV: Parachute MV was seen in one woman (20%) [12]. Dysplastic MV leaflets were observed in one case (20%) and mild MV stenosis seen in one (20%) woman [9,11]. Supra-valvular mitral ring was seen in one of the women (20%) [10]. Valve area varied between 1.2 and 2.17 m² and gradient across MV varied between 14 and 22 mmHg [10,12,13]. Overall, MV stenosis was found in three of the five case reports (60%).

2) Aortic valve: BAV with AS was seen in three of the five case reports (60%). Three women had AS with peak gradients varying from 35 to 80 mmHg with one patient having mild AS [9,11,13]. Subaortic membrane was resected (40%) in two cases [12,13] with the aortic valve being normal (40%) in two [10,12].

3) Co-A: Two of the women had Co-A at the time of C-section (40%) with gradients varying from 37 to 70 mmHg [10,13]. One woman had proximal aortic aneurysm (20%) and one had a normal (20%) aorta [9,11]. Two of the women had Co-A repaired (40%) during childhood [12,13].

The echocardiographic findings in the review highlight that MV stenosis along with BAV seems to be the most common findings in SS in pregnancy. It is important that if MV stenosis of non-rheumatic origin or a parachute MV is noted on the echocardiogram, the cardiology team should look out for other lesions to confirm the diagnosis of SS.

Multidisciplinary input

Of the five case reports two of them (40%) had multidisciplinary input in them [12,13]. Multidisciplinary input by the obstetric cardiac team is recommended for heart disease in pregnancy as per the European Society of Cardiology guidance [6].

Mode of delivery

This will be dictated by a number of factors including both obstetric as well as cardiac. In women with severe cardiac lesions, significant pulmonary hypertension, heart failure, and a dilated aortic root, a C-section might be the preferable mode in line with the European Society of Cardiology recommendations [6]. Vaginal delivery (20%) was reported in just one of the case reports with SS [10]. C-section (80%) was reported in four other cases [9,11–13].

Anesthesia and analgesia

Three of the five cases (60%) having C-section described the anesthetic management in detail [9,11,13]. Use of de novo epidural anesthesia was reported in two cases [11,13]. One proceeded uneventfully; the other case resulted in significant hypotension, fetal distress, and a conversion to an unplanned GA [11]. Thiopentone and suxamethonium were utilized in that case. Planned GA was administered using etomidate, propofol target-controlled infusion, remifentanil, and rocuronium in one case to manage a SS lady who also had an ascending aortic aneurysm, which was being repaired at the time of CS [9]. No analgesia was utilized in the case of the woman having a vaginal delivery [10]. If choosing a GA technique, a rocuronium-sugammadex combination for muscle relaxant and a reversal might avoid the tachycardia seen with glycopyrrolate and neostigmine and might be advantageous in this cohort.

Blood pressure management and monitoring

Phenylephrine was used in two (40%) of the five case reports [11,13]. Ephedrine should be avoided in this cohort. Arterial line monitoring was utilized in three (60%) of the five reports [9,10,13]. Central venous access was utilized in two (40%) of the case reports [9,13]. Though fluid was administered in one case report using the central venous pressure (CVP) monitor, we are unsure in a patient with valvular stenosis how reliable CVP monitoring would be to guide fluid replacement.

In women presenting with active Co-A, the post ductal BP is more suggestive of uterine perfusion. BP should be maintained to avoid compromising utero-placental blood flow and systemic hypertension [15].

Oxytocic

Two of the five case reports (40%) describe the use of oxytocin infusion to maintain uterine tone [9,13]. Regarding oxytocic
agents, it is best to avoid ergometrine in SS as it does cause hypertension with tachycardia and prostaglandin F2 alpha in the presence of pulmonary hypertension as it can increase PVR. The cardiac output does peak again post-delivery and these patients are at risk of pulmonary edema following delivery; hence fluid should be administered cautiously aiming for a neutral fluid balance.

Neonatal outcomes

Preterm (gestational age < 37 weeks) birth was reported in two of the five case reports (60%) as was seen in our case as well [9,13]. Mean gestational age at the time of delivery was 35.75 weeks on our review. Three of the other case reports described normal APGAR scores (60%) with mostly good outcomes [10,11,13]. In one of the case reports where GA was administered, the neonate was intubated (20%) and ventilated [9].

The information detailed in the review of literature could provide useful information for the obstetric cardiac team when pre-conception counseling and risk-assessment are undertaken in women with SS. Based on the review of the literature, we provide a summary of recommendations, which could be utilized by the multidisciplinary cardiac, obstetric, anesthetic, and neonatal team when they encounter a parturient with SS (Table 2).

Limitations of our review include limited number of patients, some information that was missing in the case reports, and it being limited to only the last two decades. There is also a possibility that we might have missed case reports in other languages as the literature review was limited to case reports in English.

In conclusion, our case report along with the review of literature raises awareness about this condition, highlights the safe use of CSE anesthesia, and provides guidance to the multidisciplinary obstetric, cardiac, anesthetic, and neonatal team on the varied presentation and the optimum management of women with SS during the peripartum period.

Conflicts of Interest

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

Author Contributions

Kailash Bhatia (Conceptualization; Formal analysis; Supervision; Writing – review & editing)
Jennifer Eccles (Methodology; Writing – review & editing)
Dinesh Meessala (Writing – original draft)

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References


Hyper- and hypocoagulability in COVID-19 as assessed by thromboelastometry -two case reports-

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Background: Coronavirus disease (COVID-19)-associated coagulopathy is most often characterized by elevated D-dimer, interleukin-6, and plasma fibrinogen concentrations as well as hypercoagulability in thromboelastometry with increased clot firmness in the EXTEM, INTEM, and FIBTEM assays. Clinically, it manifests with a very high incidence of thrombosis, particularly in the pulmonary system, whereas bleeding complications are infrequent.

Case: Here, we describe two critically ill patients with COVID-19 admitted to our intensive care unit demonstrating different thromboelastometry and biomarker patterns. One patient presented with hypercoagulability and the other patient with hypocoagulability and fibrinolysis shutdown in thromboelastometry. The pathophysiology and the potential impact on treatment options are discussed.

Conclusions: A combination of biomarkers and thromboelastometry results can be helpful in the future to decide which therapeutic strategy might be most appropriate for critically ill patients with COVID-19. This would be an important step to establish precision medicine in this high-risk patient population.

Keywords: Anticoagulants; COVID-19; Fibrinolysis; Hemostasis; Thrombelastography; Thrombosis.

Coronavirus disease (COVID-19)-associated coagulopathy is most often characterized by elevated D-dimer, interleukin-6 (IL-6), and plasma fibrinogen concentrations as well as hypercoagulability in thromboelastometry with increased clot firmness in the EXTEM, INTEM, and FIBTEM assays [1]. Clinically, it manifests with a very high incidence of thrombosis, particularly in the pulmonary system, whereas bleeding complications are infrequent [2]. In contrast, sepsis-associated coagulopathy due to bacterial infection is characterized by hypocoagulability in thromboelastometry which has been shown to be a good predictor of increased mortality [3]. Here, we describe two critically ill patients with COVID-19 admitted to our intensive care unit (ICU) at Brighton and Sussex University Hospitals NHS Trust presenting with different thromboelastometry phenotypes, clinical courses, and outcomes.
from each patient.

Case 1

A 48-year-old South Asian woman (Patient A) from Bangladesh (height 168 cm, weight 80 kg) was admitted to the medical ward for three days after which she was transferred to the ICU; she had cough and increasing dyspnea for three days before hospital admission. Comorbidities included hypertension, hypercholesterinemia, coronary artery disease, previous stroke (fully recovered), and type 2 diabetes. On admission, her laboratory results were as follows: hemoglobin (Hb): 143 g/L, white blood cells (WBC): 9.0 × 10⁹/L, lymphocytes: 1.4 × 10⁹/L, platelets: 261 × 10⁹/L, international normalized ratio (INR): 1.1, D-dimer: 510 μg/L, fibrinogen plasma concentration: 8.4 g/L, and C-reactive protein (CRP): 52 mg/L. Her chest radiograph showed cardiomegaly and extensive bilateral peripherally predominant ground-glass opacities. Polymerase chain reaction (PCR) result was positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and negative for influenza/respiratory syncytial virus (RSV).

Blood cultures were negative. The patient was treated with nasal oxygen therapy and antibiotics (ceftriaxone and doxycycline, according the hospital's COVID-19 protocol). Antiviral therapy and dexamethasone were not administered. Later, CRP increased to 137 mg/L on the second day of hospitalization. The patient was transferred to the ICU on the third day because of increased respiratory rate and oxygen requirement. ROTEM performed 2 hours after ICU admission (Fig. 1A) revealed that Patient A was hypercoagulable with the EXTEM assay showing an increased clot firmness with an amplitude of clot firmness 5 minutes after coagulation time (CT) (A5) of 65 mm and a maximum clot firmness (MCF) of 78 mm, indicating hypercoagulability with a high risk of thrombosis [4]. FIBTEM also showed increased clot firmness (A5 41 mm and MCF 50 mm), indicating increased fibrinogen concentration and fibrin polymerization. Furthermore, the EXTEN lysis index 60 minutes after CT (LI60) was 97%, i.e., in the physiologic range (82–97.9%), whereas FIBTEM LI60 was 100% [5]. Treatment consisted of continuation of antibiotics, enoxaparin 40 mg twice a day in view of ROTEM results, and high flow nasal oxygen and intermittent face mask continuous positive airway pressure (CPAP) therapies. The patient did not need intermittent positive pressure ventilation (IPPV) or any vasoactive support. Laboratory results on the second day in the ICU were as follows: Hb: 131 g/L, WBC: 10.8 × 10⁹/L, platelet count: 307 × 10⁹/L, INR: 1.1, activated partial thromboplastin time (APTT) ratio: 1.3, D-dimer: 510 μg/L, and CRP: 196 mg/L. The patient recovered well and was transferred from the ICU to the medical ward after two days in the ICU with a CRP of 73 mg/L and was discharged three days later with a prescription of her usual medication plus enoxaparin 40 mg once daily for 2 weeks. The patient did not show any clinical signs of thrombosis during her hospital stay.

Case 2

A 68-year-old Caucasian man (Patient B) from the United Kingdom (height 177 cm, weight 85 kg) was admitted with cough and a week-long increasing dyspnea, before which he was healthy. His wife and daughter probably had COVID-19 with resolving symptoms, and they were all living in the same house. The patient markedly experienced shortness of breath on the day of admission to the emergency department (ED) and, therefore, called an ambulance. His laboratory results on admission were as follows: Hb: 140 g/L, creatinine: 117 μmol/L, WBC: 8.6 × 10⁹/L, lymphocytes: 0.2 × 10⁹/L, platelet count: 126 × 10⁹/L, INR: 1.4, APTT ratio: 1.3, D-dimer > 20,000 μg/L (i.e., higher than the upper limit of the measurement range), fibrinogen plasma concentration: 6.8 g/L, and CRP: 336 mg/L. His chest radiograph showed dense bilateral mid-zone and right lower zone consolidation. PCR result was positive for SARS-CoV-2 and negative for influenza/RSV. Blood cultures showed coagulase-negative staphylococci. The patient was treated with antibiotics (ceftriaxone and doxycycline, according the hospital’s COVID-19 protocol). Antiviral therapy and dexamethasone were not administered. As the patient was severely hypoxemic in the ED, he was transferred directly to the ICU. Orotracheal intubation and IPPV (positive end-expiratory pressure 15 mmHg) were performed about 3 hours after ICU admission as respiratory effort was not improved by face mask CPAP therapy. Chest radiography repeated after intubation showed bilateral interstitial lung changes similar to the imaging conducted earlier on the same day. Prone position did not improve oxygenation. Laboratory results on the next day were as follows:

Hb: 133 g/L, creatinine: 265 μmol/L, WBC: 16.3 × 10⁹/L, platelet count: 56 × 10⁹/L, INR: 1.6, APTT ratio: 1.5, D-dimer: 4,340 μg/L, fibrinogen plasma concentration: 2.9 g/L, and CRP: 478 mg/L. By ROTEM, Patient B presented with hypocoagulability in the EXTEN assay with a prolonged CT of 99 s, clot formation time (CFT) of 253 s, and decreased clot firmness amplitudes (A5, 22 mm and MCF, 48 mm) (Fig. 1B). Furthermore, EXTEN and FIBTEM analyses demonstrated a complete fibrinolysis shutdown [5]. Both hypocoagulability and fibrinolysis shutdown have been shown to be associated with increased mortality in bacterial sepsis [3,6]. The FIBTEM trace was within normal limits which may be owing to impaired fibrin polymerization, given that fibrinogen
**Fig. 1.** ROTEM graphs and results of Patient A and Patient B. (A) Critically ill Patient A with COVID-19, with a hypercoagulable phenotype. (B) Critically ill Patient B with COVID-19 with a hypocoagulable phenotype. EXTEM: extrinsically activated (tissue factor) thromboelastometric assay, FIBTEM: extrinsically activated thromboelastometric assay with the addition of cytochalasin to eliminate platelet contribution to clot firmness, CT: coagulation time, CFT: clot formation time, alpha: alpha angle, A5: amplitude of clot firmness 5 minutes after CT, A10: amplitude of clot firmness 10 minutes after CT, MCF: maximum clot firmness, LI60: lysis index in percentage of maximum clot firmness 60 minutes after CT, ML: maximum lysis during run time, *Reference range for physiological fibrinolysis in EXTEM as published by Stettler et al. [5].

**Table 1.** EXTEM and FIBTEM variables and reference ranges for Patient A and Patient B.

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<tr>
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**Table 2.** EXTEM and FIBTEM variables and reference ranges for Patient A and Patient B.

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https://doi.org/10.4097/kja.20327
concentration was elevated. The patient deteriorated within a few hours of ICU admission and died the following day despite invasive ventilation, norepinephrine for hypotension, and renal replacement therapy for acute kidney failure. Patient B did not show any clinical signs of thrombosis during his hospital stay.

Discussion

We have presented two cases that illustrate the additional value of using thromboelastometry to monitor patients with COVID-19. Increased clot firmness in EXTEM and INTEM (amplitude of clot firmness 10 minutes after CT (A10) > 61.5 mm or MCF > 68 mm) assays has been shown to be associated with an increased incidence of thrombosis in adults and neonates undergoing cardiac and non-cardiac surgery [4]. Furthermore, increased clot firmness in the FIBTEM assay (MCF > 25 mm) has been shown to be associated with an increased incidence of thrombosis in patients with cirrhosis and hepatocellular carcinoma as well as in patients with thrombophilic predisposition after liver transplantation [7,8]. Thromboelastometry in Patient A showed hypercoagulability despite upper normal ranged D-dimer levels and a normal INR. Patients with D-dimer > 3,000 µg/L and/or sepsis-induced coagulopathy score ≥ 4 seem to benefit from increased anticoagulation [9]. However, in critically ill patients with COVID-19, the incidence of thrombosis and pulmonary embolism is high despite pharmacological thromboprophylaxis [2].

The case of Patient B demonstrated that not all critically ill patients with COVID-19 present the same thromboelastometric pattern. This might be attributed to ethnic and genetic difference, such as gene polymorphisms, bacterial superinfection, or the phase of the disease. Both hypocoagulability and fibrinolysis shutdown, as presented by Patient B, have been shown to be associated with increased mortality in cases involving bacterial sepsis [3,6]. Furthermore, lymphocytopenia has been shown to be associated with poor outcomes in COVID-19 [10]. Although thrombocytopenia, which is an important determinant of clot firmness, is rare in COVID-19, it is associated with poor outcomes in the patient population [7,11]. Furthermore, the mismatch between FIBTEM MCF (14 mm) and Clauss fibrinogen plasma concentration (6.8 g/L) in Patient B might reflect an acquired factor XIII deficiency, which often occurs in sepsis, cirrhosis, acute renal failure, and malignancies [12]. Unfortunately, factor XIII activity is not available for Patient B, which leaves this interpretation speculative. The rapid deterioration of Patient B with acute renal failure and a fatal outcome is in-line with the data published by Wright et al [13], showing that patients with the combination of high D-dimer (> 2,600 µg/L, here > 20,000 µg/L) and fibrinolysis shutdown (lysis 30 minutes after maximum amplitude in thrombelastography (TEG LY30) of 0% or ROTEM LI60 of 100%) are associated with the highest incidence of thrombosis (50%) and acute renal failure (80%). Here, increased D-dimers and fibrinolysis shutdown may reflect an imbalance in hemostasis with increased clot formation but impaired fibrinolysis – similar to disseminated intravascular coagulation. It remains to be determined whether fibrinolytic therapy with recombinant tissue plasminogen activator (rtPA) has a therapeutic role in critically ill patients with COVID-19 who cannot be oxygenated adequately despite mechanical ventilation and prone positioning. Notably, extracorporeal membrane oxygenation is associated with very high mortality in patients with COVID-19, particularly in patients with hyperinflammation characterized by high IL-6 levels. Although this might support the use of fibrinolytic therapy with rtPA in these patients, Campello et al. [14] demonstrated that a FIBTEM MCF < 14.5 mm is highly predictive of bleeding complications (such as hemorrhagic stroke) after rtPA. Therefore, hypocoagulability in thromboelastometry, particularly a FIBTEM MCF < 14.5 mm should be considered a contraindication for fibrinolytic therapy in critically ill patients with COVID-19.

Nevertheless, this case report has several limitations. First, no follow-up ROTEM analyses are available for these patients. Accordingly, the presented ROTEM analyses only represent a snapshot of the COVID-19-associated coagulopathy that can be considered as a dynamic process. Here, different thromboelastometric phenotypes may represent different conditions of the patients or different phases of the coagulopathy. Second, the cut-off values for fibrinolysis shutdown established in trauma and bacterial sepsis cases have been used as clear cut-off values for fibrinolysis shutdown in COVID-19-associated coagulopathy have not been established yet. Further studies are needed to characterize COVID-19-associated coagulopathy and its differences from trauma- and sepsis-induced coagulopathy.

These two cases demonstrate that the thromboelastometric phenotype can be different and thromboelastometry can easily distinguish between hyper- and hypocoagulability in critically ill patients with COVID-19. Furthermore, thromboelastometry can identify patients with fibrinolysis shutdown [5,6]. The combination of thromboelastometry parameters (EXTEM and FIBTEM CT, CFT, A5, A10, MCF and LI60) and conventional biomarkers (D-dimer, Clauss fibrinogen, and IL-6) might be superior in predicting clinical outcomes such as thrombosis, renal failure and death in patients with COVID-19 than each diagnostic test alone. Therefore, these test combinations can be helpful in the future to decide which therapeutic strategy might be the most appropriate
one in critically ill patients with COVID-19. This would be an important step to establish precision medicine not only in thromboelastometry-guided bleeding management but also in this high-risk patient population [15].

**Conflicts of Interest**

Klaus Görlinger is working as the Medical Director of Tem Innovations since July 2012. Robert Kong and Nevil Hutchinson reported no potential conflict of interest relevant to this article.

**Author Contributions**

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**References**

Ultrasound-guided rhomboid intercostal block provides effective pain control after video-assisted thoracoscopic surgery: a brief report of three cases

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Rhomboid intercostal block (RIB) is a novel block that may be used for several indications such as thoracic procedures and myofascial pain [1,2]. It may be performed for open thoracotomy [3]; however, more information is needed for other thoracic procedures. Video-assisted thoracoscopic surgery (VATS) has the advantage of reduced pain over open thoracotomy. However, patients may still experience moderate to severe pain after VATS [4]. Herein, we report the use of RIB in three patients for analgesia management after VATS. Written informed consent for the procedure and future publication was obtained from the patients.

Patient 1 was a 45-year-old male with 170 cm height and 75 kg weight. He was diagnosed with lung carcinoma of the right lung. He had no additional comorbidities and was American Society of Anesthesiologists physical status (ASA PS) classification I. Patient 2 was a 53-year-old male with 165 cm height and 72 kg weight. He was diagnosed with left lung carcinoma, had no additional comorbidities, and was ASA PS classification I. Patient 3 was a 58-year-old male who was 178 cm tall and weighed 86 kg. He was diagnosed with right lung carcinoma, had no additional comorbidities, and was ASA PS classification I. All of three patients’ blood tests were within normal ranges and vital signs were stable. The patients underwent thoracoscopic surgery lasting 130, 125, and 110 minutes, respectively for the patient 1, 2, and 3 with no complications during the surgery. After RIB, the patients were extubated. After observing sufficient spontaneous respiration, they were transferred to the intensive care unit (ICU) for further monitoring. Intravenous (IV) ibuprofen (400 mg), dosed at every 8 hours postoperatively was administered for postoperative pain control. The visual analogue score (VAS) was evaluated at 1, 6, 12, and 24 hours.

For patient 1, the static and dynamic (on deep breathing) VAS scores were 0/1, 1/2, 0/2, and 1/1, respectively. The patient needed no additional analgesic drugs. After 24 hours, he transferred to the ward. After 36 hours, the chest drain was removed. On the 4th day after surgery, the patient was discharged. For patient 2, the static and dynamic VAS scores were 1/2, 2/3, 1/3, and 0/1, respectively. He needed no additional analgesic drugs. After 24 hours, he was transferred to the ward. After 48 hours, the chest drain was removed. On the 5th day after surgery, the patient was discharged. For patient 3, the static and dynamic VAS scores were 0/2, 1/2, 1/1, and 0/1, respectively. He needed no additional analgesic drugs. After 24 hours, he transferred to the ward. After 36 hours, the chest drain was removed. On the 3rd postoperative day, he was discharged.

All patients underwent unilateral thoracoscopic lobectomy due to lung carcinoma.
standard three-port VATS approach (at the 5th, 8th, and 9th intercostal space) was performed. A 24 F chest tube was placed at 8th intercostal space in the midaxillary line. General anesthesia induction was performed using IV propofol (2 mg/kg), fentanyl (1.5 µg/kg), and rocuronium bromide (0.6 mg/kg). A double-lumen tube was used for orotracheal intubation and its position was confirmed via fiberoptic bronchoscopy. The patients were placed in a lateral decubitus position for surgery. Mechanical ventilation was performed using a one-lung mechanical ventilation model. Perioperative analgesia was provided with a remifentanil infusion at a rate of 0.01–0.1 µg/kg/min. A dose of 400 mg ibuprofen and tramadol 100 mg was administered IV 20 minutes before the end of the surgery for multimodal postoperative pain management. At the end of the surgery, RIB was performed in the lateral decubitus position using a Vivid-q US system (GE Healthcare, USA) in these three patients. The same regional block technique was administered, and the same dosages of drugs were applied to the patients. After placing a linear high-frequency probe (12 MHz) medially in the sagittal plane on the medial border of the scapula at the T5-6 level, a 22 G, 80 mm needle (Braun Stimuplex Ultra, 360°) was inserted into the fascial plane between the rhomboid major and intercostal muscles in a caudal cranial direction. A dose of 20 ml 0.25% bupivacaine was injected into the fascial plane (Fig. 1).

As a new technique, the RIB defined by Elsharkawy et al. [5] in 2016 according to a cadaveric examination may be a good alternative for chest wall analgesia. This cadaveric examination of the RIB using methylene blue contrast dye showed the spread of dye from caudad to cephalad, including the T2-T8 tissue plane, as far as the lateral branches of the intercostal nerves T3-T8, the posterior primary rami near the midline, and the clavipectoral fascia within the axilla. The authors concluded that RIB may be effective for managing anterior and posterior hemithorax pain [5]. The analgesic efficacy of RIB after thoracotomy has been reported by Altıparmak et al. [3], who demonstrated that RIB provided good postoperative pain management in two patients for thoracotomy. In this paper, we also demonstrated that RIB provides effective analgesia for VATS in three patients.

In conclusion, RIB may be an alternative technique for pain management after VATS. There is a requirement for a larger comparative study to decide and advise regarding its practical applications in routine analgesic modality.

Conflicts of Interest

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

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Cold agglutinin disease (CAD) is an autoimmune disease caused by higher titers of cold-reacting autoantibodies that lead to red blood cell (RBC) agglutination and subsequent hemolysis at low temperatures [1]. In such patients, exposure to cold can lead to hemoglobinuria and critical complications such as renal failure and myocardial damage [1]. Therefore, the prevention of perioperative hypothermia is crucial in these patients undergoing surgery. Herein, we report the successful perioperative management of a patient with severe CAD by using multimodal warming measures, as described below.

A 63-year-old man diagnosed with CAD for 2 years based on repeated clinical symptoms with high titers of cold agglutinin (1:8192) measured at ambient temperature, was scheduled to undergo lumbar laminectomy for lumbar canal stenosis. Despite being on daily medication with prednisolone 10 mg, he often experienced hemoglobinuria and acrocyanosis of the distal extremities upon exposure to cold even in summer. On the day of the surgery, to prevent perioperative hypothermia, the infusion of amino acid warmed at 41°C with HOTLINE® Warmer (Smiths Medical Japan Ltd., Japan) was commenced 3 h before surgery. Skin-surface warming with an electric heating blanket was also commenced 30 min before surgery, and the operating room was pre-warmed to 26°C. In the operating room, after anesthesia induction, a temperature probe was inserted into the esophagus immediately before orotracheal intubation. Following intubation, the patient was placed in a prone position, and forced-air warming devices (EQUATOR®; Smiths Medical Japan Ltd., Japan) set at 37°C to 40°C were immediately applied to his upper and lower body. His anterior skin surfaces were also warmed using a circulating-water mattress, and his hands and feet were covered with gloves and socks, respectively. Immediately before skin incision, 100 mg hydrocortisone was administered intravenously for steroid cover. During surgery, intravenous infusion of amino acid warmed at 41°C was also continued. Surgical irrigation solutions were also pre-warmed to approximately 40°C. Fig. 1 shows the intraoperative trends of the core (esophagus) and peripheral (palm) temperatures. The patient was warmed continuously with an electric heating blanket and warmed amino acid infusions for approximately 24 h after surgery. The postoperative course was uneventful, without any evidence of hemolysis.

Cold agglutinin disease (CAD) is an autoimmune disease caused by higher titers of cold-reacting autoantibodies that lead to red blood cell (RBC) agglutination and subsequent hemolysis at low temperatures [1]. In such patients, exposure to cold can lead to hemoglobinuria and critical complications such as renal failure and myocardial damage [1]. Therefore, the prevention of perioperative hypothermia is crucial in these patients undergoing surgery. Herein, we report the successful perioperative management of a patient with severe CAD by using multimodal warming measures, as described below.

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these patients. Considering that the patient’s normal temperature was approximately 36.5°C in the present case, to ensure the safety margin, we aimed to maintain both the core and peripheral temperatures at approximately 37.0°C using multimodal warming measures such as preoperative warming [2], intraoperative forced-air warming [1], administration of pre-warmed intravenous fluids [3], and infusion of amino acids [3], which have been reported to effectively prevent perioperative hypothermia. For example, Young and Haldane [4] described the efficacy of intraoperative forced-air warming and administration of pre-warmed intravenous fluids in the management of a patient with CAD. In the present case, in addition to the conventional strategies used [4], we applied two more effective measures, including preoperative skin-surface warming [2] and perioperative warmed amino acid infusion [3], to ensure a safety margin because the patient’s CAD was clinically severe. As shown in Fig. 1, while pre-warmed amino acid infusions mainly contributed to the maintenance of the core temperature, skin-surface warming helped to maintain both the core and peripheral temperatures by avoiding heat transfer from the core to the peripheries because of increased peripheral temperatures. Intraoperative amino acid infusions enhance thermogenic effects and prevent hypothermia effectively during general anesthesia [5]. However, amino acid infusions started after the development of core hypothermia failed to accelerate rewarming [5]. Accordingly, for the prevention of hypothermia, amino acids should be administered before the development of core hypothermia. That is, the prophylactic administration of amino acids should be considered in severe cases where core hypothermia must be avoided. In the present case, the infusions of the amino acid were pre-warmed at 41°C. A previous report [3] described that the administration of amino acids heated to 40–42°C safely reduced the incidence of intraoperative hypothermia. Therefore, we considered that the administration of amino acids warmed to 41°C could safely and effectively prevent intraoperative hypothermia in the present case. We also used surgical irrigation solutions pre-warmed to approximately 40°C because these solutions warmed to 39°C were safely used in preventing intraoperative hypothermia in a previous report [1].

To our knowledge, this is the first report describing the efficacy of the combination of these four strategies for the prevention of perioperative hypothermia in patients with severe CAD. The most striking difference between the present case and previous reports [1–3] is that warmed amino acid infusion and other preventive measures were simultaneously applied in our severe case. We were able to successfully maintain the core temperature and avoid further heat transfer from the core to the peripheries perioperatively, using these multimodal warming measures. In conclusion, in the management of patients with severe CAD, multimodal warming measures from various viewpoints should be considered to maintain the core temperature and avoid initial thermal redistribution from the core to the peripheries by reducing the temperature gradient between the two regions.

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In their recent communication Yawata et al. [1] report a case of local anesthetic systemic toxicity (LAST) following ultrasound guided lumbar erector spinae plane block (ESPB) in a patient undergoing endoscopic surgery for lumbar spinal stenosis. I commend the authors for sharing their experience, although contrary to their assertion there has in fact been a previous report of this complication in the literature [2]. However, the previous report by Karaca and Pinar [2] had critical omissions that made it of limited value, most notably the body weight of the patient, and the concentration of local anesthetic (LA) drugs used.

Yawata et al. [1] report the use of a total volume of 30 ml of 0.5% (150 mg) levobupivacaine in a 58 kg man (body mass index 21.8 kg/m²). They describe the use of techniques designed to minimize the risk of inadvertent intravascular injection, observing linear spread of injectate in the plane deep to the erector spinae muscle, and the absence of blood on aspiration. In common with the previous report the principal manifestations of LAST following ESPB were neurological.

Interfascial (or fascial) plane blocks are regarded as ‘volume’ blocks. The underlying principle is that a volume of LA is injected into a fascial plane remote from the intended site(s) of action. The LA has to traverse the fascial plane to reach the intended target nerve(s). This is in direct contrast to nerve blocks or plexus blocks, where the neural target is visualized using ultrasound and LA is deliberately deposited in close proximity to neural structures, often permitting the use of lower volumes of LA. In contrast to ‘traditional’ nerve blocks fascial plane blocks are rarely used as a sole anesthetic technique.

The use of ESPB for surgery of the lumbar spine remains controversial at this time [3], although there is evidence that ESPB reliably blocks the dorsal ramus of the spinal nerves [4]. Thus, of all the reported uses of ESPB to date, its use in back surgery is one of the most promising areas for further investigation [5].

It could be argued that the risk of LAST could be reduced by using a lower concentration of LA, while still utilizing the required volume. There is a paucity of data comparing the duration of action of different concentrations of LA in fascial plane blocks. Similarly, the maximum safe dose of LA for fascial plane blocks has not yet been formally elucidated. Therefore, in the interest of patient safety it would seem wise when using large volumes of LA to use a lower concentration of LA (such as 0.25% rather than 0.5% levobupivacaine) for ESPB.

While there remain many unanswered questions about ESPB, there is certainly no evidence of reduced efficacy of ESPB with lower concentrations of levobupivacaine.
Conflicts of Interest

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

References

The use of trial sequential analysis (TSA) in the medical literature is increasing in recent times. However, not all readers may be familiar with this statistical technique. This correspondence aims to provide readers with the essentials to understand and interpret TSA.

Adequately conducted meta-analyses (MAs) are considered the best evidence in the scientific literature. Nonetheless, MAs are exposed to misleading significant results (type I errors; $\alpha$) or erroneously insignificant results (type II errors; $\beta$) caused by low quality or inadequately powered trials, publication bias, and repeated significance testing [1].

TSA is a cumulative MA method developed [1] to weigh $\alpha$ and $\beta$ errors while estimating when the effect is large enough to be unlikely to be affected by further studies. TSA is displayed as a Cartesian graph with cumulative z-score on the y-axis and number of patients on the x-axis, subdivided into four zones by four lines: monitoring boundaries for benefit, and harm, and two futility boundaries (Fig. 1). Two lines parallel to the x-axis are usually displayed, showing the conventional statistically significant line at $z$, corresponding to 1.96.

The cumulative z statistic line is constructed adding a study sequentially with chronological criteria. The end of the line corresponds to the lastly added study. It will lie in one of the following zones: “benefit”, “harm”, “inner wedge” or “not statistically significant”, representing a statistically significant result for the first two areas (“benefit” and “harm”) or a strong evidence that further studies will hardly be able to change the no-effect results (“inner wedge” area). Presence in the “not statistically significant” area means that further studies are needed.

Control of $\alpha$ and $\beta$ errors may be managed by decreasing the test statistic using a penalizing factor $\lambda$ (law of the iterated logarithm) or adjusting the significance threshold. The last described strategy is managed in TSAs using $\alpha$- and $\beta$-spending functions.

The $\alpha$ spending function determines both the benefit and harm boundaries, while the beta spending function is displayed on the graph as the futility boundaries. The spending functions used in TSA are based on the O’BrienFleming’s function. Although several examples of such functions have been described, O’BrienFleming’s function is the only function implemented in the TSA software.

The spending function is a monotonically increasing function that distributes the $\alpha$ error along the entire analysis for a pre-decided $\alpha$. The function is defined from 0 to 1, where 0 corresponds to “no patient enrolled” and 1 to the “reached information size” with the information fraction (IF) as the independent variable. The IF is given by the accumulated sample divided by the required sample.

The used $\alpha$-spending function is

$$\alpha(\text{IF}) = 2 - 2 \Phi (Z_{\alpha/2} / \sqrt{\text{IF}})$$
where $\Phi$ is the standard normal cumulative distribution function \([2]\). This function represents a generalization of the formula proposed by Lan-De Mets, allowing non-constant and flexible IF increments among trials.

Similarly, the $\beta$-spending function is monotonically increasing and defined from 0 to 1, where 1 corresponds to the threshold for the maximum $\beta$ error chosen for the non-superiority and non-inferiority tests.

Standard MA does not consider if the significance obtained is provided by an adequate cumulative information size (total number of patients among the trials). However, this is a question of paramount importance that is inadequately considered.

Choosing an adequate information size is the cornerstone in TSAs. Nonetheless, there is no standardized way or consensus to establish an adequate information size.

Similar to randomized controlled trials, information size calculation is based on the choice of a priori relative risk reduction (RRR) and of a maximum type I and II error.

RRR is the reduction of the event rate in the treatment group (Pt) compared to the control group (Pc), described as a percentage \((Pt/Pc)/Pt \times 100\%\).

The choice of RRR is critical and should be based on a realistic and clinically meaningful effect of the intervention. This should be based on previous literature, but when there is insufficient clinical experience (e.g., pilot studies), data from related areas may be used.

It seems reasonable to state that the information size of an MA should be at least as large as the sample size of an adequately powered trial investigating that specific outcome. However, researchers may be more conservative in choosing a higher power (i.e., 90–99%) and a lower $\alpha$ (i.e., 1–5%), (given that MA is at the top of the science hierarchy).

It is preferable to estimate the RRR from the analysis of the low-bias risk trials, by excluding the high-risk of bias studies that could overestimate the intervention effect. \([1]\).

Another more conservative post-hoc approach is to consider the least likely intervention effect (lower confidence limit of the intervention effect) as RRR \([3]\).

MA should compare the effect of identical studies without any
difference in the protocol, population, or outcome assessment. However, this is utopian, and a certain degree of clinical heterogeneity leading to statistical heterogeneity has to be taken into account and accepted. A correction factor for IF derived by heterogeneity magnitude is deemed necessary.

While MA usually uses inconsistency ($I^2$) as the measure between trial variance, TSA uses diversity ($D^2$). $D^2$ is defined as the proportion of the total variance in a random effect model contributed by the between-trial variation despite its estimator $[4]$. $D^2$ is always higher than $I^2$ unless all the weights in the fixed-effect model are equal; particularly, $D^2$ is 0 only when $I^2$ is 0 $[4]$.

While the use of $D^2$ has the advantage of correcting the IF to maintain the anticipated risk of both $\alpha$ and $\beta$ errors, it does not consider any adjustment in IF for any bias.

Recently, a Cochrane expert panel recommended against the use of TSA and analogous sequential methods in MA $[5]$. Cochrane highlighted that an interpretation based on estimated intervention effect and its accompanying uncertainty is preferable and recommended instead of the binary interpretation proposed by TSA.

The use of sequential analysis in MA, a retrospective analysis without any control on study design by meta-analysts, makes it impossible to establish the stopping rules that are typical of a preplanned set of interim analyses.

TSA is usually performed on the primary outcome; however, cumulative evidence from secondary outcomes would be penalized from a premature stopping rule. A striking example is depicted using network meta-analysis, where cumulative evidence will continue to affect some networks when the main effects are already well estimated.

Despite its limitations, and in particular its dichotomous interpretation, TSA is a useful tool in ‘researchers’ armamentarium.

Conflicts of Interest

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Propofol injection is associated with pain in approximately 60% of untreated cases [1]. The pain is usually sharp or burning and can be severe. Several pharmacological treatments have been shown to reduce pain associated with propofol injections [2]. Of these, premedication with lignocaine is the most frequently used and the most reported in the literature. Here, we report a case of the complete masking of pain associated with propofol extravasation in an awake patient following lignocaine premedication, which markedly delayed its diagnosis. Informed consent was obtained from the patient for this publication.

A 50-year-old lady (weight 116 kg, body mass index 43 kg/m²) with known difficult venous access presented for surveillance gastroscopy and colonoscopy under sedation. After multiple failed attempts, a cannula was inserted into the antecubital fossa vein, through which fentanyl (50 μg) and midazolam (1 mg) were administered. Lignocaine (100 mg, 10 ml) was slowly administered through the cannula before a target-controlled infusion of propofol (Provive® MCT-LCT 1%, Baxter Healthcare, Australia). Despite the injection of more than 300 mg of propofol within 2 min, the patient had no evidence of sedation. A presumptive diagnosis of propofol extravasation was made, and the infusion was discontinued. The patient did not report any discomfort, and the antecubital fossa cannula site remained soft and non-tender on examination. A second cannula was inserted in the contralateral arm, and propofol target-controlled infusion was recommended with a rapid clinical response. The remainder of the procedure and sedation were uneventful. The patient was monitored for two hours in the post-anesthesia recovery unit, where mild erythema began to develop around the original antecubital fossa cannula site. The patient also reported experiencing pain during elbow flexion. Her arm remained soft, distal pulses were present, and she was deemed safe for discharge. On a telephone follow-up the next day, the patient reported that the erythema and pain in her arm had completely resolved.

There have been numerous reports of propofol extravasation in the literature, with sequelae ranging from local erythema to tissue necrosis and compartment syndrome [3–5]. In all published cases, propofol extravasation involved patients who were unable to voice pain (anesthetized, sedated, or neonate). Missed extravasation of large volumes of propofol in an awake patient is rare because extravasation pain is usually severe, which leads to early detection and cessation of administration.

In the present case, the detection of propofol extravasation was significantly delayed due to the absence of patient discomfort. Extravasation was only suspected after a relatively large volume (30 ml) of propofol was administered without any observable pharmacodynamic response. The absence of extravasation pain, in this case, was likely due to the anesthetic effect of lignocaine and the location of the cannula. The lignocaine premedication may have also been administered into the subcutaneous tissue in the antecu-
bital fossa, which readily diffused to nearby nerve fibers, resulting in anesthesia of the region. This effectively masked the discomfort resulting from the direct chemical irritation by propofol on the local nociceptors. Furthermore, the antecubital fossa provided a large potential space that enabled a significant volume (over 40 ml in total) of extravasate to accumulate, masking the discomfort that resulted from increased compartmental pressures. A higher than normal dose of lignocaine was used during premedication in this case with the additional aims of facilitating insertion of the gastroscope and reducing cough, which further increased the risk of masking the pain associated with propofol extravasation.

Given the increasing use of propofol-based total intravenous anesthesia, clinicians need to detect extravasation promptly to minimize morbidity. Clinicians need to pay attention to all signs of extravasation, including patient discomfort, elevated injection pressure, changes at the cannula site, and the absence of clinical response, as demonstrated in this case. Antecubital fossa veins should be avoided, as signs of extravasation are harder to detect in them.

To our knowledge, this is the first reported case of lignocaine premedication masking the pain associated with propofol extravasation in an awake patient. Anesthesiologists should be aware of the possibility of painless propofol extravasation, especially after premedication with lignocaine.

**Conflicts of Interest**

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

**Author Contributions**

George Zhong (Conceptualization; Writing – original draft, review & editing; Supervision)
Shun Hin Kenjo Ho (Conceptualization; Literature Review)
Alpha Mang Sze Tung (Conceptualization; Writing – review & editing)

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**References**

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Instructions to authors

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Clinical research should be done in accordance of the Ethical Principles for Medical Research Involving Human Subjects, outlined in the Helsinki Declaration of 1975 (revised 2013) (available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). Authors should indicate whether the procedures were conducted in accordance with the Helsinki Declaration-2013 in the Text. Clinical studies that do not meet
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Authorship credit should be based on: 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; AND 2) drafting the article or revising it critically for important intellectual content; AND 3) final approval of the version to be published; AND 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet these 4 conditions. If the number of authors is equal to or greater than 2, there should be a list of each author’s role in the submitted paper. Authors are obliged to participate in peer review process. All others who contributed to the work who are not authors should be named in the Acknowledgements section. KJA has a strict policy on changes to authorship after acceptance of the article and will only consider changes in the most extraordinary situations once the article is accepted.

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

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Articles in Press (articles that have been accepted for publication but which have not been formally published and will not yet have the complete volume/issue/page information) that include errors, or are discovered to be accidental duplicates of
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See also the National Library of Medicine’s policy on retractions and the recommendations of the International Committee of Medical Journal Editors (ICMJE) concerning corrections and retractions, or https://publicationethics.org/resources/guidelines.

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Data sharing statement  

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

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

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1) Leave 1 space for each side, using arithmetic marks as +, −, ×, etc. Leave no space for hyphen between words.
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1) If a citation has 2 authors, write as “Hirota and Lambert.” If there are more than 3 authors, apply ‘et al.’ at the end of the first author’s surname. Ex) Kim et al. [1].
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4) Identify reference by several or coupled Arabic numbers, enclosed in square brackets on the line as [1,3,5].

5. Arrangement of manuscript  
ALL articles should be arranged in the following order. 
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Title Page file, uploaded separately
Manuscript, as a single file in word processing format (e.g., .doc), consisting of Title and running title, Abstract (if required for the article type; see relevant section), Body Text, References, Tables, Figure Legends, if any (in numerical order, on the same page); be sure to number all pages of the manuscript file
Figures (each Figure should be a separate file in figure file format)
Other submission elements (Supplemental Digital Content, etc.)

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

6. Statistical Analysis

1) Describe the statistical tests employed in the study with enough detail so that readers can reproduce the same results if the original data are available. The name and version of the statistical package should be provided.

2) Authors should describe the objective of the study and hypothesis appropriately. The primary/secondary endpoints are predetermined sensibly according to the objective of the study.\(^1\)

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5) When analyzing a categorical variable, if the number of events and sample is small, exact test or asymptotic method with appropriate adjustments should be used. The standard chi-squared test or difference-in-proportions test may be performed only when the sample size and number of events are sufficiently large.

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9) It is recommended using mean ± SD or median (Q1, Q3) format to present representative values of continuous variables. Results must be written in significant figures. The measured and derived numbers should be rounded off to reflect the original degree of precision. Calculated or estimated numbers (such as mean and SD) should be expressed in no more than one significant digit beyond the measured accuracy. Therefore, the mean ± SD of body weight in patients measured on a scale that is accurate to 0.1 kg should be expressed as 65.45 ± 2.52 kg.

10) Except when otherwise stated herein, authors should conform to the most recent edition of the American Medical Association Manual of Style.\(^7\)

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

\(^{7}\)http://www.amamanualofstyle.com/
7. Organization of manuscript

1) Clinical or Experimental research

① Title page
   Title should be concise and precise.
   For the title, only the first letter of the first word should be capitalized.

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

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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 control of bias in the study. Sufficient details need to be addressed in the methodology section of an experimental study so that it can be further replicated by others.
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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.

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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.

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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.

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- References should be obviously related to documents and should not be exceed 50. For exceeding the number of references, it should be negotiated with the Editorial Board. References should be numbered consecutively in the order in which they are first mentioned in the text. Provide footnotes in the body text section. All of the references should be stated in English, including author, title, name of journal, etc.
- If necessary, the editorial board may request original documents of the references.
- 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.
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- Description format
A. Regular journal
Author name. Title of journal Name of journal published...
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).

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⑦ Pathological samples should be pictured with a measuring stick.

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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.

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

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2) Systematic review and meta-analysis

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

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

· All systematic reviews and meta-analyses should be registered at an appropriate online public registry (eg, PROSPERO; http://www.crd.york.ac.uk/PROSPERO/), and registration information should be included with the submission.

· Authors of reports of meta-analyses of clinical trials should submit the PRISMA flow diagram. The PRISMA checklist should be submitted as a separate file along with the manuscript. For information regarding PRISMA guidelines, please visit http://www.prisma-statement.org or EQUATOR Network (https://www.equator-network.org/home/). Systematic reviews and meta-analyses of observational studies in epidemiology should be reported according to MOOSE guidelines. For more information regarding MOOSE guidelines, please visit http://www.equator-network.org/reporting-guidelines/meta-analysis-of-observational-studies-in-epidemiology-a-proposal-for-reporting-meta-analysis-of-observational-studies-in-epidemiology-moose-group/.

· No limitation the number of the references.

3) Case Reports

A case report is almost never a suitable means to describe the efficacy of a treatment or a drug; instead, an adequately powered and well-controlled clinical trial should be performed to demonstrate such efficacy. The only context in which a case report can be used to describe efficacy is in a clinical scenario, or
population, that is so unusual that a clinical trial is not feasible.

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

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

(2) Manuscript
   ① Title and Running title.
   ② Abstract: All case reports should contain a structured abstract that is written only in English. Provide an abstract of no more than 150 words. It should contain 3 subsections: Background, Case, and Conclusions. A list of keywords, with a minimum of 6 and maximum of 10 items, should be included at the end of the abstract. The selection of keywords should be from MeSH (http://www.ncbi.nlm.nih.gov/mesh) and should be written in small alphabetic letters with the first letter in capital letter. Separate each word by a semicolon (;), and mark a period (.) at the end of the last word.
   ③ Introduction: Should not be separately divided. Briefly describe the case and background without a title.
   ④ Case report: Describe only the clinical statement that is directly related to diagnosis and anesthetic management.
   ⑤ Discussion: Briefly discuss the case, and state conclusions at the end of the case. Do not structure the conclusion section separately.
   ⑥ References: Do not exceed 15 references. For exceeding the number of references, it should be negotiated with the Editorial Board.
   ⑦ Tables and figures: Proportional to clinical and experimental studies.

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

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

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

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

8. Recently revised instructions for authors are applied from February 2021 submissions.