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REVIEW ARTICLES

213 Open datasets in perioperative medicine: a narrative review
220 Current clinical application of dantrolene sodium
233 Predictors of fluid responsiveness in the operating room: a narrative review
244 Utilizing ChatGPT in clinical research related to anesthesiology: a comprehensive review of opportunities and limitations

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Anesthesia and Pain Medicine (APM) is the official journal of the following ten subsocieties of the Korean Society of Anesthesiologists: Korean Society of Neuroscience in Anesthesiology and Critical Care, the Korean Society for Anesthetic Pharmacology, the Korean Society of Obstetric Anesthesiologists, the Korean Society of Pediatric Anesthesiologists, the Korean Neuromuscular Research Society, the Korean Society of Cardiothoracic and Vascular Anesthesiologists, the Korean Society of Transplantation Anesthesiologists, the Korean Spinal Pain Society, the Korean Society of Regional Anesthesia, and the Korean Society for Airway Management. Its abbreviated title is ‘Anesth Pain Med’. It is published four times a year, in English, on the last days of January, April, July, and October. APM aims to improve the safety and care of patients receiving anesthesia and the quality of anesthesiologists’ clinical practice by publishing articles on anesthesiology, including perioperative management, critical care, and pain medicine.

The scope of APM includes the following:

- Anesthesia-related issues from the affiliated field of neuroanesthesiology
- Experimental and laboratory work or studies of clinical relevance in anesthetic pharmacology
- Anesthesia care and perioperative management for obstetric patient, pain relief in labor, and perinatal physiology and pharmacology
- Anesthetic care, perioperative management, and alleviation of pain in children
- Physiology of neuromuscular transmission and blockage, the pharmacology of neuromuscular blocking agents and their reversal agents, the principles and applications of neuromuscular monitoring, and drug interactions between neuromuscular blocking agents and other substances
- Anesthesia for cardiothoracic and vascular surgery and the management of patients undergoing surgery for cardiac, pulmonary, and vascular diseases
- Perioperative anesthesia care of transplantation surgery, physiology or pharmacology related to transplantation anesthesiology
- Pathophysiology, pharmacology, and all aspects of spine-related pain
- Clinical techniques of regional blocks, anatomy, patient safety issues, and basic sciences such as pharmacology of local anesthetics or sedative drugs
- All fields of airway management, including difficult airways and complications.
- Educational fundamentals and practical implications for clinical and experimental research related to anesthesia, perioperative care and pain management.

The journal’s regional focus is mainly Korea, but it welcomes submissions from researchers all over the world.

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### Table of Contents

**Vol.18 No.3 July 2023**

#### Editorial

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>211</td>
<td>Our Anesthesia and Pain Medicine is currently expanding into a global-scale journal</td>
<td>Hyungseok Seo, Hyun Kang</td>
</tr>
</tbody>
</table>

#### Reviews

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>213</td>
<td>Open datasets in perioperative medicine: a narrative review</td>
<td>Leerang Lim, Hyung-Chul Lee</td>
</tr>
<tr>
<td>220</td>
<td>Current clinical application of dantrolene sodium</td>
<td>Hong Seuk Yang, Jae Moon Choi, Junyong In, Tae-yun Sung, Yong Beom Kim, Shofina Sultana</td>
</tr>
<tr>
<td>233</td>
<td>Predictors of fluid responsiveness in the operating room: a narrative review</td>
<td>Ah Ran Oh, Jong-Hwan Lee</td>
</tr>
<tr>
<td>244</td>
<td>Utilizing ChatGPT in clinical research related to anesthesiology: a comprehensive review of opportunities and limitations</td>
<td>Sang-Wook Lee, Woo-Jong Choi</td>
</tr>
</tbody>
</table>

#### Anesthetic Pharmacology

**Clinical Research**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>252</td>
<td>Comparison of remimazolam–remifentanil and propofol–remifentanil during laparoscopic cholecystectomy</td>
<td>Tae Young Lee, Min A Kim, Deuk Won Eom, Ji Wook Jung, Chan Jong Chung, Sang Yoong Park</td>
</tr>
<tr>
<td>260</td>
<td>Appropriateness of the anxiety subscale of the Hospital Anxiety and Depression Scale for Koreans to measure preoperative anxiety and the effect of preoperative anxiety on postoperative quality of recovery</td>
<td>Minjong Ki, Dong-Chan Kim, Seon Woo You, Jeongmin Oh, Jieun Jang, Hyo Hyun Yoo</td>
</tr>
</tbody>
</table>

#### Pediatric Anesthesia

**Case Report**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>270</td>
<td>Perioperative considerations of pyruvate dehydrogenase complex deficiency: a case report of two consecutive anesthesia</td>
<td>Won Yong Lim, Hyeon-Jeong Lee, Eun Ji Park, Soeun Jeon, Wangseok Do, Hyae Jin Kim, Dowon Lee, Jeong-Min Hong</td>
</tr>
</tbody>
</table>

#### Neuromuscular Research

**Experimental Research**

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>275</td>
<td>Chronic exposure to dexamethasone may not affect sugammadex reversal of rocuronium–induced neuromuscular blockade: an in vivo study on rats</td>
<td>Ha Yeon Park, Hey Ran Choi, Yong Beom Kim, Seok Kyeong Oh, Taehoon Kim, Hong Seuk Yang, Junyong In</td>
</tr>
</tbody>
</table>
Cardiothoracic and Vascular Anesthesia

Clinical Research
284  A new hematologic predictor of major adverse events after cardiac surgery: red cell distribution width to lymphocyte ratio
Seda Kurtbeyoğlu, Aslı Demir, Eda Balci, Hülya Yiğit Özay, Bilal Katipoğlu, Hayrettin Levent Mavioğlu

Case Report
290  Anesthetic management of an elderly COVID–19 patient with pulmonary thromboembolism for hip surgery
Min Hee Heo, Hwan Yong Choi, Ji Yeon Kim, Kyung Woo Kim, Sang Il Lee, Kyung-Tae Kim, Jang Su Park, Won Joo Choe, Jun Hyun Kim

Transplantation Anesthesia

Case Report
296  Sudden mode change of permanent pacemaker during living donor liver transplantation
Sooeyeon Lee, Gaabsoo Kim

Spinal Pain

Case Report
302  Burst stimulation for refractory angina pectoris
Daehun Yun, Kaehong Lee, Ji Soo Kwak, Leegyeong Je, Taesan Kim, Yoon Sun Park, Jae Chul Koh

Regional Anesthesia

Clinical Research
307  Effect of interfascial pressure on block success during anterior quadratus lumborum block application: a prospective observational study
Korgün Ökmen, Durdu K. Yıldız

315  Removing knotted or stuck epidural catheters: a systematic review of case reports
Bikash Khadka, Apurb Sharma, Ashim Regmi, Anup Ghimire, Prajwal Raj Bhattarai

Letter to the Editor
325  Inter–transverse process blocks: caution about difference in methods
Raghuraman M Sethuraman

Image and Video
327  Massive pericardial effusion in undiagnosed turner syndrome
Divya Sethi Sethi, Garima Garg
Established scientific data of BRIDION with a long history of prescription^{1,2,3,4}

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Anesthesia and Pain Medicine (Anesth Pain Med; APM/ISSN:1975-5171) is the official journal of the Korean Society of Anesthesiologists (KSA) and represents the official journals of the following societies: the Korean Society of Neuroscience in Anesthesiology and Critical Care (KSNACC), the Korean Society for Anesthetic Pharmacology (KSAP), the Korean Society of Obstetric Anesthesiologists (KSOA), the Korean Society of Pediatric Anesthesiologists (KSPA), the Korean Neuromuscular Research Society (KNRS), the Korean Society of Cardiothoracic and Vascular Anesthesiologists (KSCVA), the Korean Society of Transplantation Anesthesiologists (KSTA), the Korean Spinal Pain Society (KSPS), the Korean Society of Regional Anesthesia (KSRA), and the Korean Society for Airway Management (KSAM). As an official journal of several societies in departments of anesthesia, we have proudly improved our roles in increasing the knowledge of advancements in anesthesia and inspiring clinical or research confidence. Recently, the APM was indexed using the Scopus database. At this point, we would like to look back on the steps we took and enforce them for further advancement.

Since the inception of our journal in 2006, our readership was expected to be limited to the domestic audience, and nearly all articles were published in Korean. However, considering the vast and rapid increase in our advancement of research and practice resources in the field of anesthesia, we cannot help but consider transitioning into a globally indexed journal. Finally, all articles have been published in English since 2019, and we decided to be indexed in PubMed Central (PMC), an archive of biomedical and life sciences journal literature at the USA National Institutes of Health’s Library of Medicine.

On the journey of being indexed in the PMC, Professor Young-Cheol Woo, the previous editor-in-chief, conducted the entire process with the critical assistance of Professor Sun Huh. Every editorial board member thoroughly participated in revising our webpage and e-submission system for 3 months; specifically, the ‘best practice’ section of our website was the most critical part for all board members concerned. Finally, we received the notification of indexing by the PMC on October 20, 2020 [1]. Owing to our efforts, a number of manuscripts have been submitted worldwide, and there has been a remarkable improvement in both quantity and quality.

In late 2022, Professor Hyun Kang was appointed the new Editor-in-Chief of APM and insisted that we should be more globalized and indexed by well-known databases. We...
organized a special team for a swift decision-making process and pinpointed revisions. Currently, we have achieved two milestones in our journey toward globalization. First, we became indexed in the Directory of Open Access Journals (DOAJ) [2], a unique trusted index of open journals worldwide. DOAJ is currently regarded as a gateway for determining whether the corresponding journal is problematic [3]. Second, the APM is indexed by Scopus as of June 20th. Scopus, which covers over 87 million documents and has 1.8 billion cited references, is one of the largest databases. This extensive coverage is helpful for our journal and articles to reach more researchers and be cited.

Through this editorial, the APM expresses great gratitude to every person, including the previous and current editorial board members and reviewers, who contributed to our journal’s improvement and sophistication. We extend special thanks to Seong Ho Chang, Keon Hee Ryu, and Young-Cheol Woo, who served as editorial board members for their unwavering dedication.

Furthermore, the APM regards every author submitting their valuable manuscript as its absolute power and always holds a deep appreciation for it. The journey of the APM to become a globally recognized journal continues. From now on, we are preparing to be covered by the Emerging Science Citation Index (ESCI) or the Science Citation Index Expanded (SCIE). Moreover, MEDLINE, created by the USA National Library of Medicine, poses another challenge. Although there are several problems in the current publication environment, such as distinct aims and scopes, ethics, data sharing, and preprints, all of our editorial board members have strict responsibilities and a passion for significantly improving our journal. We will make every effort to ensure that the APM is highly regarded and cherished by the authors, readers, esteemed members of the KSA, and the societies that constitute the APM.

FUNDING

None.

CONFLICTS OF INTEREST

Hyungseok Seo has been an editor of the Anesthesia and Pain Medicine since 2019, and Hyun Kang has been an editor-in-chief of the Anesthesia and Pain Medicine since 2023. However, They were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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REFERENCES

INTRODUCTION

There has been a significant increase in the development of machine learning and artificial intelligence (AI) models in medicine. Despite the proliferation of AI-based predictive models, there is a significant lack of external validation [1]. Before these models can be implemented in clinical practice, it is crucial to perform reproducible validation. Open datasets, which are publicly available datasets for research, play a critical role by providing high-quality data, facilitating collaboration, and enabling the objective evaluation of performance metrics for the developed models.

Previous efforts in outcome research have resulted in various registries such as the National Surgical Quality Program, American Society of Anesthesiologists Closed Claims Project, Multicenter Perioperative Outcomes Group, National Anesthesia Clinical Outcomes Registry in the United States (US), Critical Care Minimum Data Set, and National Perioperative Data Standard Program by the National Health Service of the United Kingdom [2]. However, most registries have limited access to data within the participating institutions or societies involved in data collection. On the other hand, open datasets can be accessed by any credentialed researcher who agrees to a data use agreement.

Due to the nature of medical data, the risk of re-identifica-
tion may remain in open datasets; thus, data use agreements typically include a prohibition on unauthorized use for purposes other than research and restrictions on re-identification and redistribution. According to a US government website [3], over 10 million medical records are breached annually. However, reports on re-identification of open datasets are extremely rare. Therefore, when considering the risks and benefits of releasing open datasets, potential problems such as the development of biased models and the proliferation of unvalidated models can outweigh the risk of re-identification.

There is a great example of how open datasets can be used to change medical practices. In 2020, researchers from the University of Michigan used their database, along with the eICU Collaborative Research Database (eICU-CRD), to analyze data from 10,789 patients. They reported that oxygen saturation levels measured using pulse oximetry were higher than the actual ABGA results in Black patients than in White patients, resulting in a higher incidence of occult hypoxemia [4]. Subsequently, another group conducted a causal analysis using the Medical Information Mart for Intensive Care (MIMIC)-IV dataset and found that Black patients were less likely to receive oxygen supplementation and mechanical ventilation, which was attributed to the overestimation of oxygen saturation levels by pulse oximetry [5]. Although this issue has been raised for decades [6], recent discussions on using large open datasets during the Coronavirus disease (COVID-19) pandemic have attracted attention. Consequently, the US Food and Drug Administration reviewed the regulation of pulse oximeters.

In this review, we presented a detailed comparison of each open dataset to enrich our understanding of these datasets for data science and AI research in perioperative medicine.

**SURGICAL DATASETS**

Although relatively few open datasets for surgical patients are available, the VitalDB has been widely used in numerous studies. Additionally, there is a recently released dataset or an upcoming dataset that has recently been scheduled to be released.

**VitalDB**

VitalDB is a single-center perioperative open dataset that includes 6,388 noncardiac surgeries performed under anesthesia at the Seoul National University Hospital in South Korea between August 2016 and June 2017 [7]. The dataset primarily consists of physiological and high-resolution vital sign data along with clinical information and laboratory results (Fig. 1).

One of the key features of VitalDB is its high temporal resolution, which distinguishes it from other datasets. The authors used a free research software called Vital Recorder [8] to achieve a significantly higher time resolution of the dataset. The waveform data had a high resolution (62.5-500 Hz), while the numerical data were recorded at 1-7 s intervals. The physiological signal data in VitalDB include data collected in real time from patient monitors and anesthesia machines, as well as data extracted from various medical devices, including electroencephalogram monitors, regional cerebral oxygen saturation monitors, specialized hemodynamic monitors, and drug infusion devices. VitalDB provides 12 types of waveform data, including photoplethysmography, invasive arterial pressure waveforms, and processed electroencephalogram waveforms, as well as 184 types of numerical data from heart rate, blood pressure, and pulse oximetry. Additionally, the dataset includes demographic information, such as age, sex, height, and weight, as well as clinical information, such as surgical procedures, preoperative comorbidities, and 34 types of blood tests performed from 3 months before surgery to 3 months after surgery. These clinical and laboratory data are provided in a comma-separated value (CSV) format.

The dataset can be accessed and downloaded from a website (https://vitaldb.net) after signing up and signing a data usage agreement without any user credentials. To facilitate easy utilization of the waveform and numerical data in VitalDB, researchers can utilize the open-source VitalDB Python library and PyVital, another open-source biosignal analysis library, to calculate secondary variables such as pulse pressure variation or heart rate variability.

**INSPIRE dataset**

The Informative Surgical Patient dataset for Innovative Research Environment (INSPIRE) dataset is a single-center perioperative open dataset that includes approximately 260,000 patients who underwent anesthesia for surgery at the Seoul National University Hospital in Korea over 10 years, from January 2011 to December 2020. Data were extracted from the clinical data warehouse of the hospital in six tables linked by a patient identifier (Fig. 1). Each patient has a unique subject identifier and more than one hospital
admission identifier, and each operation has an operation identifier. The dataset includes various patient characteristics such as age, sex, American Society of Anesthesiologists classification, diagnosis, and surgical information such as surgical procedure, surgical department, and anesthesia duration. It also encompasses vital signs measured during surgery by patient monitoring and using an anesthetic machine, and is recorded from admission to discharge in regular wards or intensive care units (ICU). Additionally, the dataset provides laboratory results from six months before the first admission to six months after the last discharge and medication records during the hospitalization period. Complication information includes ICU admissions, total hospital and ICU lengths of stay, and in-hospital deaths.

The vital signs in the dataset have a maximum temporal resolution of 5 min. The laboratory results and medication

| **Fig. 1. Schematic representation of data extraction and creation of surgical datasets:** (A) VitalDB, (B) INSPIRE dataset, and (C) MOVER dataset. INSPIRE: the informative surgical patient dataset for innovative research environment, CPB: cardiopulmonary bypass, ECMO: extracorporeal membrane oxygenation, IABP: intra-aortic balloon pump, SIS: surgical information systems, EPIC: Epic Systems, MOVER: Medical Informatics Operating Room Vitals and Events Repository. |
records include all predefined parameters conducted during that time. All time-related variables were transformed into relative time (min), with the first admission of each subject set to 0 to protect personal information. Diagnoses and surgical procedures are partially provided in the form of the International Classification of Diseases 10th revision (ICD-10) codes. Certain diagnoses that required special protection, such as mental and behavioral disorders and sexually transmitted infections, are also excluded.

Because the INSPIRE dataset has an overlapping patient population with VitalDB [7], it provides a linker that can be used for matching with VitalDB. Using this information, researchers can utilize pre- and postoperative vital signs, medication history, and the use of special devices in the ICU (such as continuous renal replacement therapy and extracorporeal membrane oxygenation) that are not included in the existing VitalDB. Moreover, the dataset includes rare occurrences such as patient mortality and the use of special devices, making it suitable for the external validation of various prediction models for surgical patients. However, the dataset consists of single institutional data from a single ethnicity. Therefore, caution should be exercised when validating predictive models developed for different populations.

The INSPIRE dataset will be released via the website https://inspire.or.kr, or PhysioNet [9] by 2023. It will include approximately 130,000 surgical cases randomly selected from 260,000 patients. User credentialing will be performed through PhysioNet and made available for research purposes only to researchers who sign the data use agreements.

MOVER Dataset

The Medical Informatics Operating Room Vitals and Events Repository Dataset is a single-center perioperative open dataset that includes surgeries conducted on approximately 59,000 patients, accounting for approximately 83,000 surgical cases at the University of California, Irvine Medical Center from 2015 to 2022 [10]. The dataset is divided into two parts: the Surgical Information Systems (SIS, Surgical Information Systems, USA) and the EPIC (Epic Systems, USA) datasets (Fig. 1). The SIS dataset consists of nine tables, whereas the EPIC dataset consists of ten tables. The collected data is primarily composed of waveform and alphanumeric data. Waveform data include electrocardiograms (ECG), photoplethysmography, and invasive arterial pressure measurements. The alphanumeric data includes variables such as age, sex, underlying conditions, surgical clinical information, vital signs, medication history during surgery, input/output information, intubation, various administrations, and drainage tube placement.

The SIS and EPIC datasets differ slightly in terms of included data. While demographics, medications, and vital signs are included in both datasets, the SIS dataset includes anesthesia machine data, such as ventilator settings, whereas the EPIC dataset includes information on drainage tubes, arterial and venous lines, intubation, complications, and billing codes. Furthermore, the SIS dataset has only a surgical identifier without a patient identifier, whereas the EPIC dataset includes both patient and hospital visit identifiers, allowing the tracking of patients who underwent multiple surgeries. The maximum resolution of the numerical data is 1 min.

The MOVER dataset is the largest perioperative open dataset currently available. As mentioned previously, it encompasses a wide range of data, including vital signs, laboratory results, medications, and information on drainage tubes. This dataset provides extensive research opportunities in various domains. Specifically, it includes a comprehensive categorization of postoperative complications into airway, respiratory, and cardiovascular complications, including various complications such as laryngospasm and cardiac arrest. This makes it suitable for the development of predictive models of postoperative complications. However, some data are presented in a free-text format, requiring individual researchers to perform data preprocessing as part of their analysis.

The MOVER dataset can be accessed through its website (https://mover.ics.edu). By completing the data usage agreement on the website, individuals receive an ID, password, and address to download the data via a registered e-mail.

INTENSIVE CARE DATASETS

In a recent systematic review [11], four publicly available datasets were identified for adult ICU patients: MIMIC, eICU-CRD, Amsterdam University Medical Centers Database (AmsterdamUMCdb), and the High time Resolution ICU Dataset (HiRID). Soon, we expect the release of the Intensive Care Network with Million Patients’ information for the AI-CDSS Technology (IMPACT) dataset, a multicenter dataset from Korea that is anticipated to facilitate a wide range of research studies.
MIMIC

The Laboratory for Computational Physiology (LCP) at the Massachusetts Institute of Technology (MIT) has actively released numerous open datasets since the 1980s, starting with the MIT-BIH arrhythmia dataset [12]. In 1996, researchers expanded their dataset by collecting multichannel data beyond ECG in the ICU. They named it Multi-Parameter Intelligent Monitoring for Intensive Care (MIMIC) and later changed it to Medical Information Mart for Intensive Care. This was the first publicly available multi-parameter dataset for critically ill patients, containing 20 h of data from 90 patients, including electrocardiogram, arterial blood pressure, pulmonary artery pressure, and photoplethysmography.

MIMIC-II, released between 2001 and 2008, provided ICU data matched with clinical records and social security death data. In 2013, the MIMIC-III was introduced, featuring a large-scale dataset of over 40,000 patients spanning more than 10 years [13]. The MIMIC-III also included a waveform dataset called the MIMIC-III Waveform Database, which contained a matched subset of 22,317 waveform records and 22,247 numerical records of 10,282 distinct ICU patients.

The MIMIC-IV, released in March 2021, consists of 299,712 patients including those in the emergency department [14]. Additionally, it provides interpretive reports of chest radiography (MIMIC-CXR) [15], 12-Lead ECG (MIMIC-ECG) [14], and echocardiography (MIMIC-Echo) data. The MIMIC dataset has become the most widely cited open dataset for critical care, turning the Beth Israel Deaconess Hospital into one of the most intensively studied critical care cohorts worldwide.

The MIMIC dataset is available through PhysioNet after user credentialing and signing of the data-use agreement. A training program called the Collaborative Institutional Training Initiative (CITI) is required for user credentialing.

IMPACT dataset

In 2021, the Korean government initiated the Korean Medical Information Market for Intensive Care (K-MIMIC) Project to establish a multi-institutional open dataset for intensive care. The IMPACT consortium, responsible for the K-MIMIC project, plans to collect data sourced from 19 hospitals nationwide from over 500,000 individuals by 2023 and expand it to over 1 million individuals by 2025. This dataset will be made available to researchers, both domestically and internationally. It also aims to ensure compatibility with the structure and format of the MIMIC dataset from the US, allowing for sharing of the source code. Given the limited availability of ICU datasets in Asian countries, the release of such datasets has the potential to address data imbalance issues and serve as a valuable resource for research and development in critical care medicine.

eICU-CRD

The eICU-CRD dataset, released in 2018, is a multi-institutional dataset that includes data from 335 ICUs across 208 hospitals in the US as part of the Philips eICU program [16]. The main advantage of this dataset is that it is a multi-institutional dataset covering the entire US, allowing for an assessment of model generalizability. This dataset includes data from 200,859 critically ill patients hospitalized between 2014 and 2015. It comprised admission and discharge records, medication administration records, laboratory results, diagnoses, nursing notes, and treatment records. The laboratory results encompass approximately 160 standard laboratory tests, whereas the vital sign data includes 16 variables such as blood pressure, heart rate, oxygen saturation, and body temperature recorded at 5-min intervals. However, there may be variations in the recording frequency across different institutions. Unlike the MIMIC dataset, the eICU-CRD dataset did not include patients who are also included in the MIMIC dataset, allowing cross-validation between the two datasets.

Similar to the MIMIC dataset, the eICU-CRD dataset is also available through PhysioNet after user credentialing and signing a data use agreement. For user credentialing, the CITI must be completed.

AmsterdamUMCdb

The AmsterdamUMCdb is a single-center open dataset for critical care based on data collected from 44 surgical and high-dependency intensive care beds at the Amsterdam University Medical Center in the Netherlands from 2003 to 2017 [17]. After its initial release in 2019, the dataset was further updated, and the final version, 1.0.2, which included 23,106 cases of intensive care admissions, was released in March 2020. The AmsterdamUMCdb consists of seven alphanumeric data tables provided in CSV format. It includes demographic information as well as data related to medication history, various test results, vital signs, procedures, and special interventions during the ICU stay.
The AmsterdamUMCdb is the first open dataset for critical care collected and released outside the US, contributing to increased diversity in terms of race and population groups [17]. The final dataset was de-identified to comply with the more stringent requirements of the general data protection regulation, surpassing the health insurance portability and accountability act standards. Prior to its release, the dataset was thoroughly reviewed and approved by external experts in various fields, including privacy and ethics. In particular, it includes an assessment of the risk of re-identification under different re-identification attack scenarios, demonstrating significantly lower re-identification risks than de-identification based on the HIPAA Privacy Rule.

AmsterdamUMCdb dataset can be requested through the Amsterdam Medical Data Science website (https://amsterdammedicaldatascience.nl/) and is available after signing a data use agreement and user credentialing, including completion of the CITI course.

HiRID

The HiRID dataset is the second open dataset for intensive care in Europe, following the release of the AmsterdamUMCdb in 2021 [18]. It is a single-center ICU dataset from Bern University Hospital in Switzerland, which includes records of approximately 34,000 patients admitted to the ICU between 2008 and 2016. The dataset was developed through the collaboration between the Swiss Federal Institute of Technology (ETH) Zürich and Bern University Hospital’s ICUs. The dataset consists of more than 600 variables, including basic demographic data, vital signs, laboratory results, medication records, and fluid and nutritional data. It is also divided into two main categories: Raw and preprocessed data. The Raw data corresponds to the original dataset consisting of three tables. In contrast, Preprocessed data is derived from the preprocessing phase described in the original article study [18]. This involves merging multiple variables representing a single clinical concept into a meta-variable, resulting in a set of 18 metavariables.

The HiRID dataset has a higher temporal resolution than other datasets, particularly in terms of vital sign data, which are recorded at 2-min interval. This followed the anonymization strategies employed for the MIMIC-III and AmsterdamUMCdb datasets. Time information has been modified by setting the initial admission time to an arbitrary date between 2,100 and 2,200, while maintaining seasonality, date, and time consistency.

Compared to other open datasets, the HiRID dataset was not originally developed for publication but as a step toward building a prediction model using machine learning [18]. Therefore, preprocessed data are provided, enabling researchers to quickly assess the feasibility of constructing an AI model at the initial stage of individual research.

The dataset was downloaded from PhysioNet. Users must complete a data-use agreement and the CITI training course, followed by user credentialing to access data. Compared to other open datasets, users are also required to submit their research plans with a dataset request. The dataset and corresponding code for predictive modeling can be found at https://github.com/HIRID/HirID_v1.

CONCLUSION

The advancement of scientific knowledge has been achieved through the accumulation of reproducible knowledge. Research that cannot be reproduced is not considered scientific, because it cannot be refuted. However, many medical studies are difficult to reproduce and validate owing to the inability to share data publicly [19], often due to privacy concerns. Nevertheless, similar to all other sciences, medical research needs to be transparent and reproducible, from data collection to final performance evaluation, so that future generations can build on and improve it. Thus, we can accelerate the advancement of medical knowledge and ensure the development of reliable and well-validated predictive models for use in clinical practice. Open perioperative datasets play a crucial role in knowledge advancement. Therefore, we hope that more open datasets will be released and that research using them will become more active. Standing on the shoulders of giants, we can observe this further.

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CONFLICTS OF INTEREST

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

All datasets cited in this study are publicly available and can be downloaded from the address provided in the manuscript.

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REFERENCES

INTRODUCTION

Discovered by Denborough and Lovell [1] in 1960, malignant hyperthermia (MH) is a rare autosomal dominant, pharmacogenetic, life-threatening syndrome characterized by mutations in the sarcoplasmic reticulum Ca^{2+} release channel in skeletal muscle cells [2,3-7]. MH can be triggered by depolarizing muscle relaxants, such as succinylcholine, and volatile anesthetics, such as halothane, enflurane, isoflurane, sevoflurane, and desflurane, which may lead to a fatal hypermetabolic state [1,3,8]. Clinical signs and symptoms vary from mild to potentially lethal and include tachycardia, hypercapnia, hypoxemia, muscle rigidity, hyperthermia, and metabolic acidosis. MH incidence is between 1:10,000 and 1:250,000; however, it affects all ethnic groups worldwide [4-6].

Dantrolene sodium (DS), which was initially introduced as an intracellular skeletal muscle relaxant, acts pharmacologically as a skeletal muscle contraction antagonist or ryanodine receptor (RyR) antagonist. DS has been clinically used...
since the 1980s for treating MH [4,5] and more recently for neuroleptic malignant syndrome [6], spasticity [7,8], heat stroke [9], and ecstasy intoxication [10].

DS was effective in treating porcine stress syndrome in an in vivo animal study [11], after which the United States Food and Drug Administration (USFDA) approved DS for treating human MH [12-14]. The mortality rate of MH decreased from 70–80% in 1970’s to less than 10% [6,7]. However, DS takes too long time to prepare in the clinical setting because of its chemical properties. To compensate for this drawback, new DS preparations such as azomolene, Revonto®, and Ryanodex® were introduced [15].

Most anesthesiologists who are first-liners in managing MH recognize DS as the first-line drug for treatment. However, MH is a very rare disease and DS is very expensive as well as a short life span, therefore, it is not prepared in the emergency cart of all hospitals worldwide [12,13]. There are few opportunities for anesthesiologists to experience using DS for MH. The authors summarized the pharmacological properties of DS and its derivatives as well as commented on the indications, contraindications, and interactions with other drugs.

**DS AND DERIVATIVES**

Over the past two decades, N-acyl hydrazone (NAH) cores were identified in numerous compounds as one of the most common functional groups in medicinal chemistry, acting on many different types of molecular targets [16]. DS is also an NAH-based hydantoin derivative [17].

**DS**

The chemical molecular formula of DS is C₁₄H₉N₄NaO₅. The structural formula of the hydrated salt is shown in Fig. 1 [18]. The hydrated salt contained approximately 15% water, and has a molecular weight of 399 [19].

DS is an orange-yellow crystalline powder that is poorly soluble in water. However, its slightly acidic nature some-

![Fig. 1. The chemical structure of dantrolene sodium.](www.anesth-pain-med.org)

what increases its solubility in alkaline solutions. DS for intravenous injection was commercially supplied in 70 ml vials containing 20 mg DS, 3,000 mg mannitol, and sufficient sodium hydroxide to produce a pH of approximately 9.5 when reconstituted in pure sterile water for injection (Table 1) [20].

**Revento®**

The chemical molecular formula of Revento® (US WorldMeds) is C₁₄H₁₀N₄O₅ (Fig. 2), which can result in more rapid solubility than DS using tert-butyl alcohol. Revento® has a half life of 36 months, is readily administered in 20 seconds [21], and is a sterile, non-pyrogenic, lyophilized formulation of DS for injection. Revento is available in 65 ml vials containing 20 mg DS, 3,000 mg mannitol, and sufficient sodium hydroxide to yield a pH of approximately 9.5 when reconstituted with 60 ml pure sterile water for injection (Table 1) [20].

**Ryanodex®**

Ryanodex® (Eagle Pharmaceuticals), is an intravenous

![Fig. 2. The chemical structure of Revento® and Ryanodex® (dantrolene sodium for injection). These two drugs have the same chemical structure, but the chemical mixture is different.](www.anesth-pain-med.org)
nanocrystalline suspension of DS, and is a hydrate of 1-[[5-(4-nitrophenyl)-2-furanyl]methylene]amino]-2,4-imidazolidinedione sodium salt (Fig. 2) [22]. Although Revonto® and Ryanodex® have different chemical mixtures, they both have the same chemical structures. Each Ryanodex® vial contains DS 250 mg lyophilized powder that can be rapidly reconstituted as a uniform nanoparticle suspension (less than 1 min) using only 5 ml pure sterile water for injection. This yields a suspension with a pH of approximately 10.3. Ryanodex® contains less mannitol (125 mg mannitol in a single vial) than other formulas and requires additional doses of mannitol to maintain renal function [22].

Ryanodex® is 150 times more concentrated (50 mg/ml) than regular DS (0.33 mg/ml) [23]. Schutte et al. [22,24] presented data from an MH-susceptible swine model comparing Ryanodex® with regular intravenous DS. They demonstrated that the time needed to prepare the Ryanodex® for intravenous administration was about 17 times shorter than for regular DS and therapeutic effectiveness was comparable to that of regular DS intravenous [7,22,24]. However, Ryanodex® is relatively expensive and has a short expiration date, which may limit its applicability (Table 1) [23,24].

**Azumolene**

Azumolene(1-[[5-(4-bromophenyl)-2-oxazolyl]methylene]amino]-2,4-imidazolidinedione, mono-sodium salt, CAS Number 105336-14-9, Molecular Formula C_{15}H_{11}BrN_{3}O_{3} • Na) is a crystalline solid with a Formula Weight of 371.1. Azumolene must be stored at −20°C and remains stable for ≥ 2 years [18,25]. Azumolene is an analog of dantrolene and was synthesized by replacing the para-nitrophenyl group in DS with a para-bromo-phenyl group (Fig. 3). These chemical changes increase water solubility [26]. Azumolene is equipotent to DS in treating and preventing the clinical manifestations of an MH crisis secondary to inhalational anesthetics or depolarizing muscle relaxants in MH-susceptible patients. The main advantage of azumolene is its high water solubility, as it is approximately 30-fold more water-soluble than DS [27].

**PHARMACOLOGIC PROPERTIES**

### Pharmacodynamics

DS was originally reported to inhibit the excitation-contraction coupling of skeletal muscles [11,28]. RyRs are high-conductance L-type Ca\(^{2+}\) channels that release Ca\(^{2+}\) from intracellular stores, such as the endo/sarcoplasmic reticulum (ER/SR) [29,30]. RyRs are ubiquitous in all cell types and involved in various cellular processes (E-C coupling, neurotransmission, and secretion etc.) [31]. There are three known subtypes of RyRs in mammals classified according to the initially identified tissue: skeletal-type (RyR1) is the dominant isoform in skeletal muscle, commonly referred to as skeletal ryianodine receptor; cardiac-type (RyR2) is found in the heart muscle, also known as cardiac ryanodine receptor; and brain-type (RyR3) is expressed at low levels in several tissues, but it is particularly associated with the diaphragm and brain [31-33]. For these subtypes, DS suppresses Ca\(^{2+}\) release from RyR1 and RyR3 [31,32]. Therefore, DS shows beneficial effects not only on MH but also on various pathologies caused by the breakdown of calcium homeostasis (e.g., stroke, ischemia/ reperfusion injury, and neurodegenerative diseases) [33,34]. DS acts directly on RyR1 and RyR3 to reduce channel activation by CaM, thereby decreasing the Ca\(^{2+}\) sensitivity of channel activation [35,36].

### Pharmacokinetics

Following ingestion by mouth, approximately 70% of DS is absorbed, with peak plasma concentration being reached within 6 h. In a study where the USFDA recommended regimen for spasticity was administered orally before surgery to MH- susceptible patients, preoperative oral DS maintained the protective plasma level (> 2.8 µg/ml) for 6–18 h after induction of anesthesia, and the elimination half-life was 15.8 ± 6.0 h [37].

After intravenous administration of DS to conscious patients, the plateau maximal depression of muscle twitch response (75% depression) and the maximal depression of grip strength (42% depression) coincided with the administration of a cumulative doses of 2.2–2.4 mg/kg. This achieves a blood DS concentration of 4.2 µg/ml. Thereafter, the elimination half-life is 12.1 h, although blood concentration is
maintained at a steady value within the therapeutic range for about 5 h. Residual DS concentration in the blood at 24 h after such a dose is 1.7 μg/ml and this is reflected subjectively by patients, in a feeling of weakness. This may persist for up to 48–50 h, during which time the residual blood concentration of DS decreases to 0.3 μg/ml [38].

ADMINISTRATION AND DOSAGE

DS is available as an intravenous injection and oral administration. Oral DS is much less expensive than an intravenous preparation and is usually administered for treating spasticity. It does not carry the risks of thrombophlebitis or tissue necrosis [39].

Management of MH crisis

1. Intravenous DS should be administered by continuous rapid intravenous push beginning at a minimum dose of 1–2 mg/kg, with 15 min interval and continuing until symptoms subside or the maximum cumulative dose of 10 mg/kg is reached. If symptoms do not improve despite administering 7–10 mg/kg, a differential diagnosis should be made rather than additional DS administration [40–42].

The prepared DS solution should be protected from light and stored at 15–25°C, and once prepared, should be used within 6 h. The resulting alkaline solution (pH 9.5) is highly irritating to the peripheral veins and should therefore be injected into a large vein or as a fast-running fluid infusion [40–42].

If physiological and metabolic abnormalities recurred, the treatment regimen was repeated. Intravenous DS administration should be continued until symptoms subside. The effective dose to reverse the crisis is directly dependent on the individual’s degree of susceptibility to MH, amount and time of exposure to the triggering agent, and time elapsed between the onset of the crisis and initiation of treatment (Table 1). The dose of intravenous DS administered to pediatric patients was the same as that administered to adults [4,43,44].

2. Ryanodex® is simplified and rapidly reconstituted to prepare a single vial within 10 s [1,4]. The time to administer a 2.5 mg/kg loading dose of Ryanodex® for a 100 kg patient is 1 min compared to > 22 min for other approved formulations [22,45]. Ryanodex® requires fewer vials (depending on the patient) and less sterile water for injection than other DS formulations [5–7]. Each vial of Ryanodex® contains 250 mg DS, and the same amount of DS as 12.5 vials of other approved formulations. Ryanodex® requires reconstitution with only 5 ml of sterile water for injection vs. 60 ml per vial for other formulations (Table 1) [5–7,22]. Ryanodex® was approved by the USFDA in 2014 [1,22,45].

Prevention of recurrence after MH crisis

Post-Crisis Follow-Up: DS capsules, 4–8 mg/kg/day, in 4 divided doses should be administered for 1 to 3 days following an MH crisis to prevent the recurrence of MH. Intravenous DS may be used postoperatively to prevent or attenuate the recurrence of MH when oral DS is not practical. The intravenous dose of DS in the postoperative period must be individualized, starting with 1 mg/kg or higher, as the clinical situation dictates [20,41,42,45].

Prophylaxis of MH before Anesthesia

There are no specific regimens for preoperative oral or intravenous DS to prevent MH. For preoperative oral DS prophylaxis, it is very difficult to maintain an effective DS blood concentration to prevent MH during the perioperative period in each patient. Moreover, a failure of oral DS therapy to prevent MH in humans has been reported previously [37,38]. Currently, prophylactic intravenous DS as well as oral DS is no longer recommended. This is based on the likelihood of adverse effects with DS prophylaxis, such as muscle weakness, hepatotoxicity, and drowsiness, and the availability of DS and appropriate patient management during MH [18]. Anesthesiologists should be aware that known triggering agents must be avoided even when DS is prepared in the emergency cart [37,38].

Preparation for intravenous injection

Each vial of intravenous DS, or Revonto®, should be reconstituted by adding 60 ml of sterile pure water for injection USP (without a bacteriostatic agent), and the vial shaken until the solution is clear. Ryanodex® is reconstituted with 5 ml. Dextrose 0.9% sodium chloride, and other acidic solutions are not compatible with intravenous DS, Revonto®, and Ryanodex® [19–22,26]. Vial contents must be protected from direct light and used within 6 h of reconstitution. Reconstituted solutions should be stored between 15 to 30°C [40–42].
Management of overdosage

Symptoms that may occur in cases of overdose include, but are not limited to, muscular weakness and alterations in consciousness (e.g., lethargy, coma), vomiting, diarrhea, and crystalluria. General supportive measures should be used to prevent acute overdose. Large quantities of intravenous fluid should be administered to avoid crystalluria. An adequate airway should be maintained and artificial resuscitation equipment should be used. Electrocardiographic monitoring should be instituted and the patient should be carefully monitored. The value of dialysis in DS overdose is currently not known [40-42].

Recommendations

As DS is not readily available in many hospitals worldwide, anesthesiologists should prepare for early diagnosis with close monitoring. Prompt effective therapies are crucial for patients with MH to survive with an initial dose of DS [3,4,44]. DS vials may be safely stored at the initial dose (e.g., 60-70 kg x 2.5 mg/kg = 150-175 mg, 8-9 vials of 20 mg DS), and the remaining DS should be immediately obtained from other centers while the initial dose was being administered [12-14]. Fig. 4 schematically illustrates the treatment algorithm for MH [3,4].

**DRUG INTERACTION**

DS interacts with many other medications, such as cardiac or antiarrhythmic agents (e.g., Ca\(^{2+}\) channel blockers), opioids, hypnotics, neuromuscular blockers, and medications for anxiety or seizures. Interactions between DS and these drugs can create serious problems; therefore, it is necessary to check them before administration.

**Non-depolarizing neuromuscular blocking agents**

DS has muscle relaxation properties and can potentiate non-depolarizing neuromuscular blocking agents (such as
rocuronium, vecuronium, and cisatracurium). Anesthetic providers should recognize this interaction and monitor neuromuscular blockade using appropriate monitoring devices. Moreover, anesthetic providers should keep in mind that there are no antagonists for DS-induced muscle relaxation [46,47].

**Ca²⁺ channel blockers**

In an in vivo study, the interaction between verapamil, a Ca²⁺ channel blocker, and DS resulted in hyperkalemia and cardiovascular collapse [48,49]. DS causes cardiac arrest, atrioventricular block, acute heart failure, circulatory collapse, and ventricular fibrillation in patients with coronary artery disease treated with verapamil [50,51]. However, no such complications occurred when nifedipine was used instead of verapamil. Therefore, verapamil should be changed to nifedipine in cardiovascular patients susceptible to MH who were given verapamil and diltiazem before anesthesia [50]. The risk of serious cardiac disturbances associated with combining amlodipine and DS appears insignificant, even when amlodipine is administered at very high doses of 0.4 mg/kg [52].

**Theophylline**

DS and theophylline have pronounced effects on several muscle systems. Regular doses of DS (2 or 4 mg/kg) increase the theophylline lethality. This may have resulted from the synergistic action on the heart or blood vessels. In contrast, low-dose DS decreased the incidence of theophylline-induced seizure and death. This may be due to the effect of DS on Ca²⁺ release in skeletal muscles. The dose of DS should be decreased when used with theophylline [53].

**Benzodiazepine**

DS and benzodiazepines are among the available anti-spasmodic agents indicated for cerebral palsy, spasticity and associated pain. One comparative study observed the efficacy of DS compared with that of diazepam in children with cerebral palsy. In a double-blind study, there was no significant difference in efficacy between the two drug groups, and the combination of both drugs was more effective than each drug alone [54].

**ADVERSE EFFECTS**

The adverse effects of DS include dizziness; drowsiness; weakness; hives; swelling of the face, lips, tongue, throat; jaundice; difficulty breathing; chest pain; ongoing vomiting; diarrhea or constipation; problems with vision or speech; headache; and seizures [55].

However, serious adverse effects of DS are very rare when DS is administered for a short time. The severity and onset of side effects differ according to the patient’s condition, total amount of DS, and administration route and time [56]. The North American Malignant Hyperthermia Registry reported that the incidence of adverse effects associated with DS was 35.1%, including, gastrointestinal upset, muscle weakness, excessive secretion, hyperkalemia, renal failure, and interactions with verapamil [55,56]. Of these, more than two adverse effects occurred simultaneously in 10.1% of patients. The factors responsible for the adverse effects were total dose of DS, patient age and body weight, amount of fluid administered, and severity of underlying medical conditions. Furosemide administration reduces the adverse effects of DS. The severity of the MH events did not affect the likelihood of DS-related complications [56,57].

**Cardiovascular and Respiratory systems**

Cardiopulmonary depression was not observed at any degree of DS-induced paralysis. At the maximum relaxant doses, DS did not produce cardiopulmonary depression in anesthetized dogs or unanesthetized sheep [58-60]. Second-degree atrioventricular block occurred at 1 and 5 weeks after MH. Decreased heart rate during sleep time was recorded using 24 h Holter monitoring [61].

Intravenous or oral administration of DS in healthy volunteers results in skeletal muscle weakness, dyspnea, respiratory muscle weakness, decreased inspiratory capacity, and pleural effusion [60,62,63]. In a dose-response study by Flewelling et al. [38], there was no change in peak expiratory flow rate, vital capacity, end-tidal carbon dioxide concentration, respiratory rate, mean arterial pressure, and heart rate.

**Central nervous system (CNS)**

DS has no effect on the CNS because it cannot penetrate the blood-brain barrier. However, dizziness, floating, light-headedness, drowsiness, feelings of inebriation, slurred speech, ataxia, and blurred vision can occur, regardless of
the intravenous route or oral administration. It occurred immediately after DS administration and recovered over time, although it persisted for 48 h in some patients [31,57]. To decrease the incidence of side effects, the administered dose should be gradually increased [64].

Liver toxicity

DS causes liver toxicity as an adverse effect from mildly elevated liver enzyme levels during overt clinical hepatocellular injury [56,57]. Baseline liver function studies, including those of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin, are warranted prior to starting DS to rule out preexisting liver injury [65]. Medication should be stopped immediately if liver function becomes impaired [66]. The incidence of hepatic toxicity is related to the total amount of DS, duration of administration, and female sex, especially over 35 years of age as well as old age. It usually recovers completely within 1–3 months [67].

Gastrointestinal disturbances

These complications commonly occur when DS is orally administered. Anorexia, gastric irritation, abdominal cramping, constipation, dysphagia, nausea, vomiting, and diarrhea usually occurs [55-57].

Volume overload and electrolyte imbalance

Because each 20 mg vial of DS requires 60 ml of sterile water diluent, the median (1st and 3rd quartile) of co-administration of sterile water is required to be 666 (284, 1,800) ml, respectively [56,57]. The complications associated with administration increased with the dose of DS, and could be significantly increased by fluid administration and decreased by the administration of furosemide. Severe complications were most likely due to the patient’s underlying medical condition rather than DS administration. When DS is administered, clinicians should exercise vigilance for changes in intravascular fluid volume and the subsequent development of cardiorespiratory complications [55-57].

Thrombophlebitis

When DS is infused through a small peripheral vein, extravasation, thrombophlebitis, and tissue necrosis may occur. A lyophilized formulation of an alkaline solution (pH 9.5) induces an acute inflammatory reaction in the vascular endothelium. DS should be administered to large veins through a free-flowing large-bore intravenous catheter [56,57].

EFFECTS OF DS ON PREGNANCY AND FETUS

Pregnancy

DS is an FDA pregnancy category C. DS should be used during pregnancy only if its potential benefits justify the potential risks to the fetus [64,68]. The prevalence of MH susceptibility is approximately 1/125,000 in Cesarean deliveries, which is similar to the prevalence reported in non-obstetrical surgery inpatients. Previous studies have suggested that stocking DS in maternity units is justified [64,68]. In an animal study, postpartum uterine atony was reported in a woman who received prophylactic intravenous DS using oxytocin after delivery [69,70].

There have been no adequate or well-controlled studies in pregnant women. Available data from case reports of the intravenous administration of DS during pregnancy are insufficient to evaluate the drug-associated risk of major birth defects, miscarriages, or adverse maternal and fetal outcomes. DS readily crosses the placenta; however, no serious adverse events have been reported in neonates following the maternal administration of DS prior to delivery. Although an equilibrium between maternal and fetal plasma DS concentrations was apparent at 5 min, the fetal levels of DS were approximately 10% of the mother’s [71-73].

Lactation

DS has been detected in human milk at concentrations of less than 2 μg/ml during repeat intravenous administration over 3 days. The estimated half-life of DS in breast milk is approximately 9 h. Based on these data, the amount of infant exposure to DS through breastfeeding would be negligible 2 days after the last maternal dose. If used in the short term, the data suggest that alternate feeding methods may be pursued during active DS treatment and breastfeeding may be restarted 1–2 days after treatment is stopped [74].

Fetus and neonate

DS is administered to mother during the cesarean section,
fetal blood concentration will be 65% of maternal plasma level [61,64]. No adverse effects of DS have been detected by extensive testing of fetuses and neonates in certain reports [64,68]. In rare cases, Floppy infant syndrome has been reported in affected fetuses and neonates [57]. The use of dantrolene in MH-susceptible pregnant patients did not cause noticeable adverse effects in the fetus or neonate [64].

INDICATION OTHER THAN MH

DS can be used for the treatment of MH and other diseases related to abnormalities in L-type calcium channel receptors, such as RyRs [1-3,5-7].

Spasticity

USFDA-approved uses for DS include muscle spasticity disorders, as seen with upper motor neuron disorders, including stroke, traumatic brain injury, spinal cord injury, cerebral palsy, and multiple sclerosis [7,8]. It is the only USFDA-approved oral peripherally-acting antispasmodic medication for these disorders [75-77]. It can be administrated at an initial daily dose of 25 mg, which can be increased to 100 mg 4 times a day for a maximum total dose of 400 mg per day [78].

Neuroprotection

Induced normothermia or hypothermia has become a treatment modality for reducing fever burden in neurological injury [79-84]. DS reduces the metabolic effects of fever in the presence of neurological injury by reducing shivering gain and shivering threshold [31,85,86]. Although occasionally used as an add-on to anti-shivering drug, DS usually causes less sedation and muscle relaxation than the medications commonly used to treat shivering, and, at the same time, may also be neuroprotective [87].

Ca\(^{2+}\) signaling is crucial for maintaining normal neuronal functions such as membrane excitability, neurotransmitter release, cellular growth, differentiation, and cell death. DS is also an effective drug for disrupting Ca\(^{2+}\) homeostasis, as reported in neurodegenerative diseases including Alzheimer’s disease, Parkinson’s disease, Huntington’s disease, amyotrophic lateral sclerosis, and spinocerebellar ataxia [5,79,80]. Binding of DS to RyRs in the brain may protect neurons from disruptions in Ca\(^{2+}\) homeostasis [79-84].

Neuroleptic malignancy

DS is also used for treating drug-induced fever, such as neuroleptic malignant syndrome [6], overdose of 2,4-dinitrophenol (a banned “fat burner” medication that interrupts ATP synthesis and causes hyperthermia) [88,89], lysergic acid diethylamide (LSD), and MDMA (3,4-methylenedioxymethamphetamine, ‘Ecstasy’) toxicity [10,36,90]. It can also be used to treat the serotonin syndrome, anticholinergic poisoning, sympathomimetic poisoning [91,92].

Sepsis and toxic shock

In sepsis and toxic shock syndromes such as Staphylococcus aureus bacteremia with skeletal muscle hypermetabolism, DS may be considered early if specific antibiotic therapy alone is not successful [93].

MH is triggered by halogenated inhalational anesthetics and viral infections. The mechanisms underlying rhabdomyolysis and fever in corona virus disease 2019 (COVID-19) may be similar to those in MH. Therefore, DS will be effective in most patients with severe COVID-19 with acute respiratory distress syndrome and lymphopenia as well as disorders of the central or peripheral nervous system, cardiac arrhythmias, cardiomyopathy, rhabdomyolysis, coagulopathy, and shock [94-96].

Classic heat stroke and emotional heat stroke (EHS)

Heat stroke is usually diagnosed when core temperature exceeds 40.6°C [97]. The symptoms of heat stroke are similar to those of MH [97,98]. As a rapid decrease in body temperature is important for managing heat stroke, DS has been used in conjunction with various physical cooling techniques [10,99]. Individuals genetically susceptible to MH, with a positive MH response in the in vitro contracture test, may be at an increased risk of exertional heat illness and exertional rhabdomyolysis [100]. One well-known case report was that of a child who had an unequivocal MH episode during anesthesia and later died of EHS [100]. DS antagonizes RyRs within the SR, inhibiting Ca\(^{2+}\) release into the cytosol and reversing muscle rigidity as well as body heat production. However, DS did not reduce cooling time, multiple organ injury, or length of hospital stay in patients with classic heat stroke and EHS in several studies [97-100].
Cardinal arrhythmias

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is one of the most malignant genetic arrhythmogenic disorders. It manifests as exercise- and/or stress-induced premature ventricular complexes, polymorphic or bidirectional ventricular tachycardia, or sudden death and is usually associated with vigorous physical exercise or mental stress [101, 102]. The most common CPVT subtype, type 1, is a dominantly inherited disease caused by mutations in the cardiac RyR2 gene [103]. Mutations in RyR2 cause increased Ca\(^{2+}\) sensitivity, which can lead to spontaneous Ca\(^{2+}\) release from the SR, generation after depolarization, and triggered activity. Intravenously administered DS suppresses ventricular arrhythmias in congenital RyR2 defect [103]. DS corrects defective interdomain interactions within RyR2 in failing hearts and CPVT, inhibits spontaneous Ca\(^{2+}\) leakage, and improves cardiomyocyte function. Thus, DS has the potential to treat heart failure and CPVT by specifically targeting RyR2 [101-104]. DS is safe and clinically effective for treating cardioglycoside poisoning [105].

CONTRAINDICATION AND WARNING

There are no contraindications to using intravenous DS for treating of MH. However, caution should be exercised when administering DS to patients with hypersensitivity, impaired hepatic function, liver cirrhosis, non-alcoholic steatohepatitis, and hepatitis B or C [66, 106].

According to the manufacturer’s manual, Pharmaceutical, Inc., and USFDA, DS should be used with particular caution in females and in patients over 35 years old, in view of the apparent greater likelihood of drug-induced, potentially fatal hepatocellular disease in these groups. Other reports suggested a higher proportion of hepatic events with fatal outcomes in elderly patients undergoing DS. However, most of these cases were complicated by confounding factors such as intercurrent illnesses and/or concomitant potentially hepatotoxic medications. In general, dose selection for elderly patients should be performed with caution, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, concomitant disease, or other drug therapy. Similar to all patients undergoing DS, elderly should patients receive the lowest dose compatible with an optimal response [19, 67, 107, 108].

CONCLUSION

In the field of Anesthesiology, DS is the drug of choice in the emergency care setting for treating MH crisis. Additional personnel and efforts are required to assist in the preparation process. Therefore, it is necessary to understand the pharmacological properties of DS so that it can be used according to its indications and adverse effects.

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None.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

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INTRODUCTION

Fluid administration is a first-line treatment for hemodynamically unstable patients in the operating room to increase cardiac output and improve tissue oxygenation. However, many classical methods that seem to determine the need for fluid bolus infusion failed to increase cardiac output according to fluid administration [1], which means fluid had been inadvertently loaded into the patients who did not need fluid administration [2,3]. Therefore, the need for predicting fluid responsiveness has been raised to avoid unnecessary fluid administration and improve the patient’s outcomes because fluid overload is associated with postoperative complications, including pulmonary edema [4], acute kidney injury [5], and increased risk of mortality [6].

Historically, so-called “static” parameters of cardiac preload, such as central venous pressure and pulmonary artery occlusion pressure, have been used for decades. But those variables cannot accurately predict fluid responsiveness in many previous studies [7,8]. After the first study of systolic pressure variation in patients with sepsis-induced hypotension who required mechanical ventilation in the surgical intensive care unit (ICU) [9], numerous studies have demonstrated many parameters that can predict fluid responsiveness in various conditions. So, at present, a variety of predictors of fluid responsiveness such as pulse pressure variation...
(PPV), stroke volume variation (SVV), respiratory variation of inferior vena cava diameter, end-expiratory occlusion (EEO) test, passive leg raising (PLR) test, mini-fluid challenge test, and many other parameters have been widely used in daily clinical practice.

However, many previous studies have been performed in the ICU patients. Considering that the environments of the operating room (OR) and the ICU are different in many ways, a parameter that is helpful in the ICU to predict fluid responsiveness can be challenging or even unavailable for the prediction of fluid responsiveness during the surgical procedure under anesthesia in the OR. Therefore, in the present review, we summarized the existing and recently updated results and limitations of the representative parameters for fluid responsiveness prediction, focusing on the OR environment. The pitfalls in fluid management based on the predictors of fluid responsiveness were also addressed.

**PARAMETERS BASED ON HEART-LUNG INTERACTION**

### Pulse pressure and stroke volume variations

PPV and SVV are some of the firstly verified predictors of fluid responsiveness in mechanically ventilated patients [10]. The physiology of those parameters is based on heart-lung interaction according to positive pressure ventilation, which means the changes in intrathoracic pressure during mechanical ventilation affect the cardiac preload and afterload differently between the left- and right-sided hearts, leading to the circulated changes in pulse pressure and stroke volume in continuous arterial pressure waveforms (Fig. 1) [11]. Many studies in the ICU and the OR have confirmed the validity of PPV and SVV as a predictor of fluid responsiveness, and they have been widely used to guide fluid management in daily clinical practice [10,12,13]. A meta-analysis showed that PPV could predict fluid responsiveness with a sensitivity of 88%, a specificity of 89%, and an area under the receiver operating characteristic curve (AUROC) of 0.94 [13]. Zhang et al. [14] also demonstrated SVV has an odd diagnostic ratio of 18.4 in predicting fluid responsiveness with a sensitivity of 81% and specificity of 80%.

Despite the high accuracy and reliability of PPV and SVV, they cannot be accurately served as a predictor of fluid responsiveness in many conditions, such as patients with spontaneous breathing activity [15], cardiac arrhythmias [11], low tidal volume (<8 ml/kg) [16], low lung compliance [15], open-chest condition [17], increased intra-abdominal pressure (Table 1) [18,19]. Currently, the patients in the ICU have been less sedated and frequently ventilated using low tidal volume. So, the reliability and use-frequency of PPV and SVV for fluid responsiveness prediction seem to be decreasing in the ICU environment. On the contrary, PPV and SVV are still used a lot in the OR because they can retain the predictive value accurately, as the required conditions their applicability are generally fulfilled during general anesthesia for surgical procedures.

Several recent studies have suggested that temporally increasing tidal volume can restore the predictability of PPV and SVV in various clinical situations of the ICU and OR. Myatra et al. [20] showed that the increases in PPV and SVV related to the transient increase in tidal volume from 6 to 8 ml/kg for 1 min could be a reliable predictor of fluid responsiveness in ICU patients. Min et al. [21,22] also demonstrated that augmentation of PPV using a temporary increase in tidal volume from 8 to 12 ml/kg and the Valsalva maneuver could restore its predictability of fluid responsiveness in the anesthetized patients in the “gray zone” and with the open-chest condition, respectively. So, employing a temporary increase in tidal volume can be an alternative option to overcome some limitations of PPV and SVV.

### Respiratory variation of inferior vena cava diameter

Respiratory variation in the diameter of the inferior vena cava has been suggested as a non-invasive parameter to predict fluid responsiveness and is widely used in ICU patients [23]. This method does not require arterial catheterization and can be easily obtained using ultrasound with minimal training. However, based on the recent results, it seems to need more studies to confirm the diagnostic accuracy of respiratory variation of inferior vena cava to predict fluid responsiveness.

Initial small-scaled validation studies in the ICU reported that respiratory variation of inferior vena cava diameter could be a reliable parameter for predicting fluid responsiveness in mechanically ventilated patients [24-26] and even spontaneously breathing patients with cardiac arrhythmia [27]. A systematic review also suggested that respiratory variation in the diameter of the inferior vena cava had diagnostic accuracy higher than central venous pressure, lower than the PLR test, and equivalent to SVV and PPV [28]. However, in a recent study of 540 patients in the ICU, respiratory variation of inferior vena cava diameter showed lower diagnostic accuracy in predicting fluid responsiveness than the
Fig. 1. PP variation and SV variation. During inspiration in positive-pressure mechanical ventilation, the increase in intrathoracic pressure leads to an increase in cardiac preload, which results in the largest PP and SV at the end of inspiration. Conversely, intrathoracic pressure decreases during expiration, resulting in a decrease in PP and SV. Consequently, PP and SV are smallest at the end of expiration. PP: pulse pressure, SV: stroke volume, PPV: pulse pressure variation, SVV: stroke volume variation.

initial validation studies (threshold value: 8%, AUROC: 0.635, sensitivity: 55%, and specificity: 70%) [29]. Two recent meta-analyses reported that the pooled AUROCs, sensitivities, and specificities of respiratory variation of inferior vena cava diameter in mechanically ventilated patients were 0.75, 79%, and 70% [30] and 0.82, 69%, and 88% [31], respectively.

Although the exact reasons for those divergent results have not been fully explained, it seems to play a role in those discrepancies that the compliance of inferior vena cava depends on many factors, such as volume status, intra-abdominal pressure, and measurement location [29,32].

In addition, the respiratory variation of inferior vena cava
diameter shares most limitations of PPV and SVV except for cardiac arrhythmia and spontaneous breathing activity because those parameters are based on the same physiology that is heart-lung interactions [27]. Moreover, because the diameter of the inferior vena cava is measured in the subcostal region [25], measurement of the inferior vena cava using ultrasound is sometimes impossible in certain types of procedure (i.e., intra-abdominal surgery) because performing that method can interfere with the operation and contaminate the surgical field (Table 2). Therefore, respiratory variation in the diameter of the inferior vena cava seems to play a limited role in predicting fluid responsiveness in the OR.

### End-expiratory occlusion test

The EEO test is based on the simple physiology that insufflation during mechanical ventilation can decrease cardiac preload [33]. Eliminating the rise in intrathoracic pressure during the inspiratory phase increases venous return, which acts as a fluid challenge to predict fluid responsiveness. The EEO test can be performed simply to stop the mechanical ventilation at the end-expiration and to measure the resulting changes in cardiac output for longer than 12 seconds [34]. This method is very easy-to-perform and reliable in certain conditions where PPV and SVV can be unreliable, such as low tidal volume ventilation, low pulmonary compliance (i.e., acute respiratory distress syndrome), and cardiac arrhythmia [15,35,36]. Because of its brevity, the EEO test requires a precise, continuous, and real-time hemodynamic assessment to detect the changes in cardiac output properly [34].

Since the first report by Monnet et al. [35] in 2009, several studies showed that hemodynamic response to an EEO test could accurately predict fluid responsiveness in ICU patients [20,36]. But it would be hard to conclude whether the EEO test has a diagnostic accuracy to predict fluid responsiveness in the OR. Biais et al. [37] showed that changes in stroke volume index induced by the EEO test could predict fluid responsiveness in patients with low tidal volume ventilation (6.9 ml/kg of ideal body weight). Whereas the EEO test failed to discriminate fluid responders during laparotomic surgery [38,39] and in a prone position during neurosurgery [40], which may affect venous return by involving alterations in intra-abdominal pressure and vena cava pressure [41,42]. In addition, even a recent meta-analysis that stated the EEO

<table>
<thead>
<tr>
<th>Test</th>
<th>Monitoring techniques</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart-lung interaction indices</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse pressure variation/ Stroke volume variation</td>
<td>Arterial catheter</td>
<td>No requirement for the direct measurement of cardiac output</td>
<td>Cannot be used in patients with spontaneous breathing, cardiac arrhythmia, intra-abdominal hypertension, and open chest</td>
</tr>
<tr>
<td></td>
<td>Transthoracic echocardiography</td>
<td>Applicable in patients with spontaneous breathing and cardiac arrhythmia</td>
<td>False negative in low-tidal volume ventilation/low lung compliance</td>
</tr>
<tr>
<td>Inferior vena cava diameter</td>
<td>Transthoracic echocardiography</td>
<td></td>
<td>Transthoracic approach may not be feasible due to operation field</td>
</tr>
<tr>
<td>End-expiratory occlusion test</td>
<td>Pulse contour analysis</td>
<td>Easy to perform</td>
<td>Requires precise and real-time measurement</td>
</tr>
<tr>
<td>Fluid loading methods</td>
<td></td>
<td></td>
<td>Cannot be used in spontaneous breathing patients</td>
</tr>
<tr>
<td>Passive leg raising test</td>
<td>Pulse contour analysis</td>
<td></td>
<td>Limited evidence in the operating room</td>
</tr>
<tr>
<td></td>
<td>Echocardiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oesophageal Doppler</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulse oximeter</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bioreactance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mini-fluid challenge</td>
<td>Pulse contour analysis</td>
<td>Applicable in patients with spontaneous breathing and cardiac arrhythmia</td>
<td>Requires a very precise measurement due to low cut-off values</td>
</tr>
<tr>
<td></td>
<td>Echocardiography</td>
<td></td>
<td>Repeated use may cause fluid overload</td>
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</tbody>
</table>

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Table 1. Summary of Available Tests to Predict Fluid Responsiveness with Main Advantages and Limitations in the Operating Room
test successfully predicted fluid responsiveness in the ICU and OR was based merely on two previous studies: One that the EEO test could predict fluid responsiveness in patients with protective ventilation in the OR [37] and the other that EEO test failed to predict fluid responsiveness in patients undergoing laparotomic surgery [38]. Therefore, to ascertain the diagnostic accuracy of the EEO test as a predictor of fluid responsiveness in the OR, further studies conducted in the OR environment will be needed.

**Table 2. Overview of Monitoring Devices Available for the Prediction of Fluid Responsiveness**

<table>
<thead>
<tr>
<th>Monitoring devices</th>
<th>Requirement</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
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<tbody>
<tr>
<td><strong>Invasive method</strong></td>
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</table>
| Pulmonary artery catheter                   | • Central venous catheter                        | • Direct measurement of hemodynamic parameters, including pulmonary artery pressure, cardiac output | • Delay in determining cardiac output
• Invasiveness and complications (bleeding, infection, arrhythmias, and vessel damage) |
| **Less-invasive methods**                   |                                                  |                                                                                               |                                                                                                |
| Pulse contour analysis                      | • Arterial catheter                              | • Continuous cardiac output monitoring                                                      | • Lack of accuracy in hemodynamically unstable patients or during use of vasoactive drugs
• Not reliable in patients with arrhythmia |
| Transesophageal echocardiography            |                                                  | • Real-time measurement of hemodynamic parameters and cardiac function                        | • Time and resource-intensive (equipment, trained personnel…)
• Operator dependency
• Not suitable for patients with esophageal pathology |
| Esophageal doppler                           |                                                  | • Real-time monitoring of cardiac output                                                      | • Risk of dislocation, misplacement
• Not suitable for patients with esophageal pathology |
| **Non-invasive methods**                    |                                                  |                                                                                               |                                                                                                |
| Transthoracic echocardiography              | • Arterial catheter                              | • Real-time measurement of hemodynamic parameters and cardiac function                        | • Time and resource-intensive (equipment, trained personnel…)
• Operator dependency
• Limited acoustic window due to patient position and operative field |
| Bioimpedance                                | • Simple, easy-to-use                            | • Real-time monitoring of cardiac output                                                      | • Lack of reliability in patient movement, adipose tissue, edema, or the presence of electrical interference |

**Tests That Assess Fluid Responsiveness by Mimicking Classic Fluid Loading**

**Passive leg raising test**

The PLR test involves positional changes from the semi-recumbent position to the position of the 45° of leg elevation with the horizontal trunk, which causes transferring blood from the lower limbs and splanchnic territory towards the intrathoracic compartment, thus increasing circulatory volume around 150–300 ml [43,44]. This reversible “self-transfusion” allows the assessment of fluid responsiveness without actual fluid infusion to the patient [43]. Also, the PLR test is independent of the heart-lung interaction; therefore, it can be successfully used to assess fluid responsiveness in patients with spontaneous breathing activity, cardiac arrhythmia, low tidal volume ventilation, and low pulmonary compliance [45]. Numerous studies have repeatedly established the high reliability of the PLR test as a predictor of fluid responsiveness in a wide variety of clinical situations [45,46]. A meta-analysis also demonstrated that PLR-induced changes in cardiac output ≥ 10% very reliably predict fluid responsiveness with good AUROC, sensitivity, and specificity (0.95, 85%, and 91%, respectively) [45]. Therefore, the Surviving Sepsis Campaign has involved the PLR test in the hemodynamic management of septic shock [47].

Because the effects of the PLR test should be measured
using cardiac output, not arterial pressure [48] and usually reach the maximum within 1 minute and then diminish, a real-time cardiac output monitoring device, such as arterial pulse contour analysis, echocardiography, and esophageal Doppler, should be used for assessing the changes in PLR-induced cardiac output [45,49]. More recently, less-invasive and easy-to-use cardiac output measuring devices such as perfusion index from plethysmography and bioreactance-based cardiac output have been suggested as the alternative methods to assess the changes in cardiac output by PLR. Beurton et al. [50] showed that an increase in perfusion index during a PLR test ≥ 10% could predict fluid responsiveness with a sensitivity of 91% and a specificity of 79% (AUROC = 0.89) in ICU patients with acute circulatory failure. Galarza et al. [51] also reported that changes in bioreactance-based cardiac output during PLR test ≥ 10% successfully discriminated fluid responders with a sensitivity of 92% and a specificity of 80% (AUROC = 0.88) in critically ill patients in the ICU. The previous study found that the bioreactance monitor, which averaged cardiac output over a 30-s period, was not able to measure the effects of PLR accurately due to its longer averaging time [52]. However, the latest version of the Starling-stroke volume system, which only takes 8 seconds to average cardiac output, allows for a more accurate assessment of the PLR effects [51]. This highlights the significance of utilizing a real-time cardiac output monitor to effectively monitor the effects of a brief test like PLR.

Five rules should be followed when accurately implementing the PLR test because the performing method fundamentally affects the hemodynamic effects and reliability of the PLR test as follows [53]. First, the PLR test must start from the semi-recumbent position. Second, cardiac output, not arterial pressure, should be measured to assess the effect of the PLR test. Third, real-time cardiac output monitoring devices should be used. Forth, the cardiac output should be reassessed after returning to the semi-recumbent position after the PLR test and should return to the value before the PLR test. Fifth, any confounding factors that provoke adrenal stimulation, such as pain, cough, discomfort, and awakening, should be avoided during the PLR test.

Considering those rules when performing the PLR test and their effect on the reliability of the PLR test in predicting fluid responsiveness, it seems to be questionable whether the PLR test can be performed accurately during surgery in the OR. First, the presence of surgical equipment or the surgical procedure can make the positional change impossible or not allowed. In addition, the patients should be in a lateral or prone position in some operations. Second, each time the PLR test is performed, the operation should be stopped because a precise surgical procedure is impossible when changing the patient’s position. The surgical procedure can also be a potential confounding factor that causes adrenal stimulation. Third, applying elastic compression stockings, frequently used to prevent venous thromboembolism in the OR, may compromise the reliability of the PLR test to predict fluid responsiveness by reducing returning blood volume [54]. Last, the reliability of the PLR test has been questioned in cases of intra-abdominal hypertension [55], which may restrict applying the PLR test in a specific type of surgical procedure that increases intra-abdominal pressure, such as laparoscopic surgery with intra-abdominal carbon dioxide insufflation. So, despite the proven safety and accuracy in predicting fluid responsiveness, it seems that the PLR test can merely be used in very limited cases during surgical procedures in the OR.

**Mini-fluid challenge**

From decades ago, the fluid challenge technique has been suggested for fluid management [56] because infusing fluid bolus and measuring its effect on cardiac is the most definite way in practice to determine the presence of fluid responsiveness. However, the “classic” fluid challenge with the administration of 300–500 ml of fluid is irreversible and can lead to fluid overload, especially if repeated, in case of the absence of fluid responsiveness, which occurs in about half of the patients. Therefore, the classic fluid challenge seems to be considered the treatment rather than the challenge. Thus, a “mini-fluid challenge” with rapid infusion (1–2 min) of a small amount (100–150 ml) of crystalloid or colloid has been introduced as an alternative method [48,57]. The mini-fluid challenge is also independent of heart-lung interaction, like the PLR test, so it can be used to predict fluid responsiveness in various clinical conditions where PPV and SVV cannot be applied.

Since the first report in 2011 [57], which reported an increase in the variation of subaortic velocity time index after 100 ml of colloid infusion over 1 min could predict fluid responsiveness with a sensitivity of 95% and a specificity of 78% (AUROC = 0.92) in mechanically ventilated patients in the ICU, several studies have shown the reliability of mini-fluid challenge to predict fluid responsiveness in the ICU [20,58,59] and the OR [60,61]. A recent meta-analysis has confirmed the reliability of mini-fluid challenge as a pre-
Fluid responsiveness in operating room

Predictor of fluid responsiveness by demonstrating that the pooled AUROC for the mini-fluid challenge was 0.91 with the best threshold of 5% and that pooled sensitivity and specificity were 82% and 83%, respectively [62]. In addition, a multi-center trial has shown that the mini-fluid challenge of 100 ml over 1 min successfully predicted fluid responsiveness with a sensitivity of 98% and specificity of 87% for cut-off value of 4% (AUROC = 0.95) in patients undergoing laparotomy [63]. Considering those results, the mini-fluid challenge can be an attractive option if other predictors of fluid responsiveness are not feasible or applicable.

However, the mini-fluid challenge has several limitations as follows. First, critical methodological issues have been recently raised regarding the existing results of the mini-fluid challenge, in which the predictor parameters after the mini-fluid challenge of 100 ml and the outcome parameters after 500 ml of fluid administration were calculated from the same baseline, leading to potential mathematical coupling and overestimation of the observed predictive power [64]. Second, even in cases where preload responsiveness is present, a small volume of fluid administration will elicit small changes in cardiac output [65]. Therefore, a precise device to measure cardiac output should be needed to detect a relatively small diagnostic threshold for the mini-fluid challenge (around 5%) [48]. Last, the mini-fluid challenge entails the administration of fluid which cannot be removed. Although the risk is lower compared to a traditional fluid challenge, there is still a potential for fluid overload if the mini-fluid challenge is repeated.

PITFALLS IN FLUID MANAGEMENT

Gray zone: Uncertainty exists in every test

No single test or value is perfect for predicting fluid responsiveness tests or for any diagnostic tests. There are inherent limitations in every test. In statistical analysis, fluid responsiveness is typically described in a dichotomous manner as either present or absent. But the response to fluid administration is a continuous parameter. Thus, the diagnostic threshold derived from the quantitative test is arbitrary and does not reflect the full range of potential responses. So, the "gray zone," which represents a zone of uncertainty, has been introduced as a complement to the binary constraint of ROC curve analysis [66]. Cannesson et al. [67] first reported that the gray zone of PPV to predict fluid responsiveness was between 9% and 13% in approximately 24% of patients. In addition, previous studies have shown that 17% and 19% of patients were included in the gray zone for the EEO test [37] and mini-fluid challenge [61], respectively. Therefore, anesthesiologists should recognize that relying solely on a single parameter within the gray zone may not provide definitive guidance for fluid administration decisions.

Fluid responsiveness is not an omnipotent rule

The decision to administer fluid should not be solely based on the presence of fluid responsiveness. While fluid responsiveness indicates the likelihood of a patient’s potential to increase cardiac output in response to fluid administration, it does not necessarily mean that fluid should always be given. It is crucial to consider the patient’s overall fluid status, underlying pathology, and potential risks associated with fluid overload. Although fluid administration may be necessary to optimize hemodynamics in some patients, excessive fluid administration may lead to complications such as pulmonary edema and impaired organ function in certain conditions, such as congestive heart failure, chronic kidney disease, or acute respiratory distress syndrome [4]. Alternative treatments, such as vasopressors or inotropes, may be more appropriate in these cases. Therefore, fluid therapy should always be individualized based on careful evaluation of the patient’s clinical condition, focusing on achieving adequate tissue perfusion while avoiding complications associated with fluid overload.

No need to determine fluid responsiveness in every patient

In the OR, the ultimate goal of fluid management is to optimize the patient’s hemodynamic status by promptly addressing blood volume depletion or other contributing factors to hemodynamic instability. Therefore, immediate fluid loading will be more effective than testing fluid responsiveness if the clinical situation corresponds to the obvious hypovolemia (i.e., massive bleeding). However, it should be remembered that in most other cases, fluid administration increases cardiac output sufficiently in around half of patients.

CONCLUSION

For the optimal fluid management in each patient, it is crucial to determine fluid responsiveness accurately before fluid administration to prevent unwanted fluid overload and
the related risks. However, several well-known existing methods for assessing fluid responsiveness, such as respiratory variation of inferior vena cava diameter, the EEO test, and the PLR test, require numerous prerequisites, and even when certain limitations are addressed, their applicability in the operating room remains restricted. So, despite its inevitable limitations resulting from the heart-lung interaction, PPV and SVV will be the first choice as a test for fluid responsiveness prediction in the OR environments if the patient is not in a situation where PPV and SVV cannot be applied, such as the presence of spontaneous breathing or cardiac arrhythmia. If PPV and SVV are not applicable, a mini-fluid challenge seems helpful for predicting fluid responsiveness in the OR. Further studies will be needed to evaluate the optimal method for determining fluid responsiveness focusing on OR environments.

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**CONFLICTS OF INTEREST**

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

**DATA AVAILABILITY STATEMENT**

Data sharing is not applicable to this article, as no datasets were used or analyzed for this study.

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INTRODUCTION

A large language model is an artificial intelligence (AI) model that can understand and generate natural languages. Chat generative pre-trained transformer (ChatGPT) is a large language model developed by OpenAI, a non-profit startup founded by Elon Musk and Sam Altman. Microsoft invested approximately $3 billion USD in the development and implementation of the current model. It is now being applied to Microsoft’s search engine Bing [1]. ChatGPT was trained using a large number of documents available on the Internet, as well as various books and documents from various fields. Currently, publicly available large language models include OpenAI’s ChatGPT and Google Bard.

ChatGPT 3.5 is generally trained on data until June 2021.
depending on the direction or form of the user’s question, making it very different from conventional search engines (Table 1).

BERT, or Bidirectional Encoder Representations from Transformers, is a language model developed by researchers at Google AI Language in 2018. BERT was trained on many documents and understands the context of sentences input by users and provides information that can be used for natural language processing (NLP) tasks by utilizing each word. It contains approximately 300 million parameters. Additionally, Turing, an AI verification algorithm developed by Microsoft, contains 17 billion parameters. However, ChatGPT 3.5 has over 1.7 trillion parameters, which is more than ten times that of Turing. The large number of parameters in ChatGPT enables it to produce dimensionally different responses from those of previous language models. Future studies should include additional parameters.

In this review article, the transformer model on which ChatGPT is based; its use in scientific writing, anesthesiology, and clinical research; and its limitations are discussed.

**TRANSFORMER**

The recurrent neural network (RNN) was first introduced in 1986 and was initially developed as a tool for learning time-series data [3]. RNNs have been widely used to process time-series data [4]. An RNN has a hidden state value that exists between the input and output, and it updates the output by learning the previous hidden state and the new input value at each time step to generate a new hidden state [4]. Long short-term memory (LSTM), one of the most prominent RNN algorithms, was introduced in 1997, and its sequence-to-sequence technique has become popular in fields such as translation [5]. LSTM is a representative RNN algorithm and was the most commonly used time-series data processing technique until the emergence of the transformer algorithm [5]. LSTM is used in time-series analysis to learn patterns of changes and predict trends. It can be applied to stock or weather forecasting, and such characteristics can be used to recognize speech, predict changes in speech over time, and improve speech recognition performance. The sequence-to-sequence model is often used to examine the translation process using an RNN. This model converts the given input words into vector format numerical data, which are then fed as inputs to each LSTM layer in the encoder. The encoder reads the input data and converts them into context-formatted data, which are then converted into embedded values of the target language using the LSTM layers in the decoder. Data may be lost during this process of sequentially reading input data in a time-sequence order and compressing it into a vector format, causing a bottleneck when processing a large amount of document data as input, leading to significantly decreased performance.

The convolutional neural network (CNN) was the dominant trend in deep learning until the emergence of AlphaGo in 2016. CNNs use a feature extraction method for convolution layers, which demonstrates excellent performance in processing dimensional image data [6]. CNN development has been a revolutionary turning point in image and video data processing, and CNN algorithms have been used in numerous medical imaging data processing applications. However, the CNN algorithm has limitations when processing time-series data other than image data.

“Attention Is All You Need” is a groundbreaking paper published by Google in 2017 that introduced a new neural network architecture called the transformer model for solving various NLP problems, including machine translation [7]. This paper announced the first appearance of the algorithm upon which ChatGPT is based. The transformer model was proposed to overcome the limitations of existing models based on RNNs. Its main features and advantages include the utilization of the self-attention mechanism to capture interactions between words within a sentence, allowing it to maintain the order information of the input data while managing long-range dependencies. The transformer simultaneously processes the input data, leading to faster

<table>
<thead>
<tr>
<th>Table 1. Comparison of ChatGPT and Conventional Search Engines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Feature</strong></td>
</tr>
<tr>
<td>Technology utilized</td>
</tr>
<tr>
<td>Information generation</td>
</tr>
<tr>
<td>User interaction</td>
</tr>
<tr>
<td>Query &amp; context understanding</td>
</tr>
</tbody>
</table>

AI: artificial intelligence, GPT: generative pre-trained transformer.
training and inference speeds, in contrast to the sequential computational structure of RNNs [7]. The transformer employs multihead attention, which is its core principle, enabling it to simultaneously learn multiple perspectives of the input data, thereby capturing various contextual information [7]. The attention method assigns weights to the input and output values and learns them. This is similar to the manner in which humans learn. Humans focus on a few critical pieces of information, rather than all the information, when acquiring information to understand the overall context and meaning. The attention module followed a similar learning method by assigning weights to important information during learning. The transformer algorithm processes data in parallel because this attention module is included in both the input and output interfaces. It also incorporates position encoding to add the position information of words, allowing the model to learn order information. Furthermore, the transformer model features an encoder-decoder structure with multiple layers in each encoder and decoder, which allows the model to learn more complex patterns. The encoder and decoder blocks are structured with a self-attention layer that demonstrates the relationships between words within the input sentence, and a fully connected feed-forward layer that is equally applied to all words [7]. In addition, the decoder block has an encoder-decoder attention layer between the two layers (Fig. 1). The transformer model has been shown to solve various NLP problems efficiently and has become the foundation for representative models such as the GPT and BERT. Almost all language models have utilized the transformer model since Google proposed it in 2017 by stacking it as building blocks in various ways, making it a fundamental technique for text data processing that involves sentence structure and changing data over time. Since Google introduced the concept of the transformer algorithm in 2017, it has become a new trend in deep learning algorithms, and language models based on it, such as GPT and BERT, have been continuously introduced [7]. Before the emergence of the transformer algorithm, RNN-based algorithms evolved from serially processing input sequences to processing them in parallel, optimized for parallel computing hardware such as graphics processing units (GPUs), which further accelerated algorithm advancement. The characteristic of a GPU compared to a central processing unit (CPU) is that it processes data in parallel. GPUs are primarily used in computers to process graphics, facilitating the quick rendering of images and animations, especially in video games. However, the use of GPUs has been extended beyond graphics. They are also used in various fields, such as scientific computing, AI training, and virtual reality, owing to their ability to process large amounts of complex data quickly. For example, in the case of AI, training on large amounts of data can be significantly accelerated using GPUs.

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**Fig. 1.** Overview of the transformer architecture.
which is why many researchers have used them in AI research.

**USING ChatGPT IN SCIENTIFIC WRITING**

Utilizing ChatGPT, an AI chatbot, can greatly assist in writing scientific research papers through automatically generating drafts, summarizing papers, and providing translations [8-14]. In addition, it can write cover letters to send to editors, suggest titles for articles, and summarize the main content of a text to create abstracts [15]. This tool can streamline tasks and facilitate a smooth workflow for scientific writing.

ChatGPT can be used to review and summarize extensive text documents such as academic papers. Utilizing ChatGPT to summarize or condense lengthy papers can be very helpful. In addition, this feature can assist in writing the abstracts of research papers. The model can accept up to 25,000 words as input starting from GPT-4; therefore, summarizing the entire content of most papers should not be a significant challenge, considering that most papers contain approximately 5,000 words [16].

One of the most beneficial applications of ChatGPT is English proofreading. This demonstrates a high level of correction performance and explains the changes made. Hence, ChatGPT can be a useful tool for English proofreading and enhancing the quality of written content.

**UTILIZING ChatGPT FOR CLINICAL RESEARCHERS RELATED TO ANESTHESIOLOGY**

ChatGPT can be used to brainstorm research ideas, allowing users to discover and combine diverse subjects, ultimately leading to innovative research ideas. For example, ChatGPT can be asked to suggest relevant research topics when planning a clinical study related to robot-assisted surgery using remimazolam (Fig. 2). ChatGPT is an asset in various academic and professional settings. Furthermore, it can review and summarize extensive text documents such as academic papers, thereby streamlining the process of condensing content and writing abstracts.

ChatGPT can help create lecture materials and assist in drafting lecture outlines. For example, ChatGPT could efficiently organize the content if you were to request an outline for a lecture on anesthesia management for patients with hypertension, targeting anesthesiologists (Fig. 3). While ChatGPT can be very useful in this regard, more detailed information must be added when creating the actual lecture material.

Moreover, ChatGPT demonstrates excellent performance in writing R or Python code. Error messages are occasionally encountered when running R or Python code. Persistent errors that are difficult to resolve may occur even after multiple attempts. In such cases, ChatGPT can be a valuable resource for correcting and improving the code.

**THE ROLE OF ChatGPT IN FUTURE CLINICAL FIELDS**

ChatGPT not only helps with scientific writing and clinical research, but has recently been used to prepare regular discharge summaries and even directly generate medical records [17]. ChatGPT is believed to assist in automatically creating medical records by organizing patient test results generated in hospitals and documenting the patient’s condition. ChatGPT may also contribute to future clinical decision-making based on this capability. However, the reliability of the information generated by ChatGPT needs to be further ensured before this becomes possible, because of the nature of medical practice dealing with lives.

**LIMITATIONS OF ChatGPT AND ETHICAL CONCERNS**

ChatGPT has many problems despite its differentiated performance compared to previous language models. The first is the AI hallucination phenomenon, in which the AI talks about things that are untrue as if they are true, which can make the generated information less reliable. The most critical limitation that makes it difficult to use ChatGPT in clinical research is the difficulty in finding references for the information generated by ChatGPT, and the fact that the references provided are often inaccurate. Additionally, the training data of ChatGPT 3.5 only extends up to June 2021, suggesting a lack of information on subsequent developments. However, this problem can be resolved by expanding the training dataset. Additionally, it can provide biased information based on training data. Reinforcing existing stereotypes is a risk, as evidenced by Google’s initial introduction of the AI Interviews, which was later discontinued because of its tendency to be more blatantly discriminatory based on race and gender than humans. This indicates that AI can perpetuate existing discriminatory structures. Moreover, AI has no criteria for judging right or wrong when used
for criminal purposes, thereby raising ethical concerns. These are the fundamental limitations of generative AI. Human workers were employed to label answers for GPT 3.5 to calibrate the model to avoid politically sensitive responses. However, despite these efforts, ethical issues associated with AI continue to arise.

Concerning the authorship of text generated by ChatGPT, a question arises: Can ChatGPT be considered an author, given that it created the content? Alternatively, should the user who directs the GPT to generate the text retain the copyright? This inquiry is relevant for discussing the implications of AI-generated content in scientific writing. In recent years, ChatGPT has been recognized as a contributing author to scientific research. Notably, several articles listing ChatGPT as authors have been registered and are now accessible through the Web of Science Core Collection [18-20].
I’d like to give a lecture on anesthesia management for hypertensive patients to anesthesiologists, so could you make a lecture about it?

**Title: Anesthesia Management for Hypertensive Patients: Strategies and Challenges**

**Introduction:**
1. Briefly introduce the topic and its relevance to anesthesiologists.
2. Explain the prevalence of hypertension and its potential complications during anesthesia.
3. Outline the objectives of the lecture: to review the pathophysiology of hypertension, discuss preoperative assessment and optimization, and explore anesthetic techniques for hypertensive patients.

**I. Pathophysiology of Hypertension:**
A. Definition and classification of hypertension
B. Factors contributing to hypertension (renal, vascular, and neural mechanisms)
C. Complications of hypertension
   1. Target organ damage (heart, brain, kidneys, and eyes)
   2. Increased risk of perioperative cardiovascular events

**II. Preoperative Assessment and Optimization:**
A. Thorough patient history and physical examination
B. Laboratory and diagnostic tests (e.g., blood tests, ECG, echocardiography)
C. Assessing blood pressure control
   1. Optimal preoperative blood pressure targets
   2. Antihypertensive medications: adjusting or continuing therapy
   D. Risk stratification and determining the need for further cardiac evaluation
   E. Patient education and addressing patient concerns

**III. Anesthetic Management:**
A. Choice of anesthesia
   1. General anesthesia
      a. Induction agents and their effects on hypertensive patients
      b. Neuromuscular blocking agents
      c. Maintenance and emergence considerations
   2. Regional anesthesia
      a. Advantages and disadvantages
      b. Techniques: spinal, epidural, and peripheral nerve blocks
      B. Intraoperative hemodynamic management
   3. Monitoring: arterial line, central venous pressure, and other advanced monitoring techniques
   4. Management of blood pressure fluctuations
      a. Hypotension: vasopressors and fluid therapy
      b. Hypertension: short-acting antihypertensive medications
      C. Postoperative care and pain management
   5. Pain control strategies: multimodal analgesia and regional techniques
   6. Monitoring for postoperative complications
   7. Blood pressure management in the postoperative period

**Conclusions:**
1. Recap the key points of the lecture.
2. Emphasize the importance of a comprehensive approach to managing hypertensive patients undergoing anesthesia.
3. Encourage anesthesiologists to stay updated on new developments and guidelines in the field to optimize patient outcomes.

Of course, this is a suggested outline for the lecture, and you can adjust the topics and depth of content based on the audience’s expertise and interests. Be sure to include relevant clinical case examples, recent research, and guidelines to illustrate your points and promote discussion among your peers.

**Fig. 3.** Example of developing a lecture outline using ChatGPT. GPT: generative pre-trained transformer.
However, at present, most traditional journals, along with most others, do not recognize AI systems such as ChatGPT as authors. Additionally, many traditional journals recommend that researchers refrain from using ChatGPT for scientific writing due to a lack of guidelines regarding plagiarism and originality of content generated by ChatGPT. The Editor-in-Chief of Science addressed this topic in an editorial emphasizing the importance of human authorship in scholarly publications [21]. In brief, the fundamental principle remains that the author of an academic paper should be a human, while AI systems such as ChatGPT can serve as invaluable tools for researchers to generate hypotheses, design experiments, and draw inspiration from results [21]. The ownership of the paper should belong to humans, as they are ultimately those utilizing AI systems such as ChatGPT and deriving the outcomes. ChatGPT is acknowledged as a tool; however, its authorship has not yet been recognized. The debate on AI authorship has elicited a variety of opinions. However, the editor suggests a more conservative approach to the authorship of ChatGPT, as loosening regulations is much easier than reversing them. Consequently, they suggest a high likelihood of changes in policies regarding AI authorship as technology advances.

Most journals do not recognize ChatGPT as an author. However, there seems to be no consensus among journals on obtaining ChatGPT’s help in writing papers. Several journals have taken an open stance, requiring that the use of AI be mentioned in the acknowledgments or methods sections, whereas others outright prohibit its use [22,23].

CONCLUSION

In summary, the key points discussed reveal that generative AI, such as ChatGPT, is most effective when users ask precise questions because the response depends on question refinement. Notably, the original content should still be created by humans, and ChatGPT should only be used to provide an overall direction and not as a source of absolute truth. ChatGPT, developed using Google’s 2017 transformer model, can be a helpful tool in various aspects of work, such as summarizing lengthy articles or assisting in paper reviews. However, its application in clinical research remains limited, and direct inclusion of the generated text in published papers is not advised. The ultimate goal of using ChatGPT is to facilitate brainstorming and idea generation, rather than to seek definitive answers. Individuals should tailor their approach when using ChatGPT to maximize their work efficiency. AI can be beneficial for tasks such as reviewing long papers, writing R code, and proofreading English. ChatGPT is not perfect when used efficiently; however, it saves time and allows individuals to focus on more productive tasks. This makes ChatGPT a valuable tool for enhancing productivity and optimizing various aspects of work.

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None.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS


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INTRODUCTION

Various hypnotics are used for general anesthesia in many surgeries including laparoscopic surgery. It is very important for an anesthesiologist to select the most ideal drug considering the patient and surgical characteristics. In particular, in laparoscopic surgery where pneumoperitoneum occurs, starting and maintaining anesthesia with an intravenous anesthetic showed better advantages than inhalational anesthesia [1]. Propofol is currently the most commonly used intravenous anesthetic. It has a rapid onset of action, a short half-life and is associated with rapid recovery of cognitive

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**Background:** Remimazolam is a novel benzodiazepine with fast onset and short half-life. We compared the effects of remimazolam and propofol on recovery profiles for general anesthesia in patients undergoing laparoscopic cholecystectomy.

**Methods:** We randomly assigned 108 patients to either a remimazolam (n=54) or propofol (n=54) group. Remimazolam and propofol were used for induction and maintenance of anesthesia. Following anesthesia, we recorded the time until an Aldrete score of 9 was achieved as the primary surrogate marker of complete recovery. The time to reach a Modified Observer’s Assessment of Alertness/Sedation (MOAA/S) score of 2 and the time from the end of anesthesia to eye opening time, recovery time of orientation, time to spontaneous breathing, extubation time, and the time required for analgesics were measured. Heart rate, blood pressure, and bispectral index were assessed before, during, and after pneumoperitoneum.

**Results:** We included 101 patients in the analysis. In the remimazolam group, it took longer to reach an Aldrete score of 9 after the drug infusion ended (P = 0.031). There was no difference in the time to reach MOAA/S 2 between the two groups. The time to eye opening, recovery time of orientation, and time required for analgesics were longer and heart rate was higher in the remimazolam group. Neither blood pressure nor extubation time differed between groups.

**Conclusions:** Remimazolam and propofol provided safe induction and maintenance of anesthesia in patients undergoing laparoscopic cholecystectomy. The recovery time from anesthesia was longer than that with propofol. Fewer hemodynamic changes were observed with remimazolam, but further studies are needed.

**Keywords:** Benzodiazepine; Cholecystectomy; Laparoscopy; Propofol; Remifentanil.
ability [2-4]. However, propofol can lead to injection pain, propofol infusion syndrome, and hemodynamic and respiratory depression [4,5]. Midazolam is associated with relatively less cardiovascular and respiratory depression than propofol [6]. However, it has a slower onset of action and active metabolites can cause prolonged recovery time. Therefore, it is relatively difficult to control the depth of anesthesia with midazolam [7]. Therefore, there is a need for new anesthetic drugs with high efficacy and fewer side effects while providing stable and controllable anesthesia.

Remimazolam, a newly developed anesthetic, is an ultra-short-acting intravenous benzodiazepine with a high affinity for the benzodiazepine binding site of the γ-Aminobutyric acid type A (GABA-A) receptor. It is rapidly hydrolyzed to an inactive metabolite by non-specific tissue esterases. These properties allow for faster and more predictable recovery after sedation with remimazolam compared to other benzodiazepines, such as midazolam [8]. Moreover, it has the hemodynamically stable properties of benzodiazepines and the rapid onset-offset properties of propofol [8-12]. Since remimazolam was recently approved as a general anesthetic, many studies have demonstrated the efficacy and safety of remimazolam during induction and maintenance of general anesthesia [13-17]. However, recovery after the end of general anesthesia is important for the patient's prognosis. There have been few studies on recovery from anesthesia after using remimazolam for general anesthesia induction and maintenance. Therefore, this study aimed to compare recovery profiles after intravenous anesthesia with remimazolam and propofol in patients undergoing laparoscopic cholecystectomy.

**MATERIALS AND METHODS**

This prospective, single-center, randomized, single-blind, controlled study was approved by the Institutional Review Board of our hospital (DAUHIB-21-211) and registered at the Korea Clinical Research Information Service (permit number: 0006702). The trial was conducted at the our hospital between November 2021 and March 2022, in accordance with the Declaration of Helsinki. All patients provided informed consent before enrollment to the study.

The inclusion criteria were as follows: age 20–80 years, American Society of Anesthesiologists physical status I–III, scheduled for elective laparoscopic cholecystectomy, and provided informed consent. The exclusion criteria were as follows: ASA physical status IV or V, body mass index ≥ 35 kg/m², expected difficult airway intubation, history of surgery, and refusal to provide informed consent.

Patients were randomly distributed into a remimazolam or propofol group using computer-generated randomization prior to surgery. An anesthesiologist explained the purpose of the study and the possible side effects to the patient and obtained informed consent for the induction of anesthesia before surgery.

Routine monitoring, including electrocardiogram, non-invasive blood pressure (BP), pulse oxygen saturation, and bispectral index (BIS), were performed upon the arrival of each patient in the operating room. During this time, to ensure that the patient is blinded to the procedure, the arm that was to be injected with the drug during anesthesia induction was abducted by 90°, and a shield was temporarily placed to cover the arm, using a surgical cloth.

Before the induction of general anesthesia, oxygen (flow rate, 10 L/min) was administered through a mask for 2 min to all patients in the supine position. After preoxygenation, target-controlled infusion (TCI) of remifentanil with an effect-site concentration (Ce) of 4.0 ng/ml was initiated. Moreover, remimazolam was simultaneously administered to induce anesthesia with a bolus of 0.2 mg/kg slowly within 1 min [13,14]. In the control group, 2.0 mg/kg propofol was administered as a bolus. Pain was assessed during drug injection. The time to loss of consciousness (LOC) was recorded. LOC was defined as a Modified Observer's Assessment of Alertness/Sedation score < 2 [11]. After confirming LOC, neuromuscular blockade was performed with 0.8 mg/kg rocuronium. An i-gel (Intersurgical) was inserted when the train-of-four (TOF) count was zero. At the same time, the shield used for blinding was removed and a drug infusion line using a syringe pump was connected to the patient to maintain anesthesia.

The respiratory settings were as follows: inspired fresh gas at 3 L/min through the circle anesthesia breathing system, inspired tidal volume preset at 9 ml/kg, and inspiratory/expiratory ratio of 1:2. The respiratory rate was adjusted to maintain the end-tidal carbon dioxide values at 30–40 cmH₂O.

Initially, Remimazolam at 1.5 mg/kg/h and propofol at 8 mg/kg/h were administered to each group to maintain anesthesia. The Ce of remifentanil was 2.5 ng/ml. During surgery, systolic BP (SBP), diastolic BP (DBP), heart rate (HR), and BIS were monitored and recorded in both groups at baseline (immediately after entering the operating room), before intubation, 1 min after intubation, 5 min before CO₂ pneumo-
peritoneum, 5 min after the start of CO₂ pneumoperitoneum, 5 min before pneumoperitoneum removal, and 5 min after pneumoperitoneum removal (T0-T6, respectively).

Doses were adjusted according to changes in hemodynamics or BIS. When BIS was > 60 or < 40, remimazolam and propofol were adjusted within the range of 1-2 mg/kg/h and 4-12 mg/kg/h, respectively. When the SBP decreased by 20% of that initially and was maintained for 1 min, the Ce of remifentanil was reduced by 0.5 ng/ml. However, if the SBP increased by 20% of that initially and was maintained for 1 min, the Ce of remifentanil was increased by 0.5 ng/ml. Phenylephrine (intravenous [IV], 100 μg) was administered if hypotension was detected (SBP < 90 mmHg, despite reducing remifentanil). Atropine (0.5 mg IV) was administered when bradycardia (HR < 50) occurred. The frequency of vasopressor or atropine administration was recorded.

All drug infusions were terminated at the end of surgery. Sugammadex was administered to counteract the effects of rocuronium as follows: if the TOF count was 0, 4 mg/kg sugammadex was administered; if the TOF count was 1-4, 2 mg/kg sugammadex was administered.

After terminating drug infusion, recovery from anesthesia was evaluated by checking the time to eye opening, spontaneous breathing, extubation, orientation recovery (Orientation check asks the patient for their name), requirement for analgesics in the recovery room, and the time to complete recovery (Aldrete score of 9). A modified Brice interview [18] was conducted to evaluate awareness during the operation.

The primary outcome was complete recovery. The secondary outcomes were (i) the time to LOC (time to MOAA/S < 2); (ii) hemodynamic changes during maintenance of anesthesia; (iii) time to opening eyes, spontaneous breathing, and extubation after discontinuation of drug infusion; and (iv) time to recovery of orientation.

In a pilot study of 40 patients (20 patients in each group), the time to an Aldrete score of 9 was 42.5 ± 9.8 min in the remimazolam group and 37.1 ± 9.0 min in the propofol group. A sample size of 49 patients in each group was calculated with a type I error of 0.05 and power of 80%. Considering a 10% loss to follow-up, 54 patients were required per group.

Statistical analyses were performed using SPSS Statistics Version 18.0 (IBM Co.). Data are expressed as mean ± standard deviation and number of patients (%). Student’s t-test was used to analyze continuous data and the chi-squared or Fisher’s exact test were used to analyze categorical data. Statistical significance was set at P < 0.05.

RESULTS

We recruited 111 patients to the study, but 3 patients refused to participate. Thus, 108 patients were included in this study. However, seven patients were excluded from the analysis: one patient in the remimazolam group and three in the propofol group because laparoscopic cholecystectomy was changed to open cholecystectomy during surgery, and two patients in the remimazolam group and one patient in the propofol group underwent endotracheal tube intubation. Finally, the data of 101 patients were evaluated (Fig. 1).

There were no differences in demographic or surgical data between groups (Table 1). The anesthesia induction and recovery times are presented in Table 2. Complete recovery time (22.72 ± 7.06 vs. 25.75 ± 6.84 min, P = 0.031), as assessed by Aldrete’s score, was longer in the remimazolam group than in the propofol group. There was no difference in the LOC time between groups. The time to eye opening, recovery orientation, and requirement for analgesics in the recovery room were longer in the remimazolam group than in the propofol group. The time to return to spontaneous breathing and extubation time were not significantly different between groups.

Injection pain was significantly higher during drug injection in the propofol group than in the remimazolam group (98% vs. 1.9%, P < 0.001). HR was significantly higher in the remimazolam group than in the propofol group at T1 (73.5 ± 13.4 vs. 82.6 ± 14.9 bpm, P = 0.002), T2 (71.9 ± 14.3 vs. 80.6 ± 15.8 bpm, P = 0.005), T4 (77.5 ± 13.2 vs. 83.1 ± 14.7 bpm, P = 0.048), T5 (76.9 ± 12.4 vs. 83.6 ± 15.1 bpm, P = 0.016), and T6 (73.9 ± 11.7 vs. 80.1 ± 12.2 bpm, P = 0.010) (Fig. 2). Moreover, there was no difference in the frequency of atropine administered between groups (Table 3). There were no significant differences between groups regarding changes in SBP or DBP (Fig. 2). However, the frequency of administration of vasopressor was lower in the remimazolam group than in the propofol group (Table 3). The BIS was higher in the remimazolam group than in the propofol group at all measured timepoints (P < 0.001) (Fig. 3). No patient developed awareness while maintaining anesthesia in either group.

DISCUSSION

Remimazolam is a novel, ultra-short-acting benzodiazepine. It acts mainly on GABA-A receptors and is advantageous due to fast induction, fast recovery, and hemodynam-
ic stability. It is currently being used for several clinical pro-
cedural sedation and anesthetic procedures, such as induc-
tion and maintenance of general anesthesia, hysteroscopy,
endoscopy, and bronchoscopy [16, 17]. However, studies on
its clinical application in laparoscopic surgery are lacking.
This study compared remimazolam and propofol, focusing
on the recovery profile after general anesthesia, and also in-
vestigated the effects of anesthesia induction and intraoper-
ative hemodynamic changes in patients undergoing laparo-
scopic cholecystectomy.

As of now, there are no TCI models integrated into com-
mercially available infusion pumps for administering remim-
azolam. Therefore, we anesthetized participants by adminis-
tering a single bolus of remimazolam in the same manner as
propofol during anesthesia induction [14]. The average time
to LOC after bolus administration of remimazolam was simi-
various procedures, including general anesthesia, laparoscopic surgery, and dental anesthesia. Propofol is a commonly administered intravenous anesthetic with rapid induction and recovery. However, it decreases systemic BP due to a reduced cardiac output [4].

In this study, SBP and DBP were not significantly different between groups. However, the frequency of vasopressor use was higher in the propofol group than in the remimazolam group. Therefore, the BP increased by vasopressor administration may be reflected at each timepoint in the propofol group, although without statistical significance. Although

Patients undergoing laparoscopic surgery experience hemodynamic changes during pneumoperitoneum. Intravenous anesthesia is advantageous due to hemodynamic stability and faster recovery than with inhalation anesthesia in laparoscopic surgery. Propofol is a commonly administered intravenous anesthetic with rapid induction and recovery. However, it decreases systemic BP due to a reduced cardiac output [4].

In this study, SBP and DBP were not significantly different between groups. However, the frequency of vasopressor use was higher in the propofol group than in the remimazolam group. Therefore, the BP increased by vasopressor administration may be reflected at each timepoint in the propofol group, although without statistical significance. Although

![Fig. 2. Changes in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR). Baseline (T0), before intubation (T1), 1 min after intubation (T2), 5 min before CO2 pneumoperitoneum (T3), 5 min after the start of CO2 pneumoperitoneum (T4), 5 min before pneumoperitoneum removal (T5), and 5 min after pneumoperitoneum removal (T6). *P < 0.05 indicates a significant difference from the propofol group.](image-url)

**Table 2. Induction and Recovery Times**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Propofol (n = 50)</th>
<th>Remimazolam (n = 51)</th>
<th>P value</th>
<th>Median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss of consciousness (s)</td>
<td>33.4 ± 6.3</td>
<td>35.8 ± 9.6</td>
<td>0.139</td>
<td>2,404 (–0.795 to 5.603)</td>
</tr>
<tr>
<td>Eyes open (min)</td>
<td>8.9 ± 3.6</td>
<td>10.6 ± 3.7</td>
<td>0.018</td>
<td>1,748 (0.307 to 3.189)</td>
</tr>
<tr>
<td>Spontaneous breathing (min)</td>
<td>9.4 ± 3.3</td>
<td>9.8 ± 3.1</td>
<td>0.524</td>
<td>0.405 (–0.852 to 1.661)</td>
</tr>
<tr>
<td>Extubation (min)</td>
<td>9.7 ± 3.3</td>
<td>10.1 ± 3.2</td>
<td>0.585</td>
<td>0.359 (–0.941 to 1.659)</td>
</tr>
<tr>
<td>Orientation recovery (min)</td>
<td>14.6 ± 5.3</td>
<td>19.5 ± 5.7</td>
<td>&lt; 0.001</td>
<td>4,811 (2,621 to 7,001)</td>
</tr>
<tr>
<td>Analgesic request (min)</td>
<td>19.2 ± 6.1</td>
<td>22.8 ± 7.4</td>
<td>0.028</td>
<td>3.56 (0.872 to 6.248)</td>
</tr>
<tr>
<td>Complete recovery (min)</td>
<td>22.7 ± 7.1</td>
<td>25.7 ± 6.8</td>
<td>0.031</td>
<td>3.025 (0.282 to 5.768)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. CI: confidence interval.

**Table 3. Medications during Maintenance of General Anesthesia**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Propofol (n = 50)</th>
<th>Remimazolam (n = 51)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total propofol (mg/kg)</td>
<td>5.3 ± 1.7</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total remimazolam (mg/kg)</td>
<td>-</td>
<td>1.1 ± 0.3</td>
<td>-</td>
</tr>
<tr>
<td>Total remifentanil (µg/kg)</td>
<td>5.3 ± 1.5</td>
<td>6.0 ± 2.1</td>
<td>0.141</td>
</tr>
<tr>
<td>Phenylephrine (n)</td>
<td>18 (36.0)</td>
<td>9 (17.6)</td>
<td>0.045</td>
</tr>
<tr>
<td>Atropine (n)</td>
<td>9 (18.0)</td>
<td>3 (5.9)</td>
<td>0.072</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number (%).
HR was higher in the remimazolam group, each value was within the clinically normal range. In our study, there was no case of additional administration of atropine for bradycardia after phenylephrine bolus administration. However, phenylephrine is a pure vasopressor that only has activity on the alpha-adrenergic receptors. Because it does not have any beta agonist properties to support the cardiac output, activation of the baroreceptor may result in bradycardia.

It is important to monitor the depth of general anesthesia. The BIS is a safe and effective method for monitoring the depth of anesthesia during surgery [19]. Intense anesthesia can cause hemodynamic changes, whereas too-shallow anesthesia risks recall or awareness during anesthesia. Awareness during anesthesia is a serious complication with potential psychological sequelae, such as anxiety and posttraumatic disorders. Thus, the BIS value is generally maintained between 40 and 60 to prevent awareness during general anesthesia [20].

In our study, BIS was higher during induction and maintenance of anesthesia in the remimazolam group than in the propofol group. The BIS of remimazolam was often close to 60 (Fig. 3) and even exceeded 70 in some cases.

A modified Brice interview [18] of patients was conducted within 24 h after the end of anesthesia. No patient in either group developed awareness while maintaining anesthesia.

However, even if there were no patients with intraoperative recall based on the questionnaire, it is possible that sedation was insufficient because the BIS remained high in the remimazolam group. Moreover, to adjust the BIS between 40 and 60, the frequency of dose increase was higher in the remimazolam group, which may have resulted in a longer recovery time.

Therefore, during anesthesia with remimazolam, it is necessary to use supportive indicators as well as BIS to assess the depth of sedation [21].

In the present study, flumazenil was not administered for comparison with propofol after discontinuation of drug infusion. Complete recovery time, eye opening, orientation recovery and analgesic requirement were longer in the remimazolam group than in the propofol group. In a previous study, flumazenil was routinely administered to patients in the remimazolam group immediately after the completion of anesthesia, and the same dose of saline was administered to those in the propofol group. Recovery of consciousness, extubation, and postanesthetic care unit stay times were shorter in the remimazolam group than in the propofol group [13]. Therefore, rapid recovery from anesthesia can be expected by administering flumazenil to patients in the remimazolam group.

This study has limitation. First, for LOC during anesthesia induction, we administered 0.2 mg/kg of remimazolam as a single bolus to all age groups. However, older adults may require a lower dose of anesthetic than younger or middle-aged patients due to the physiological changes associated with aging. Therefore, it is necessary to adjust the dose of remimazolam according to age. An other study has shown that the 95% effective dose of remimazolam bolus required to reach LOC during induction of anesthesia varies with age. The dose of remimazolam for induction of anesthesia was lower in the elderly group ≥ 60 years of age than in the younger group < 60 years [22].

In conclusion, remimazolam provides safe induction and maintenance of anesthesia, and may be an effective alternative to propofol. Patients in the remimazolam group took longer to completely recover from anesthesia. Additionally, remimazolam may provide hemodynamic stability and satisfactory anesthetic effects in patients undergoing laparoscopic cholecystectomy. Nevertheless, large-cohort multicenter studies are warranted to validate the findings.

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CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

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REFERENCES


Clinical Research

Appropriateness of the anxiety subscale of the Hospital Anxiety and Depression Scale for Koreans to measure preoperative anxiety and the effect of preoperative anxiety on postoperative quality of recovery

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Background: The reliability and validity of the anxiety subscale of the Hospital Anxiety and Depression Scale for Koreans (K-HADS-A) has not been studied in Korean surgical patients. This study aimed to validate the usefulness of K-HADS-A for measuring preoperative anxiety in Korean surgical patients. Additionally, the effect of preoperative anxiety on postoperative quality of recovery was evaluated.

Methods: Preoperative anxiety in 126 inpatients with planned elective surgery was measured using the K-HADS-A. The postoperative quality of recovery was measured using the Korean version of the Quality of Recovery-15. The validity and reliability of the K-HADS-A were evaluated. The differences in quality of recovery on the first and seventh day postoperatively were then compared between the anxious and non-anxious groups.

Results: There was a statistical correlation between the K-HADS-A and Anxiety Likert Scale. The goodness-of-fit indices of the structural equation model showed how well the data from the K-HADS-A matched their concept. The Kaiser-Meyer-Olkin value was 0.848, and the P value of Bartlett’s test of sphericity was < 0.001. Cronbach’s alpha was high at 0.872. The K-HADS-A had an acceptable level of validity and reliability. Postoperative quality of recovery was significantly lower in the anxious group (postoperative day 1: t = 2.058, P = 0.042; postoperative day 7: t = 3.430, P = 0.002).

Conclusions: The K-HADS-A is an acceptable tool for appropriately assessing preoperative anxiety in Korean surgical patients. Assessing preoperative anxiety is valuable, because preoperative anxiety affects the postoperative quality of mental and physical recovery.

Keywords: Anesthesia; Hospital Anxiety and Depression Scale for Koreans; Postoperative recovery; Preoperative anxiety; Quality of Recovery-15; Surgery.

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INTRODUCTION

Many patients scheduled for elective surgery under general or regional anesthesia experience anxiety [1]. Anxiety is a fearful concern that a person normally experiences in life. Moreover, preoperative anxiety is defined as discomfort and tension before surgery about the unknown, such as disease, hospital admission, anesthesia, and surgery [2,3]. This is a normal reaction to potential danger, but it also causes autonomic and somatic symptoms also appear [4]. It eventually increases blood pressure, heart rate, and myocardial workload and affects perioperative outcomes. This process is explained as a pathophysiological response in which the activation of the autonomic system is due to anxiety [5].

Preoperative anxiety affects the intensity of postoperative pain and the required amount of intraoperative anesthetic agent. In addition, it also increases postoperative morbidity and mortality in certain types of surgery [2,6-9]. Anxiety can be measured through several methods. Among the evaluation tools for evaluating anxiety, the State-Trait Anxiety Inventory, Beck Anxiety Inventory, Zung’s Self-rating Anxiety Scale, and Hospital Anxiety-Depression Scale (HADS) are representative self-report tests. HADS consists of two sub-scales of anxiety and depression [10]. Oh et al. [11] developed the Korean version of HADS-A (K-HADS-A) and proved its validity for screening anxiety disorders. The K-HADS-A enables easy and rapid measurement of anxiety even by primary care physicians and non-psychiatrists. In addition, K-HADS-A is widely used to measure preoperative anxiety as it does not require specific skills.

Assessment of postoperative recovery quality has become an important research aspect that indicates patient perceptions of postoperative outcomes. Previous studies measured postoperative pain, analgesic requirements, hospital stay, morbidity, and mortality as indicators of postoperative recovery [8,12-14]. However, these indicators do not fully represent the postoperative recovery quality. The postoperative quality of recovery score (QoR) is a widely used questionnaire to evaluate postoperative recovery quality. It has been used to self-evaluate the postoperative recovery quality among patients and has a clinically practical value [15,16]. The QoR was recently translated into a Korean version (QoR-40K, 15K), and its reliability and validity were evaluated [17,18].

Although K-HADS-A was primarily developed to screen patients with anxiety disorders, no studies have verified its reliability and validity in measuring the preoperative anxiety of Korean surgical patients [19]. Therefore, this study primarily aimed to validate the appropriateness of K-HADS-A for measuring preoperative anxiety in Korean surgical patients. In addition, the effect of preoperative anxiety on postoperative quality of recovery was evaluated using the objective and integrated QoR-15K rather than a single indicator.

MATERIALS AND METHODS

Study participants

The Institutional Review Board of Jeonbuk National University Hospital approved this prospective study (approval no. 2020-01-036-001). All procedures involving human participants were conducted in accordance with the ethical standards of the institutional and national research committee and with the 1964 Declaration on Helsinki and its later amendments. Written informed consent was obtained from all participating patients.

Inpatients with planned elective surgery were enrolled. The inclusion criteria were Korean reading and writing ability and hospitalization for 2 nights before surgery and 2 days after surgery. The exclusion criteria were as follows: (1) cognitive impairment, (2) age < 18 year or > 74 year, (3) American Society of Anesthesiologists physical status IV or above, (4) a history of alcohol or any other substance abuse, (5) patients with anxiety disorders, (6) postoperative sedation, (7) patients who cannot provide cognitive function assessments after specific surgeries, and (8) refusal to participate in the study.

Evaluation of preoperative anxiety using K-HADS-A

Preoperative anxiety was measured using K-HADS-A. The study authors evaluated the K-HADS-A score after explaining about surgery and anesthesia on the day before surgery. The anxiety subscale consisted of 7 items, with possible scores ranging from 0 to 21 (Appendix 1) [11]. The cut-off score for distinguishing between the anxious and non-anxious groups was set as 8 based on previous studies [10,11]. In addition, the 5-point Anxiety Likert Scale (ALS) was also used to measure preoperative anxiety. The ALS presents statements such as "I often feel anxious", and respondents choose one of the following options: "Strongly Agree," "Agree," "Neutral," "Disagree," or "Strongly Disagree." The score of the respondent’s selected answers for each statement is interpreted as a score representing the degree of
anxiety. In general, a low score indicates a low level of anxiety, while a high score indicates a high level of anxiety. The ALS is useful for measuring anxiety symptoms and is widely used for measuring everyday anxiety symptoms [20]. Additionally, this scale is also used to track and evaluate the progression of anxiety symptoms in clinical research. Therefore, the ALS was selected as a standard control group to measure criterion validity.

Subgroup analyses were also performed to measure preoperative anxiety using K-HADS-A, and variables were classified into two groups. The variables are sex, age, education, previous experience with anesthesia, American Society of Anesthesiologists physical status, and religion. Age was classified at a cut-off of 45 year, and educational background was classified based on high school graduation.

**Validity and reliability for K-HADS-A**

The validity of the K-HADS-A was assessed to determine the accuracy of its concepts. Validity was verified using construct validity, goodness-of-fit indices of the structural equation model, and factor analysis. Construct validity was assessed using convergent validity, and correlations between the K-HADS-A and ALS were compared. The goodness-of-fit indices of the structural equation model assess how well the data from the K-HADS-A matches its concepts. The goodness-of-fit indices of the structural equation model were evaluated by absolute fit index, incremental fit index (IFI), and parsimonious fit index. The absolute fit was measured using the Root Mean Square of Error Approximation, Standardized Root Mean Square Residual (SRMR), and Goodness-of-fit index [21]. The IFI was calculated using the comparative fit index (CFI), Tucker-Lewis index (TLI), and normed fit index [22]. Lastly, the parsimonious fit was examined using the chi-squared/degree of freedom, which should be less than five.

Furthermore, the assessment of factor analysis was confirmed by the Kaiser-Meyer-Olkin (KMO) value and Bartlett’s test of sphericity. A KMO value of 0.6 or higher is considered acceptable, or 0.7 or higher if strictly applied. Bartlett’s test for sphericity indicates that the factorization model is appropriate if the P value is less than 0.05, which is the level of significance.

Reliability was used as an indicator of the consistency of the K-HADS-A. Reliability was assessed by internal consistency measured using Cronbach’s alpha. Internal consistency coefficients were interpreted as follows: 0.9 or more, excellent; 0.8–0.9, very good; and 0.7–0.8, adequate [23].

**Relationship between preoperative anxiety and postoperative quality of recovery**

Two groups were classified based on the K-HADS-A score, and the postoperative quality of recovery, as measured using the Korean version of the Quality of Recovery-15 (QoR-15K) [17], was compared. The QoR-15K includes 15 items in 5 subscales: physical comfort, physical independence, emotional state, psychological support, and pain. Psychological support and emotional state represent mental well-being. Physical independence, physical comfort, and pain represented physical well-being. The score for QoR-15K items ranges from 0 to 10, and the global QoR-15K score is the sum of all item scores. The scores range from 0 to 150. The higher the score, the higher the quality of recovery. In addition, the 100-mm Visual Analog Scale for Recovery (VAS-R) was also used to measure postoperative recovery quality. The VAS-R is a subjective rating scale commonly used to assess an individual’s perception of their recovery status. It is a straight line with endpoints representing extreme states, such as "Complete Recovery" and "No Recovery." Participants are asked to place a mark on the line to indicate their current perception of their recovery status. Participants’ responses on the VAS for recovery can be measured by measuring the distance (in millimeters) from the "No Recovery" endpoint to the mark they placed on the line. This measurement provides a numerical value representing their perceived level of recovery. The QoR-15K and VAS-R were evaluated on the first and seventh day postoperatively by the study authors.

**Intraoperative anesthesia protocol**

A standardized anesthetic protocol was established in this study. There were no interventions or pharmacological premedications such as sedatives aimed at decreasing anxiety levels. Noninvasive blood pressure, temperature, electrocardiogram, pulse oximetry, and bispectral index (BIS) were monitored during surgery. BIS value was maintained between 40 and 60. Volatile anesthetics (sevoflurane) and opioids (remifentanil) were chosen to maintain general anesthesia.

**Sample size calculation and statistical analysis**

When validating a questionnaire, the sample size is typi-
cally set to 10–20 times the total number of items [17]. Given that the K-HADS-A had seven items, we multiplied that by 15 and determined that the required sample size was 105 patients. Considering a dropout rate, the total sample size was determined to be 126.

All descriptive data were expressed as the number of patients or as the mean ± standard deviation (SD). First, the measurement model was assessed to evaluate the reliability and validity of the measurement scales. Confirmatory factor analysis was performed to examine the fit between the observed variables and their respective latent constructs. Model fit indices, including the chi-square test, CFI, TLI, Root Mean Square Error of Approximation, and SRMR, were examined to assess the goodness-of-fit of the measurement model. Next, associations were measured using Spearman’s correlation coefficient. Continuous variables of the QoR-15K were analyzed using an independent sample t-test after the normality test. All statistical analyses were performed using IBM AMOS 23.0. (International Business Machines Co.), and IBM SPSS Statistics Version 27.0 (IBM Co.). A P value of less than 0.05 was considered statistically significant.

RESULTS

Among the 126 patients enrolled, 9 patients were excluded due to canceled surgery (n = 1) and loss to follow-up (n = 8); thus, 117 patients were included and completed the questionnaire. The Consolidated Standards for Reporting of Trials flow diagram is presented in Fig. 1. The completion rate of the questionnaire was 92.9%. Based on a cutoff of preoperative K-HADS-A score of 8, 91 and 26 patients were classified into the non-anxious and anxious groups, respectively. Therefore, the incidence of preoperative anxiety in the present study was 22.2%. The mean K-HADS-A scores in the

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**Fig. 1.** CONSORT flow diagram. CONSORT: Consolidated Standards for Reporting of Trials, QoR-15K: Korean version of the Quality of Recovery-15.
non-anxious and anxious groups were 3.89 ± 2.25 and 9.46 ± 2.06 (P < 0.001). The study population included a broad range of patients and surgical procedures. However, demographic data showed no significant between-group differences (Table 1).

Validity and reliability for K-HADS-A

For the convergent validity of the K-HADS-A, we compared K-HADS-A and ALS. The K-HADS-A showed a significant positive correlation with ALS (r = 0.562, P < 0.001). The goodness-of-fit indices of the structural equation model (Fig. 2) were used to evaluate how well the data from the K-HADS-A matched the model. The goodness-of-fit indices are described in Table 2. Moreover, we checked the assessment of confirmatory factor analysis to take the measure of sampling adequacy. The KMO value was 0.848, and the P value of Bartlett’s test of sphericity was < 0.001 (approximate chi-square = 368.76, degree of freedom = 21).

With respect to the reliability of the K-HADS-A, Cronbach’s alpha was high at 0.872, exceeding the recommended reliable value of > 0.7 [23].

Relationship between preoperative anxiety and quality of recovery

Pearson’s correlation analysis to check the correlation between the QoR-15K and VAS-R showed that the global QoR-15K score on a postoperative day (POD) 1 had a significant positive correlation with VAS-R on POD1 (r = 0.468, P < 0.001). In addition, the global QoR-15K score on POD7 showed a significant positive correlation with the VAS-R on POD7 (r = 0.574, P < 0.001).

There were significant between-group differences in the global QoR-15K (t = 2.058, P = 0.042), emotional state (t =

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Table 1. Clinicodemographic Patient Characteristics by Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-anxious group (n = 91)</th>
<th>Anxious group (n = 26)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>40.53 ± 9.61</td>
<td>37.69 ± 9.72</td>
<td>0.188</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>35/56</td>
<td>6/20</td>
<td>0.147</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.59 ± 12.66</td>
<td>67.39 ± 17.36</td>
<td>0.560</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.80 ± 9.44</td>
<td>162.29 ± 8.15</td>
<td>0.799</td>
</tr>
<tr>
<td>ASA PS classification (1/2/3)</td>
<td>28/61/2</td>
<td>8/17/1</td>
<td>0.895</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General surgery</td>
<td>30</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Gynecologic</td>
<td>39</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Orthopedic</td>
<td>20</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Duration of anesthesia (min)</td>
<td>105.83 ± 39.33</td>
<td>105.92 ± 44.23</td>
<td>0.992</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>72.22 ± 38.09</td>
<td>71.27 ± 39.11</td>
<td>0.911</td>
</tr>
<tr>
<td>PACU stay (min)</td>
<td>54.48 ± 13.56</td>
<td>52.92 ± 14.97</td>
<td>0.616</td>
</tr>
<tr>
<td>Duration of admission (days)</td>
<td>5.66 ± 2.06</td>
<td>5.50 ± 1.56</td>
<td>0.722</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number only. ASA PS: American Society of Anesthesiologists physical status, PACU: post-anesthesia care unit.

---
2.331, P = 0.021), and mental well-being (t = 2.396, P = 0.018) scores on POD1. There were significant between-group differences in the global QoR-15K (t = 3.430, P = 0.002), emotional state (t = 3.566, P = 0.001), physical comfort (t = 3.079, P = 0.004), pain (t = 3.308, P = 0.001), physical well-being (t = 3.247, P = 0.003), and mental well-being (t = 3.272, P = 0.003) scores on POD7. Quality of recovery on POD1 and POD7 was also significantly different between the two groups (POD1: t = 2.058, P = 0.042; POD7: t = 3.430, P = 0.002). Further, it was significantly lower in the anxious group than in the non-anxious group. The differences in the postoperative quality of recovery between the two groups are presented in Table 3.

### Influencing factors of preoperative anxiety

In previous studies, sex, age, education, experience of anesthesia, American Society of Anesthesiologists physical status classification, and religion were confirmed to influence preoperative anxiety [1]. Subgroup analyses in the current study showed that preoperative anxiety was significantly different according to sex and age. Female patients and patients aged < 45 year felt more anxious in the preoperative period. Meanwhile, there was no significant difference in preoperative anxiety in the groups classified by education, previous experience with anesthesia, American Society of Anesthesiologists physical status classification, and religion (Table 4).

### Table 2. Fit Indices of the Structural Equation Model for K-HADS-A

<table>
<thead>
<tr>
<th>Index</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>χ²</td>
<td>48,688</td>
</tr>
<tr>
<td>df</td>
<td>14</td>
</tr>
<tr>
<td>χ²/df</td>
<td>3.48</td>
</tr>
<tr>
<td>RMSEA (90% CI)</td>
<td>0.146 (0.103, 0.192)</td>
</tr>
<tr>
<td>SRMR</td>
<td>0.0614</td>
</tr>
<tr>
<td>GFI</td>
<td>0.894</td>
</tr>
<tr>
<td>IFI</td>
<td>0.905</td>
</tr>
<tr>
<td>CFI</td>
<td>0.903</td>
</tr>
<tr>
<td>TLI</td>
<td>0.855</td>
</tr>
<tr>
<td>NFI</td>
<td>0.872</td>
</tr>
</tbody>
</table>

K-HADS-A: the anxiety subscale of the Hospital Anxiety and Depression Scale for Koreans, χ²: Chi-square, df: degree of freedom, χ²/df: the ratio of chi-square to degrees of freedom, RMSEA: Root Mean Square of Error Approximation, CI: confidence interval, SRMR: Standardized Root Mean Square Residual, GFI: Goodness-of-fit index, IFI: incremental fit index, CFI: comparative fit index, TLI: Tucker-Lewis index, NFI: normed fit index. χ² statistic for K-HADS-A is significant at P < 0.001.

### Table 3. Differences in Postoperative Quality of Recovery Between the Non-anxious and Anxious Groups

<table>
<thead>
<tr>
<th>QoR-15K</th>
<th>Non-anxious group (n = 91)</th>
<th>Anxious group* (n = 26)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POD 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global QoR-15K score</td>
<td>108.85 ± 26.54</td>
<td>96.77 ± 25.88</td>
<td>0.042</td>
</tr>
<tr>
<td>Physical comfort</td>
<td>36.46 ± 11.13</td>
<td>32.85 ± 9.40</td>
<td>0.134</td>
</tr>
<tr>
<td>Emotional state</td>
<td>31.43 ± 8.35</td>
<td>26.73 ± 11.24</td>
<td>0.021</td>
</tr>
<tr>
<td>Psychological support</td>
<td>17.35 ± 3.61</td>
<td>15.88 ± 4.08</td>
<td>0.078</td>
</tr>
<tr>
<td>Physical independence</td>
<td>12.65 ± 6.37</td>
<td>11.31 ± 5.67</td>
<td>0.335</td>
</tr>
<tr>
<td>Pain</td>
<td>10.95 ± 4.65</td>
<td>10.00 ± 4.36</td>
<td>0.351</td>
</tr>
<tr>
<td>Mental well-being</td>
<td>48.78 ± 11.13</td>
<td>42.62 ± 13.03</td>
<td>0.018</td>
</tr>
<tr>
<td>Physical well-being</td>
<td>60.07 ± 17.22</td>
<td>54.15 ± 15.77</td>
<td>0.120</td>
</tr>
<tr>
<td><strong>POD 7</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global QoR-15K score</td>
<td>127.55 ± 18.94</td>
<td>106.58 ± 29.49</td>
<td>0.002</td>
</tr>
<tr>
<td>Physical comfort</td>
<td>44.45 ± 6.83</td>
<td>37.54 ± 10.78</td>
<td>0.004</td>
</tr>
<tr>
<td>Emotional state</td>
<td>34.25 ± 6.42</td>
<td>26.96 ± 9.85</td>
<td>0.001</td>
</tr>
<tr>
<td>Psychological support</td>
<td>17.62 ± 3.47</td>
<td>15.81 ± 4.98</td>
<td>0.092</td>
</tr>
<tr>
<td>Physical independence</td>
<td>15.66 ± 4.49</td>
<td>13.81 ± 5.54</td>
<td>0.127</td>
</tr>
<tr>
<td>Pain</td>
<td>15.57 ± 4.06</td>
<td>12.46 ± 4.79</td>
<td>0.001</td>
</tr>
<tr>
<td>Mental well-being</td>
<td>51.87 ± 8.15</td>
<td>42.77 ± 13.49</td>
<td>0.003</td>
</tr>
<tr>
<td>Physical well-being</td>
<td>75.68 ± 12.30</td>
<td>63.81 ± 17.45</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. POD: postoperative day, QoR-15K: Quality of Recovery-15. *Patients with preoperative the anxiety subscale of the Hospital Anxiety and Depression Scale for Koreans scores of 8 or higher are classified into the anxious group.
DISCUSSION

This study shows that the K-HADS-A is an acceptable tool for appropriately assessing preoperative anxiety in Korean surgical patients. To evaluate the appropriateness of using K-HADS-A as a method to measure preoperative anxiety in surgical patients, the validity and reliability of K-HADS-A were assessed. The relationships between the K-HADS-A and ALS were statistically well correlated. This shows that K-HADS-A has significant convergent validity. The good-ness-of-fit indices of the structural equation model were sufficiently strong to conclude that the K-HADS-A had an acceptable level of construct validity. The results of the internal consistency of the K-HADS-A also showed that it had an adequate level of reliability. In addition, factor analysis as a validation method through KMO measurement and Barlett’s test showed that most items of the K-HADS-A were valid.

In addition, we found that preoperative anxiety can affect not only postoperative mental well-being, but also postoperative physical well-being. The dimensions of QoR-15K offer excellent assessment and discrimination capabilities to quantify changes in the postoperative health state. The QoR-15K mental well-being scale score is significantly different on POD1 and POD7 between the non-anxious and anxious groups. This means that the effects of preoperative anxiety persisted until POD7. Meanwhile, physical well-being is not significantly different between groups on POD1, but significant differences are found on POD7. This shows that preoperative anxiety continues to affect postoperative mental and physical well-being. Our findings confirm that preoperative anxiety could delay postoperative recovery.

The minimal clinically important difference (MCID) for the QoR-15K score is 8, and an MCID of 8 or more points indicates a clinically meaningful improvement [24]. In this study, the MCID of the non-anxious and anxious groups was 18.70 ± 23.73 and 9.81 ± 31.56, respectively. The non-anxious and anxious groups showed a clinically meaningful improvement in postoperative recovery quality. However, the global QoR-15K score was significantly lower in the anxious group than in the non-anxious group on POD1 and POD7. Although both groups showed clinically significant improvement, that is, recovery state, the anxious group showed relatively delayed postoperative recovery.

The influencing factors of surgical outcome include demographic factors, clinical, damage to specific anatomic structures, comorbid health conditions, and psychological factors [25]. Psychological factors have been found to substantially impact surgical recovery [20]. Anxiety is important as it can considerably impact perioperative situations, such as preoperative preparation, intraoperative anesthesia re-

| Table 4. Differences in Preoperative Anxiety according to Sex, Age, Education, Previous Experience of Anesthesia, ASA Physical Status, and Religion |
|---------------------------------|-----------------|-------|--------|---------|---------|
| Group                          | Number of patients | Mean   | SD     | t       | P value |
| Sex                            |                  |        |        |         |         |
| M                              | 41               | 3.39   | 2.836  | –4.381  | 0.000   |
| F                              | 76               | 6.07   | 3.008  |         |         |
| Age                            |                  |        |        |         |         |
| Young (< 45 yr)                | 72               | 5.71   | 3.265  | 2.534   | 0.013   |
| Old (≥ 45 yr)                  | 45               | 4.2    | 2.905  |         |         |
| Education                      |                  |        |        |         |         |
| College graduate               | 73               | 5.45   | 3.383  | 1.414   | 0.180   |
| High school graduate           | 44               | 4.59   | 2.839  |         |         |
| Previous experience of anesthesia |              |        |        |         |         |
| First time                     | 55               | 5.22   | 3.624  | 0.281   | 0.780   |
| Previous experience            | 62               | 5.05   | 2.808  |         |         |
| ASA classification             |                  |        |        |         |         |
| ASA 1                          | 36               | 5.11   | 3.379  | –0.038  | 0.970   |
| ASA 2.3                        | 81               | 5.14   | 3.145  |         |         |
| Religious practices            |                  |        |        |         |         |
| Religion                       | 63               | 5.05   | 3.381  | –0.293  | 0.770   |
| No religion                    | 54               | 5.22   | 3.014  |         |         |

ASA: American Society of Anesthesiologists.
quirements, postoperative opioid demands, and surgical outcome. Previous studies \cite{2,6-9,20,25} have identified a relationship between preoperative anxiety and surgical outcome, and consistent findings were observed in the present study.

Preoperative anxiety is caused by fear of the unknown, thinking of postoperative pain, and possible complications. Influencing factors of preoperative anxiety include sociodemographic and psychosocial factors, type of surgery, and type of anesthesia. Sociodemographic factors include age, sex, American Society of Anesthesiologists physical status classification, and education. Previous studies have shown that preoperative anxiety is more frequent in women and younger patients, and the present study supports this. However, there was no difference in preoperative anxiety according to the American Society of Anesthesiologists physical status classification and education level in the present study.

The main strength of our study was that the postoperative quality of recovery was measured using the objective and integrated QoR-15K to demonstrate postoperative outcome differences. In addition, a wide range of surgical patients and surgical settings were evaluated. Further, the present study used the K-HADS-A questionnaire to measure preoperative anxiety. The K-HADS-A is an easy and convenient tool for examining the degree of anxiety in a short time without special skills. Moreover, the present study showed that the K-HADS-A is an acceptable method of appropriately assessing preoperative anxiety in surgical patients by evaluating its validity and reliability.

However, there are also limitations in the present study. Given that the K-HADS-A measures pathological anxiety, it could not differentiate between state and trait anxiety. Suppose state anxiety can be measured under exceptional circumstances such as surgery. In that case, it is expected that the effect of preoperative emotional pressure on the postoperative recovery quality can be subdivided and compared. Further, among seven questions of the K-HADS-A, when a question with low agreement was removed, it showed better goodness-of-fit as a measure of preoperative anxiety. More accurate results are expected if preoperative anxiety is measured with the 6-item K-HADS-A. However, this scale's cutoff value for diagnosing anxiety is unknown. Thus, further research is needed.

In conclusion, the K-HADS-A is a valid and reliable tool for appropriately assessing preoperative anxiety in Korean surgical patients. Preoperative anxiety affects the postoperative quality of recovery, both mentally and physically, but it is a preventable risk factor. Assessment of preoperative anxiety is valuable to improve postoperative quality of recovery, and thus, methods to reduce preoperative anxiety should be developed and applied.

FUNDING

None.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

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REFERENCES


Appendix 1. Anxiety subscale of the Hospital Anxiety and Depression Scale for Koreans

병원 불안 척도(Hospital Anxiety Scale, K-HADS-A)

* 다음을 읽고 당신의 상태를 가장 잘 나타낸다고 생각되는 문항을 골라 ‘O’를 하십시오.
1) 나는 긴장감 또는 “정신적 고통”을 느낀다.
   0. 전혀 아니다. 1. 가끔 그렇다. 2. 자주 그렇다. 3. 거의 그렇다.

2) 나는 무언가 무서운 일이 일어날 것 같은 느낌이 든다.
   0. 전혀 아니다. 1. 조금 있지만 걱정하지 않는다. 2. 있지만 그렇게 나쁘지는 않다.
   3. 매우 분명하고 기본이 나쁘다.

3) 마음속에 걱정스러운 생각이 든다.
   0. 거의 그렇지 않다. 1. 가끔 그렇다. 2. 자주 그렇다. 3. 항상 그렇다.

4) 나는 편하게 긴장을 풀 수 있다.
   0. 항상 그렇다. 1. 대부분 그렇다. 2. 대부분 그렇지 않다. 3. 전혀 그렇지 않다.

5) 나는 초조하고 두렵다.
   0. 전혀 아니다. 1. 가끔 그렇다. 2. 자주 그렇다. 3. 매우 자주 그렇다.

6) 나는 가만히 있지 못하고 안절부절 한다.
   0. 전혀 그렇지 않다. 1. 가끔 그렇다. 2. 자주 그렇다. 3. 매우 그렇다.

7) 나는 갑자기 당황스럽고 두려움을 느낀다.
   0. 전혀 그렇지 않다. 1. 가끔 그렇다. 2. 자주 그렇다. 3. 거의 항상 그렇다.

총점
Pyruvate dehydrogenase complex (PDHC) deficiency is a rare mitochondrial disorder that primarily affects the brain and results in decreased adenosine triphosphate (ATP) production and energy deficiency [1]. It is caused by a genetic mutation affecting the activity of the PDHC enzyme, which plays a major role in the tricarboxylic acid (TCA) cycle. PDHC deficiency can lead to a variety of symptoms, including intrauterine growth retardation, developmental delay, hypotonia, intermittent ataxia, lactic acidosis, facial dysmorphism, and cerebral atrophy [2]. The exact prevalence of PDHC deficiency remains unknown owing to its rarity [3]. To the best of our knowledge, few cases related to surgery or anesthesia have been reported. This makes it challenging to determine the best anesthetic method for patients with PDHC deficiency. Therefore, further research and case reports are required to establish appropriate anesthesia protocols and improve the perioperative outcomes of patients with PDHC deficiency. Anesthesiologists need to raise
awareness about PDHC deficiency and develop safe and effective anesthetic plans. In this context, we present the anesthetic management of a 24-month-old male patient with PDHC deficiency who underwent two consecutive surgeries under general anesthesia. We aimed to provide insights into the perioperative considerations in the management of patients with PDHC deficiency patients undergoing surgery and anesthesia.

**CASE REPORT**

The current report was approved by the Institutional Review Board of our hospital, and the requirement for informed consent was waived (IRB no. 2303-013-125). A 24-month-old male patient with a height of 87 cm and a weight of 10.5 kg presented to the emergency room due to respiratory failure, mental decrease to a stupor state, systemic cyanosis, and lactic acid increase up to 12.3 mM/L (normal range: 0.7–2.5 mM/L). Initial arterial blood gas analysis result was pH 6.80, PaCO$_2$ 131 mmHg, PaO$_2$ 75 mmHg. The child was previously diagnosed with pyruvate dehydrogenase E1-alpha deficiency two months after birth. At the time of diagnosis, the child’s laboratory result showed lactic acid 6.4 mM/L. There were no abnormal findings in the parental phenotype, and the parental genetic test results were normal. Therefore, the patient had a de novo pathogenic variant of pyruvate dehydrogenase E1-alpha deficiency two months after birth. At the time of diagnosis, the child’s laboratory result showed lactic acid 6.4 mM/L. There were no abnormal findings in the parental phenotype, and the parental genetic test results were normal. Therefore, the patient had a de novo pathogenic variant of pyruvate dehydrogenase E1-alpha deficiency. He had a history of multiple admissions and discharges with similar events. The main clinical features of the child were lactic acidosis, mental decline, respiratory failure, and systemic cyanosis. The child received mechanical ventilation and bicarbonate administration after hospitalization. During this hospitalization period, he presented with abdominal distension and ileus, and aggravation and remission continued repeatedly. Computed tomography (CT) scan was conducted on the 30th day of hospitalization to determine the cause. CT scan revealed a pneumothorax, pneumomediastinum, pneumoperitoneum, and multiple air pockets in the heart, retroperitoneum, extraperitoneal space, scrotum, and renal vessels (Fig. 1). It was assumed that the ventilator-induced lung injury occurred due to the long period of mechanical ventilation, resulting in these conditions. There were no other events, such as an accidental air injection.

Bilateral chest tube insertion was performed before surgery and loop ileostomy was planned for an emergency surgery. The patient arrived in the operating room in an intubated state with an endotracheal tube (Inner diameter 4.5 mm). Anesthesia was induced with 2.0 vol% sevoflurane and 10 mg rocuronium. Invasive blood pressure monitoring was performed via arterial cannulation of the left radial artery. Capnography, electrocardiography, pulse oximetry, core temperature, anesthetic agent concentration, and airway pressure was also monitored. Neuromuscular monitoring was excluded because the appropriate monitoring size was unavailable. A circulating-water mattress was used to maintain the patient’s body temperature. Maintenance of anesthesia was performed with 2.0 vol% sevoflurane, 0.02–0.03 mg/h of intravenous remifentanil infusion. Mechanical ventilation was set at a tidal volume of 60 ml, respiratory rate 24 per min, and FiO$_2$ 0.74 (2.0 L/min oxygen, 1.0 L/min air). Oxygen saturation was maintained at 95% and end-tidal CO$_2$ at 32 mmHg. Balanced crystalloid solution was administered as an intravenous fluid. The vital signs of the patient maintained stable throughout the surgery. The duration of the operation was 1 h and the anesthesia lasted for 1 h and 35 min. The patient was transferred to the surgical intensive care unit while maintaining intubation. Preoperative venous blood gas analysis and postoperative arterial blood gas analysis data are presented in Table 1.

For the first week after the surgery, hyperbaric oxygen therapy with FiO$_2$ 1.0 was conducted to resolve air pockets in the heart. After terminating the hyperbaric oxygen therapy,
PDHC is a complex of five components that converts pyruvate into acetyl-CoA, which then enters the TCA cycle for ATP production. The five components are E1, an α-keto acid decarboxylase; E2, a dihydrolipoyl transacetylase; E3, a dihydrolipoyl dehydrogenase; protein X, an extra lipoate-containing protein; and pyruvate dehydrogenase phosphatase [1]. E1 enzyme contains subunits, which are divided into alpha and beta subunits. If any of these components are missing, the conversion of pyruvate to acetyl-CoA cannot proceed, resulting in the accumulation of pyruvate and lactate [4], leading to symptoms such as lactic acidemia and central nervous system abnormalities. The most common type is pyruvate dehydrogenase E1-alpha deficiency, which accounts for 76–85% of PDHC deficiencies. Approximately 60–63% of pyruvate dehydrogenase E1-alpha deficiencies are de novo pathogenic variants and the rest are exhibited in X-linked inheritance [2].

The presentation of this disease varies depending on the onset age. There are three main categories: neonatal onset, infantile onset, and later childhood onset. The neonatal form has the most severe enzyme deficiency and presents with lethal lactic acidosis and structural brain anomalies such as agenesis of the corpus callosum. Patients with infantile onset may present with chronic lactic acidosis, psychomotor retardation, and cystic lesions in the brainstem and in the basal ganglia. If the disease appears in late childhood, patients have less impaired enzyme activity and may present intermittent

**DISCUSSION**
First, airway problems can be caused by facial dysmorphism, which can be observed in patients with PDHC deficiency. Such facial features include a flat wide nasal bridge, long philtrum, thin upper lip, low-set ears, and a high arched palate [3,9]. Intubation can be difficult due to facial dysmorphism [10]. Therefore, additional methods such as using a video laryngoscope can be considered. In this case, he showed a wide nasal bridge and flared nostrils. However, no other facial deformities were observed. Thus, no airway problems were identified.

Second, close attention should be paid to the acid-base imbalance. Precipitating factors that trigger an increase in lactate levels should be avoided. Sepsis, hypothermia, hypoxemia, hypocarbia, and decreased cardiac output all contribute to lactate increase [4,11]. Anesthetic management should be performed carefully to avoid these events and make stress-free situations. If possible, arterial blood gas analysis should be performed at regular intervals to closely monitor lactic acidosis.

The selection of intraoperative intravenous fluids also needs to be carefully considered. Lactate containing intravenous solutions should not be administered as the lactate load only increases [12]. In this case, we used a balanced crystalloid solution that did not contain lactate during the first surgery, and we used 5% dextrose water for the second surgery. Both fluids were helpful as they did not contribute to an increase in lactate levels. Furthermore, owing to a decent amount of estimated blood loss during the second surgery, we used one packed red blood cell for transfusion and no side effects were observed.

Third, the choice of drugs for anesthesia induction and maintenance is influenced by the inhibitory effect of the drug-induced suppression of gluconeogenesis, which can exacerbate coexisting metabolic acidosis [13]. To the best of our knowledge, no recommendations are currently available for which anesthetic agents should be used. In this case, anesthesia was maintained with sevoflurane and no complications were observed. According to previous literature, successful cases using sevoflurane have been observed [12,13]. Also, there have been two successful cases of total intravenous anesthesia using propofol and fentanyl [10], and midazolam and remifentanil [11]. Based on the reported cases so far, we can confirm that either method can be utilized with a close monitoring. However, anesthesiologists should be aware of the possibility of malignant hyperthermia when using volatile agents. On the other hand, the possibility of propofol infusion syndrome should be considered when propofol is used as the primary anesthetic agent. Proper monitoring such as capnography, electrocardiography, and core temperature monitoring should be applied to detect early signs of these events.

Since there was no appropriate size of neuromuscular monitoring for this patient in our hospital, it was not possible to check the neuromuscular transmission status of the patient. However, we had to use a neuromuscular blocking agent more frequently because of multiple episodes of spontaneous respiration. Based on this finding, it is likely that there was no prolongation of the muscle relaxation effect.

Through this case and literature review, we confirmed that anesthesiologists should consider the multiple factors mentioned above when anesthetizing a patient with PDHC deficiency. Moreover, monitoring lactic acid levels might be a helpful indicator to predict the clinical course of a patient with PDHC deficiency during the perioperative period.
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The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.


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Chronic exposure to dexamethasone may not affect sugammadex reversal of rocuronium-induced neuromuscular blockade: an in vivo study on rats

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Background: Chronic glucocorticoid exposure is associated with resistance to nondepolarizing neuromuscular blocking agents. Therefore, we hypothesized that sugammadex-induced recovery would occur more rapidly in subjects exposed to chronic dexamethasone compared to those who were not exposed. This study evaluated the sugammadex-induced recovery profile after neuromuscular blockade (NMB) in rats exposed to chronic dexamethasone.

Methods: Sprague–Dawley rats were allocated to three groups (dexamethasone, control, and pair-fed group) for the in vivo study. The mice received daily intraperitoneal dexamethasone injections (500 µg/kg) or 0.9% saline for 15 days. To achieve complete NMB, 3.5 mg/kg rocuronium was administered on the sixteenth day. The recovery time to a train-of-four ratio ≥ 0.9 was measured to evaluate the complete recovery following the sugammadex injection.

Results: Among the groups, no significant differences were observed in the recovery time to a train-of-four ratio ≥ 0.9 following sugammadex administration (P = 0.531). The time to the second twitch of the train-of-four recovery following rocuronium administration indicated that the duration of NMB was significantly shorter in Group D than that in Groups C and P (P = 0.001).

Conclusions: Chronic exposure to dexamethasone did not shorten the recovery time of sugammadex-induced NMB reversal. However, the findings of this study indicated that no adjustments to sugammadex dosage or route of administration is required, even in patients undergoing long-term steroid treatment.

Keywords: Dexamethasone; Neuromuscular blockade; Neuromuscular monitoring; Rats; Rocuronium; Sugammadex.
INTRODUCTION

The prevention of recurarization after using neuromuscular blocking agents (NMBAs) has been the primary concern in reducing respiratory-related adverse outcomes following anesthesia. Many anesthesiologists use sugammadex to reverse neuromuscular blockade (NMB). Sugammadex is a cyclodextrin that encapsulates lipophilic compounds [1]. It selectively binds rocuronium, which contains a steroidal nucleus. This reduces the concentration of NMBAs in the neuromuscular junction, enabling rapid and effective NMB reversal, even with a profound blockade [2].

Glucocorticoids have been prescribed for diseases caused by inflammation, such as chronic obstructive pulmonary disease, allergies, rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, eczema, and other allergic skin conditions [3]. Glucocorticoids are used by all medical specialties. However, Soltesz et al. [4, 5] reported that chronic corticosteroid treatment shortened the duration of NMB [6] because it induced modification of acetylcholine receptor (AChR) properties, leading to reduced affinity for the receptor and rocuronium molecules. Subsequently, several studies have been conducted on this topic. In particular, since the introduction of sugammadex, many studies have been conducted on the effects of a single bolus dose of the steroid on the sugammadex-induced recovery of NMB. However, clinical studies investigating chronic dexamethasone treatment at a dose known to cause muscle atrophy are still unavailable because of ethical constraints and a lack of sufficient animal testing. Nevertheless, in vivo studies in rats treated with chronic dexamethasone have not been conducted. Therefore, we conducted an in vivo study using rats to investigate the effects of chronic dexamethasone exposure on sugammadex-induced NMB reversal. We anticipated that shallow NMB would lead to a faster recovery from the blockage since chronic dexamethasone-treated AChRs have a lower affinity for rocuronium than that of untreated receptors.

Considering the resistance to NMBA caused by chronic exposure to dexamethasone, we hypothesized that chronic exposure to dexamethasone induces resistance to NMBA, resulting in faster sugammadex-induced NMB recovery.

MATERIALS AND METHODS

Assessed outcomes

The primary outcome of this study included the recovery time to a train-of-four (TOF) ratio ≥ 0.9 (TTOFr), which is the time it takes for the TOF ratio (TOFr) to recover to 0.9 or higher after the injection of sugammadex. Secondary outcomes included the time to T1 (the first twitch of TOF), recovery (TT1), and recovery index (RI). TT1 is the time taken for the T1 height to recover 95% of the baseline T1 height following sugammadex injection. RI is the time taken for the T1 height to recover from 25 to 75% of the baseline T1 height following sugammadex injection.

Animals and group assignments

Ethical approval for this study was provided by the Institutional Animal Care and Use Committee of the Asan Institute for Life Sciences, Asan Medical Center (Seoul, Korea) on February 13, 2017 (Protocol no. 2017-13-035; Chairperson Professor Jong Yeun Park). The experiments were reviewed and performed according to the guidelines and regulations established by the Institutional Animal Care and Use Committee of Asan Institute for Life Sciences, Asan Medical Center. The committee abides by the guidelines of the Institute of Laboratory Animal Resources. Rats were obtained from Orient Bio. This animal study complied with the ARRIVE guidelines [7]. The procedures were conducted in accordance with the principles outlined in the 1975 Declaration of Helsinki (revised in 2013).

We did not validate the sample size through statistical tests, but followed previous studies that have conducted experiments with approximately 10 animals per group to achieve statistically significant results [8-11]. To allow for attrition, 36 adult male Sprague–Dawley rats (7 weeks old, weighing 213–253 g) were randomly divided into three groups (n = 12 per group). Sorting was accomplished using a random number generator in Microsoft Excel 2013 (Microsoft Corp.). Only a third party who was not involved in this experiment was aware of the group allocation at different stages of the experiment. To induce chronic dexamethasone exposure at a dose previously shown to cause muscle atrophy, the dexamethasone group (Group D) received daily intraperitoneal injections of 500 μg/kg dexamethasone disodium phosphate (Yuhan) for 15 days [6, 12, 13]. One milliliter of 0.9% saline was used to suspend 500 μg of dexamethasone. Thus, rats weighing 213–253 g were injected with 106.5–126.5 μg of dexamethasone suspended in 1 ml of 0.9% saline. The control group (Group C) received an equivalent volume of 0.9% saline daily for 15 days. The rats in the pair-fed group (Group P) were fed with the same amount of food daily for...
15 days as those in Group D. All treatments were performed in the laboratory by a third party who was not involved in the experiments.

The amount of food consumed by Group D was weighed daily, and Group P was provided with the same amount of food as Group D. Group P was pair-fed with Group D for 15 days to evaluate whether muscle dysfunction following dexamethasone treatment was caused by the anorexia typically associated with glucocorticoid therapy. Food was available ad libitum to the rats in Groups C and D. Weight of the rats were recorded daily. Dexamethasone doses were adjusted according to the changes in body weight. Water was available ad libitum to all the groups. All the mice were bred in the laboratory animal breeding room at the Laboratory Animal Research Center, Asan Institute for Life Sciences. Under specific pathogen-free conditions, the animals were housed in individually ventilated cages (Tecniplast). The rats were raised at a constant temperature of 22°C, humidity 50 ± 10%, laboratory rodent chow, and were maintained under a regular diurnal (12-h light and 12-h dark) cycle. All the injections were administered simultaneously daily. These treatments are summarized in Fig. 1.

**General surgical procedures**

Twenty-four hours after the last drug administration, the rats were anesthetized with an intraperitoneal injection of Alfaxan™ (Jurox Pty. Limited) at 40 mg/kg body mass. Adequate depth of anesthesia was confirmed by the absence of a withdrawal response to toe clamping [14]. When there was a withdrawal response, 10–20 mg/kg body weight of anesthetic agent was administered, if necessary. The animals underwent tracheotomies, artificial ventilation to ensure normal breathing throughout the surgery, and the jugular vein catheterization to administer medications. Body temperature was monitored using an esophageal temperature probe.

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**Fig. 1.** Flow diagram of the treatment. IPI: intraperitoneal injection, Group C: control group, Group D: dexamethasone group, Group P: pair-fed group. Group C received the same volume of 0.9% saline daily as Group D. Group D received a daily IPI of 500 µg/kg dexamethasone suspended in 1 ml of 0.9% saline. Food and water were provided ad libitum. Group P received the same volume of 0.9% saline as Group D each day and was fed daily with the same amount of food and water as Group D.
(Regulation to 37 ± 1°C), and a warming pad and light source were used to maintain proper body temperature. The anterior tibialis muscle was exposed, and the distal part of the tendon was tied with 3-0 black silk. It was then connected to a force-displacement transducer (Grass FT03, Grass Instrument Co.) to measure the isometric contraction of the anterior tibialis muscle at a resting tension of 2 g. The sciatic nerve was exposed and connected to bipolar platinum electrodes to evaluate neuromuscular transmission.

**Assessment of neuromuscular transmission**

Using a nerve stimulator (S88, Grass) and a stimulation isolation unit (SIU5, Grass), TOF stimulation (frequency, 2 Hz; duration, 0.2 ms) consisting of four supramaximal square-wave pulses was applied to the sciatic nerve via bipolar platinum electrodes every 12 s throughout the study. Muscle contraction responses were recorded and digitalized with a PowerLab acquisition system (ADInstruments) and stored in LabChart7 software (ADInstruments). In all the groups, contraction responses were stabilized for at least 10 min after the initiation of TOF stimulation. The height at T1 was measured as the baseline T1 after a 10 min stabilization period. Complete NMB was achieved by administering 3.5 mg/kg of rocuronium (Esmeron™, MSD) [6], through a jugular vein catheter [15]. When the TOF count reached zero, a complete NMB was considered. The time from the rocuronium injection to the appearance of the second TOF twitch (TT2) was recorded. When T2 appeared, 0.5 mg/kg of sugammadex (Bridion™, MSD) was administered, and TTOFr, our primary outcome, was recorded. The RI and TT1 were recorded as secondary outcomes. **Fig. 2** summarizes the overall experiment.

**Specimen measurement**

On completion of the in vivo study, the rats were euthanized for specimen examination.

**Data and statistical analysis**

The primary outcome of this study was the TTOFr. The secondary outcomes were TT1 and RI. Unless otherwise specified, data were expressed as the mean ± standard deviation or median (interquartile range). Quantile–quantile plots were used to assess normality. One-way analysis of variance followed by the Tukey’s post-hoc test was applied to analyze the weight of the rats, temperature, weight of the anterior tibialis muscle, TT2, TTOFr, TT1, and RI. The Kruskal–Wallis test was used to analyze the length and width of the anterior tibialis muscle. A pairwise Wilcoxon test was applied as a post-hoc test when the Kruskal–Wallis test demonstrated a significant result.

Statistical significance was set at P values < 0.05, and all statistical tests were two-sided. SAS statistical software (version 9.3; SAS Institute Inc.) was used for statistical analysis.

**Fig. 2.** Flow diagram of the experiment. The groups included: control group (Group C), dexamethasone group (Group D), and pair-fed group (Group P). NMB: neuromuscular blockade, T2: second twitch of train-of-four stimulation, IVI: intravenous injection, and IPI: intraperitoneal injection. Group D received a daily IPI of 500 µg/kg dexamethasone suspended in 1 ml of 0.9% saline. Food and water were provided ad libitum. Group C received the same volume of 0.9% saline daily as Group D. Food and water were provided ad libitum. Group P received the same volume of 0.9% saline as Group D daily and was fed daily with the same amount of food and water as Group D.
RESULTS

Animal and specimen data

Thirty-six rats were allocated to three groups, with 12 rats assigned to each group. One rat in Group C was administered a rocuronium overdose, and another died during the surgical procedure. Thus, data from these two rats could not be used. We could not use data from two rats in Group D because of a ventilator breakdown resulting in respiratory failure and a computer system shutdown during the recovery process, resulting in recording errors. In Group P, data from two rats could not be used due to incomplete NMB in one rat, even after administration of the proper dosage of rocuronium with sufficient time for the onset of the drug, and another rat exhibited incomplete recovery of TOFr. Therefore, 30 rats (10 each in Groups C, D, and P) were included in the analysis (Fig. 3).

No significant differences were observed in the initial body weight before the intervention. However, the final body weight after the experimental treatment differed significantly between the groups (Table 1). As previously reported [16,17], food intake decreased markedly in Group D rats. The size and weight of the anterior tibialis muscles were smaller in Group D rats than those in Groups C and P. Though rats in Groups D and P were fed the same amount of food, the de-

![Fig. 3. Flow chart of an experimental procedure. Group C: control group, Group D: dexamethasone group, Group P: pair-fed group, S-D: Sprague-Dawley, NMB: neuromuscular blockade, TOFr: train-of-four ratio.](image)

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<th>Table 1. Baseline Comparison of Animals in the Study Groups</th>
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<td><strong>Factors</strong></td>
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<td>Weight (g)</td>
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Values are presented as mean ± SD or median (IQR, 3Q). Group C: control group, Group D: dexamethasone group, and Group P: pair-fed group. Group C received the same amount of 0.9% saline daily as Group D. Group D received a daily intraperitoneal injection of 500 µg/kg dexamethasone suspended in 1 ml of 0.9% saline. Group P was fed with the same amount of food as Group D. *P < 0.001 vs. Group C. †P < 0.001 vs. Group P. One-way analysis of variance is performed, followed by Tukey’s post-hoc test. The Kruskal-Wallis test was used to analyze the length and width of the anterior tibialis muscle, with a pairwise Wilcoxon test as a post-hoc test.
degree of weight loss, muscle size reduction, and muscle weight loss were more significant in Group P rats.

**NMB induction and duration**

After administering 3.5 mg/kg (estimated 2-fold ED$_{50}$) [18] of rocuronium via the jugular vein, a complete NMB was induced in each group. The TT2, which shows the duration of rocuronium-induced NMB, was significantly shortened in Group D rats compared to the rats in Group C and P (2.9 ± 1.0 min vs. 5.0 ± 1.1 and 5.1 ± 1.4 min; P = 0.001, respectively). Similarly, no significant difference was observed between Group C and P (P = 0.996).

**Recovery profiles**

The primary outcome, TTOFr, was not significantly different between the groups (4.3 ± 2.3, 3.1 ± 1.8, and 4.0 ± 3.0 min; P = 0.531 in Groups C, D, and P, respectively) (Table 2). TT1 was not shortened in Group D than in Groups C and P (3.6 ± 2.1 min vs. 4.2 ± 2.2 and 4.4 ± 2.5 min; P = 0.754, respectively) (Table 2). RI was not different between the groups (1.5 ± 0.6, 1.3 ± 0.6, and 2.2 ± 1.8 min, in Groups C, D, and P; P = 0.272, respectively) (Table 2).

**DISCUSSION**

In the present study, we hypothesized that the group receiving chronic dexamethasone would exhibit greater NMBA resistance and quicker sugammadex recovery. Although TTOFr and RI appeared to be shortened in Group D, no statistically significant difference was observed in TTOFr and RI between Group D and the other groups. TT1 seemed shorter in Group D, but given the wide range of its confidence interval, it was difficult to determine the significance of the results (Table 2). Therefore, we concluded that chronic dexamethasone treatment did not significantly affect sugammadex-induced NMB reversal. However, to maintain the same depth of NMB for similar duration, a more significant amount of rocuronium was required in patients receiving chronic dexamethasone treatment. Therefore, careful patient monitoring would be helpful to reduce potential adverse events.

We considered the following reasons for this observation. First, when sugammadex was administered intravenously, it bound to free NMBA molecules in the plasma, leading to differences in the concentration of NMBA molecules between the neuromuscular junctions and plasma. Consequently, NMBA molecules were released from the neuromuscular junction into the plasma and bound to sugammadex molecules. Therefore, regardless of the receptor affinity, the effect of sugammadex molecules continued.

Second, the reversal was extremely rapid in rats; hence, it was difficult to determine the differences in recovery profiles that might exist. The use of single-twitch stimulation would have been better. Unlike TOF stimulation, which usually occurs every 10–15 s, 1 Hz single twitch stimulation may provide a more appropriate resolution to identify fast recovery from deep neuromuscular block [18].

Concerns were raised regarding the direct binding of dexamethasone molecules to each other, which could influence NMB reversal. However, we initiated the experiment 24

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**Table 2. Effects of Chronic Exposure to Dexamethasone on Duration and Sugammadex Reversal of Neuromuscular Blockade**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Group C (n = 10)</th>
<th>Group D (n = 10)</th>
<th>Group P (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of neuromuscular blockade</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TT2 (min)</td>
<td>5.0 ± 1.1</td>
<td>2.9 ± 1.0$^*$,†</td>
<td>5.1 ± 1.4</td>
</tr>
<tr>
<td>Recovery profiles after sugammadex administration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTOFr (min)</td>
<td>4.3 ± 2.3</td>
<td>3.1 ± 1.8</td>
<td>4.0 ± 3.0</td>
</tr>
<tr>
<td>TT1 (min)</td>
<td>4.2 ± 2.2</td>
<td>3.6 ± 2.1</td>
<td>4.4 ± 2.5</td>
</tr>
<tr>
<td>RI (min)</td>
<td>1.5 ± 0.6</td>
<td>1.3 ± 0.6</td>
<td>2.2 ± 1.8</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. Group C: control group, Group D: dexamethasone group, Group P: pair-fed group. Group C received only 0.9% saline, whereas Group D received saline daily. Group D received a daily intraperitoneal injection of 500 µg/kg dexamethasone suspended in 1 ml of 0.9% saline. Group P was fed daily with the same amount of food that was consumed by Group D. Time and recovery indices are presented as min; TOF: train-of-four, T1: the first twitch of train-of-four, T2: the second twitch of train-of-four, TT2: the time from rocuronium injection to appearance of T2, TTOFr: time taken for the TOF ratio to recover to 0.9 or higher after injection of sugammadex, TT1: the time taken for T1 to recover to 95% of the baseline T1 after the injection of sugammadex, RI: recovery index (the time taken from T1 of 25% of the baseline T1 to T1 of 75% of the baseline T1). *P = 0.001 vs. Group C. †P = 0.001 vs. Group P. One-way analysis of variance is performed, followed by the Tukey post-hoc test.
h after the completion of the dexamethasone pre-treatment regimen of 14 days. Unlike the half-life of dexamethasone in humans (36–72 h), its half-life in rats is only 2.3 h [19]. Therefore, the presence of dexamethasone molecules remaining in the plasma of the experimental rats was considered negligible. Hence, it was unlikely that they would interfere with the action of sugammadex by binding to sugammadex instead of rocuronium.

It is well known that prolonged exposure to dexamethasone alters receptor characteristics. It induces nAChR upregulation [6,20,21] and the expression of the immature form of the receptor subunit [6], causing resistance to NMBA. However, this study observed that although chronic dexamethasone treatment induced resistance to NMBA, it did not affect sugammadex-induced recovery.

By comparing the results from Groups D and P, we could infer that the reduction in muscle mass caused by chronic dexamethasone exposure was not a consequence of weight loss due to reduced food intake, but rather a result of glucocorticoid-induced muscle atrophy [22]. Furthermore, by examining the recovery profiles of Groups P and C, we could deduce that although muscle mass reduction occurred, it did not affect the sugammadex-induced NMB recovery time. Therefore, reduction in muscle mass did not affect the NMB reversal time. Additionally, the duration of NMB did not change significantly in Group P. Therefore, it can be speculated that weight loss due to muscle mass reduction did not cause resistance to NMBA. However, receptor modifications due to chronic dexamethasone exposure may cause resistance to NMBA. Therefore, although Group D showed a shortened duration of NMB, the sugammadex-induced NMB recovery time remained unchanged.

Our study had some limitations. First, the sugammadex dosage used in the study was a limitation. There is no consensus on the recommended dose of sugammadex for in vivo studies in rats because of limited studies available on this topic [18,23]. Therefore, the optimal dosage of sugammadex was determined in this pilot study. The experimental dose of sugammadex was selected based on achieving a faster recovery without excessive rapid reversal from NMB. In the clinical setting, the recovery time was less than 5 min, depending on the sugammadex dose used. Using 2 mg/kg of sugammadex during moderate NMB and 4 mg/kg during deep NMB resulted in recovery times of less than 3 min and 5 min to TOFr > 0.9, respectively [24-26]. However, in our pilot study, the recovery time of TOFr was < 1 min when 2 mg/kg sugammadex was administered. Moreover, T1 recov-

erred fully within 30 s. Unfortunately, the recovery time was so short that we could not obtain sufficient data. Therefore, we reduced the sugammadex dose to 0.5 mg/kg. This discrepancy between the in vivo study and clinical setting indicated the ongoing concern of postoperative residual neuromuscular blockade. Second, this study used only young rats (approximately 8 weeks old). If we had included rats of various age groups, similar to the clinical use of steroids in patients of different age groups, it could have provided a more accurate reflection of the clinical situation more.

In conclusion, chronic exposure to dexamethasone did not shorten the recovery time of sugammadex-induced NMB reversal. In other words, the results of this study suggested that no changes may be required in the use of sugammadex, even in patients receiving long-term steroid administration.

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None.

**ACKNOWLEDGMENTS**

All the authors are members of the Asan Neuromuscular Physiology Research Team at the Asan Institute of Life Science, Seoul, Korea.

**CONFLICTS OF INTEREST**

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

**DATA AVAILABILITY STATEMENT**

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

**AUTHOR CONTRIBUTIONS**

Conceptualization: Ha Yeon Park, Junyong In. Data curation: Ha Yeon Park, Hey Ran Choi, Yong Beom Kim, Seok Kyeong Oh, Taehoon Kim, Hong Seuk Yang, Junyong In. Formal analysis: Ha Yeon Park, Junyong In. Methodology: Ha Yeon Park. Project administration: Ha Yeon Park, Junyong In. Visualization: Ha Yeon Park, Junyong In. Writing - original draft: Ha Yeon Park, Junyong In. Writing - review & editing: Ha...
REFERENCES


A new hematologic predictor of major adverse events after cardiac surgery: red cell distribution width to lymphocyte ratio

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Background: The perioperative risk factors that cause severe morbidity and prolongation of postoperative hospital stay after cardiac surgery should be determined. Various scores have been used to predict morbidity and mortality. Preoperative blood counts are considered potential biomarkers of inflammation and oxidative stress. Inflammatory and immune imbalances may have a significant impact on postoperative adverse events. The present study aimed to investigate the association and potential predictive properties of red cell distribution width/lymphocyte ratio (RLR) for major adverse events in adult patients who underwent coronary surgery with cardiopulmonary bypass.

Methods: After approval from the ethics committee, pre- and post-operative data of 700 patients were obtained from the electronic database of the hospital, intra- and post-operative anesthesia, and intensive care unit follow-up charts. We performed a stepwise multiple logistic regression analysis to investigate the association of RLR with major adverse events in adult patients who underwent coronary surgery with cardiopulmonary bypass.

Results: Among 700 patients, 47 (6.7%) had major adverse events after surgery. Multivariate logistic regression analysis showed that age (odds ratio [OR], 1.08; 95% confidence interval [CI], 1.03–1.12; P < 0.001), mean platelet volume (OR, 1.49; 95% CI, 1.07–2.06; P = 0.017), and RLR (OR, 1.21; 95% CI, 1.02–1.43; P = 0.026) were significantly associated with major adverse events.

Conclusions: RLR indicates the balance between inflammatory and immune responses. Therefore, it can be used to predict adverse events following coronary surgery.

Keywords: Blood cell count; Cardiac surgical procedures; Erythrocyte indices; Inflammatory and immune imbalances; Preoperative blood counts.

INTRODUCTION

Over the last few decades, the field of cardiac surgery has shown remarkable improvement with advances in surgical techniques and perioperative care. Complex surgeries in patients with multiple comorbidities have become routine procedures. However, the 30-day mortality rate after cardiac surgery still ranges from 1 to 4% [1]. Cardiac, pulmonary, or neurologic dysfunctions; bleeding; thrombosis; and acute kidney injuries are the major causes of in-hospital mortality.
after cardiac surgery. Recent studies have made notable efforts to predict post-operative adverse events and mortality after cardiac surgery [2]. Many preoperative predictors or algorithms are still being investigated to identify patients with an increased risk of adverse events. Current research suggests that inflammatory and immune imbalances may significantly impact postoperative adverse events. Inflammatory processes are responsible for the progression of vascular wall damage. Immune cells migrate to the endothelium after vessel damage and facilitate platelet activation. The degree of immune cell activation may enable the prediction of morbidity and mortality [3]. Several markers, including red cell distribution width (RDW), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio, and platelet-to-lymphocyte ratio (PLR), have been suggested, which are easily accessible from complete blood counts [4,5].

A new marker, RDW-to-lymphocyte ratio (RLR), a combination of two parameters, is an easily acquired parameter using a routine complete blood count and has received attention in oncological research as a predictor of worse prognosis since both RDW and lymphocytes are included in inflammatory reactions [6-8]. However, it has not yet been investigated as a predictor of adverse events in cardiac surgery patients.

The present study investigated the association between potential predictive properties of RLR for major adverse events in adult patients who underwent coronary surgery with cardiopulmonary bypass. The identification of new predictive markers may allow for determining patients at high risk.

**MATERIALS AND METHODS**

This was a retrospective, longitudinal observational study comprising adult patients who underwent elective coronary surgery with cardiopulmonary bypass (CPB) between January 2017 and January 2022. This study complied with the Declaration of Helsinki, and ethical approval was granted by the local institutional ethical board (E1-22-2658, 15.06.22). Trial Registration number: NCT05341037

The exclusion criteria were patients aged < 18 years; those with ejection fraction below 30%, preoperative kidney injuries and liver diseases, malignancies, and infections; those who underwent ventricular assist device placement, heart transplantation, emergency and repeated surgeries; or those who lacked clinical data. The pre- and post-operative data of the patients were obtained from the electronic database of the hospital, intra- and post-operative anesthesia, and intensive care unit (ICU) follow-up charts. All data were collected between June and July 2022.

Preoperative complete blood count parameters, including the number of neutrophils, number of lymphocytes, hemoglobin, RDW, number of platelets, mean platelet volume (MPV), NLR, PLR, and RLR were determined on the first day of hospital admission before surgery as baseline values. NLR was calculated as the neutrophil number divided by the number of lymphocytes, PLR as the number of platelets divided by the number of lymphocytes, and RLR as the RDW value divided by the number of lymphocytes.

Major adverse events (MAE) were determined as follows: (1) all-cause mortality; (2) major adverse cardiac events such as stroke, acute myocardial infarction, and acute heart failure [9]; (3) acute renal failure; (4) prolonged mechanical ventilation (> 24 h); (5) sternal wound infection; (6) the need for additional surgery for any reason within 30 days after surgery.

**Statistical analysis**

The SPSS for Windows 20.0 (IBM Co.) was used for statistical assessments. The Kolmogorov–Smirnov test was used to determine the distribution of data. Continuous variables with normal distribution are expressed as mean ± standard deviation, and variables without a normal distribution are given as median (interquartile range). Categorical variables are presented as numbers and percentages. Continuous variables were compared with independent two-sample t-tests or Mann–Whitney U tests where appropriate. Categorical variables were compared using chi-squared tests. Univariate and multivariate logistic regression analyses were used to calculate the odds ratio (OR) and 95% confidence interval (CI) to identify independent predictors of MAE. A stepwise multiple logistic regression analysis was fitted for the main covariates, which were determined based on their univariate associations (P < 0.100) or included based on knowledge of their strong association with MAE. The multivariate model was adjusted for variables such as age, sex, body mass index, diabetes mellitus, hypertension, and laboratory data. Multicollinearity was examined in the model, and the Box-Tidwell test was used to check the logit linearity for the continuous independent variables in the logistic regression analysis. Model fit was analyzed using the Hosmer–Lemeshow test. Potential interactions between MAE and
other covariates were examined by including an interaction term in the model, and their significance was determined. With the RLR and MPV scores as the test variables and MAE as the status variable, the receiver operating characteristic (ROC) curve was formulated, and the diagnostic value of the RLR score was determined according to the area under the curve (AUC). In statistical analysis, \( P < 0.05 \) was considered to be statistically significant.

**RESULTS**

A total of 700 adult patients who underwent coronary surgery participated in our study. Among them, 47 (6.7%) patients had MAE after surgery. The mean age was 58.4 ± 11.9 years, and 74.9% of patients were men. Approximately 2.5% (n = 18), 4.0% (n = 28), 3.1% (n = 22), 0.4% (n = 3), 2.7% (n = 19), and 3.4% (n = 24) had acute renal failure, major adverse cardiac events, prolonged mechanical ventilation, sternal wound infection, need for additional surgery, and mortality, respectively.

Table 1 compares the patients’ demographics and baseline laboratory values according to MAE occurrence. Patients in the MAE (+) group were older and had a higher percentage of hypertension \( (P < 0.001) \). The MAE (+) group also had lower lymphocyte count and higher NLR and PLR \( (P = 0.002, 0.002, \text{and} 0.002, \text{respectively}) \).

Multivariate logistic regression analysis using the MAE as the dependent variable showed that age \((\text{OR}, 1.08; 95\% \ CI, 1.03-1.12; P < 0.001)\); MPV \((\text{OR}, 1.49; 95\% \ CI, 1.07-2.06; P = 0.017)\); and RLR \((\text{OR}, 1.21; 95\% \ CI, 1.02-1.43; P = 0.026)\) were significantly associated with MAE (Table 2). The model explained 23.5\% (Nagelkerke \( R^2 \)) of the variance in MAE (Table 2). No significant violations of the linearity of the logit assumption were found in the multivariate model.

The ability of RLR and MPV to predict the presence of MAE was evaluated using ROC curve analysis. The AUC values of RLR and MPV were 0.606 (95\% CI, 0.522–0.691; \( P = 0.015 \)) and 0.552 (95\% CI, 0.470–0.633; \( P = 0.234 \)) for MAE postoperatively, respectively. The RLR predicted the MAE by a statistically significant margin (Fig. 1).

**DISCUSSION**

In the current study, the overall incidence of major adverse events was 6.7\%, and at an advanced age, higher levels of preoperative RLR and MPV were associated with higher rates of adverse events within 30 days of cardiac surgery. Additionally, the relationship between RLR and major adverse events in these patients remained significant even after adjusting for possible confounding factors. Accordingly, this finding provides evidence of the evaluated risk of major adverse events among individuals undergoing cardiac surgery.

### Table 1. Baseline Characteristics and Laboratory Data of Participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n = 700)</th>
<th>Major adverse events</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Negative (n = 653)</td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td>Positive (n = 47)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>58.4 ± 11.9</td>
<td>57.8 ± 11.6</td>
<td>66.6 ± 10.1</td>
</tr>
<tr>
<td>Sex (M)</td>
<td>524 (74.9)</td>
<td>488 (74.7)</td>
<td>36 (67.1)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>28.0 ± 4.8</td>
<td>28.1 ± 4.8</td>
<td>27.2 ± 5.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>328 (47.2)</td>
<td>298 (45.9)</td>
<td>30 (56.2)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>215 (30.7)</td>
<td>200 (30.6)</td>
<td>15 (31.9)</td>
</tr>
<tr>
<td>Baseline laboratory values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil ((\times 10^9/L))</td>
<td>5.5 ± 2.2</td>
<td>5.5 ± 2.2</td>
<td>5.9 ± 2.8</td>
</tr>
<tr>
<td>Lymphocyte ((\times 10^9/L))</td>
<td>2.2 ± 1.1</td>
<td>2.2 ± 1.1</td>
<td>1.9 ± 0.8</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>13.8 ± 1.8</td>
<td>13.9 ± 1.8</td>
<td>13.1 ± 2.7</td>
</tr>
<tr>
<td>RDW (%)</td>
<td>14.2 ± 1.7</td>
<td>14.2 ± 1.7</td>
<td>14.4 ± 1.5</td>
</tr>
<tr>
<td>Platelet ((\times 10^9/L))</td>
<td>231.7 ± 66.7</td>
<td>232.2 ± 66.5</td>
<td>226.1 ± 70.1</td>
</tr>
<tr>
<td>MPV (fl)</td>
<td>9.0 ± 1.1</td>
<td>9.1 ± 1.1</td>
<td>9.2 ± 1.1</td>
</tr>
<tr>
<td>NLR</td>
<td>3.1 ± 0.6</td>
<td>3.0 ± 0.2</td>
<td>3.4 ± 1.6</td>
</tr>
<tr>
<td>RLR</td>
<td>7.7 ± 6.6</td>
<td>7.7 ± 6.5</td>
<td>9.0 ± 6.4</td>
</tr>
<tr>
<td>PLR</td>
<td>108 (84, 137)</td>
<td>107 (83, 136)</td>
<td>120 (98, 146)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, number (%), or median (1Q, 3Q). RDW: red cell distribution width, MPV: mean platelet volume, NLR: neutrophil to lymphocyte ratio, RLR: RDW to lymphocyte ratio, PLR: platelet to lymphocyte ratio.
RDW reflects the size variability of circulating red blood cells (RBC) and is routinely measured in complete blood counts. It is calculated by dividing the standard deviation of the RBC volume by the mean corpuscular volume and multiplying it by 100 to express the result as a percentage [10]. It does not carry additional costs or risks for patients. Higher RDW values indicate greater variation in the distribution of RBC volume in the circulation. The current study suggests that higher RDW values are associated with inflammatory reactions and oxidative stress. The reason for this is that inflammation results in changes in RBC maturation by disturbing the red cell membrane, leading to increased RDW [11]. The correlation between RDW and inflammatory markers has been previously shown [10]. Erythropoiesis in oxidative stress results in large immature erythrocytes in the circulatory system, which can be concluded with elevated RDW [12]. RDW reveals the ability of cells to support the strong hypoxia stress under high-stress circumstances such as surgeries [13]. This can explain the higher rates of morbidity in patients with higher RDW values [11]. Higher values of RDW have been reported as a strong predictor of morbidity and mortality in studies including patients with coronary disease [14], aortic valve replacement [11], pulmonary hypertension [15], heart failure [16], and those undergoing percutaneous coronary intervention.

Lymphocytes are a significant part of the immune response system and play critical roles in the production of cytokines. A low lymphocyte count is linked to an increased incidence of cardiovascular events [17]. Several studies have shown the association of lymphocyte-based inflammatory markers, such as PLR and NLR, with adverse outcomes in cardiac surgery [3-5].

RLR, a combination of RDW and lymphocytes, may reflect a better balance of inflammation [6]. Higher RDW and fewer lymphocytes are associated with worse outcomes in the oncological group of patients [6-8]. They commonly claim that the level of RLR combines the overall state of the patient’s immunity and inflammation [7]. In patients with higher baseline inflammatory status, cardiac surgery may further exacerbate inflammatory mechanisms [18,19]. Consistent with this, a recent study conducted in older cardiac surgery patients suggested that elevated RLR levels are associated with a prolonged length of stay in the ICU [19]. Additionally, researchers have emphasized that preoperative RLR may have predictive value for the risk of long-term ICU stay in this population. However, they could not evaluate MAE as a study outcome. Therefore, this is one of the unique studies

![ROC curve](image)

**Table 2. Logistic Regression Analysis for the Predictors of 30-day Major Adverse Events after Coronary Artery Surgery**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio (95% CI) (multivariate)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>1.07 (1.03–1.12)</td>
<td>0.001</td>
</tr>
<tr>
<td>Sex (M)</td>
<td>0.58 (0.24–1.39)</td>
<td>0.228</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.95 (0.87–1.03)</td>
<td>0.203</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.65 (0.77–3.54)</td>
<td>0.202</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.83 (0.22–3.24)</td>
<td>0.792</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>1.12 (0.95–1.45)</td>
<td>0.142</td>
</tr>
<tr>
<td>Lymphocyte</td>
<td>0.20 (0.04–1.01)</td>
<td>0.050</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>0.92 (0.76–1.12)</td>
<td>0.400</td>
</tr>
<tr>
<td>RDW</td>
<td>0.76 (0.55–1.03)</td>
<td>0.076</td>
</tr>
<tr>
<td>Platelet</td>
<td>1.01 (1.0–1.02)</td>
<td>0.131</td>
</tr>
<tr>
<td>MPV</td>
<td>1.49 (1.08–2.06)</td>
<td>0.017</td>
</tr>
<tr>
<td>NLR</td>
<td>0.86 (0.70–1.06)</td>
<td>0.141</td>
</tr>
<tr>
<td>RLR</td>
<td>1.21 (1.02–1.43)</td>
<td>0.026</td>
</tr>
<tr>
<td>PLR</td>
<td>0.98 (0.95–1.01)</td>
<td>0.119</td>
</tr>
</tbody>
</table>

CI: confidence interval, RDW: red cell distribution width, MPV: mean platelet volume, NLR: neutrophil to lymphocyte ratio, RLR: RDW to lymphocyte ratio, PLR: platelet to lymphocyte ratio. Multivariate analysis is adjusted for variables, including age, sex, body mass index, diabetes mellitus, hypertension, and laboratory data. P < 0.05 is considered to be statistically significant.
depicting the relationship between RLR and MAE in cardiac surgery patients.

The present study demonstrated another association of an inflammatory predictor, MPV, with adverse events. MPV is an indicator of platelet activity and plays a significant role in the pathogenesis of atherosclerosis. Enlarged and reactive platelets accompany cardiovascular diseases [20]. Previous studies have shown an association between high MPV levels and adverse events after coronary surgeries [21-23].

This study had some limitations. First, it was a retrospective, non-randomized register study on patients undergoing coronary surgery. Studies on MAE after cardiac surgery generally compare surgical techniques, anesthesia, or CPB management techniques. However, this study population had the same coronary surgery technique, anesthesia, fluid, and CPB management and did not focus on intraoperative variables. Second, the authors did not perform long-term follow-up; only 30-day complications were analyzed.

In conclusion, the prediction of adverse events after cardiac surgery is crucial for managing the postoperative period. Moreover, predictors should also guide clinicians in considering the risks versus benefits [2]. RLR is a valuable parameter that can be used to identify high-risk patients, as it is significantly associated with adverse events compared to previously reported immunologic and inflammatory markers based on blood cells.

FUNDING

None.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

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REFERENCES

Red cell distribution width to lymphocyte ratio and adverse events


With the increase in elderly population, the rate of hip surgeries in elderly patients is gradually increasing. Worldwide, more than 1.5 million adults are diagnosed with hip fractures annually [1]. Early hip surgery is known to be effective in reducing mortality, and surgical treatment is recommended as soon as possible after injury [1]. Delayed surgery for hip fractures is a well-known risk factor for venous thromboembolism [2]. The overall incidence of thromboembolic disease in patients with hip fracture is 11.9%. Delayed surgery increases the incidence and relative risk of thromboembolic disease. When surgery was delayed by one day, the incidence and relative risk increased to 14.5% and 2.32, respectively, while after seven days, the incidence was 33.3% and the relative risk was 3.71 [2]. Therefore, hip surgery is recommended at the earliest following injury. However, the recent coronavirus disease (COVID-19) era has led to some delay in surgeries due to screening and quarantine [3]. Several studies have reported that COVID-19 can induce a hypercoagulable state and cause multiple thromboembolic events [4].

We report a case of intraoperative anesthetic management in a patient with preoperative asymptomatic pulmonary
thromboembolism (PTE) who tested positive for COVID-19 after a hip fracture and underwent delayed surgery 21 days after injury.

**CASE REPORT**

Written informed consent for the procedure and publication of this report was obtained from the patient and her family members. The Institutional Review Board waived the review of this case (IRB no. 2022-12-015). This case report was written according to the recommendations of the Case Report (CARE) guidelines.

An 88-year-old female patient (height, 150 cm; weight, 50 kg; body mass index, 22.2 kg/m²) was transferred to our hospital with right hip pain after falling while walking using a walker 18 days before the hospital visit. The patient had a history of hypertension and dementia. After several days of conservative observation at home, there was no improvement in the hip pain. Initially, she visited another hospital four days after the injury, was diagnosed with an intertrochanteric fracture, and underwent the planned surgical treatment. During the preoperative evaluation, the patient was diagnosed with COVID-19 and transferred to an isolation ward. After one day in the isolation ward, the patient’s blood pressure (BP) dropped to 94/39 mmHg due to urinary tract infection, sepsis, and ischemic colitis, and she was transferred to the intensive care unit (ICU). Therefore, the patient could not undergo the planned surgery. After treatment for ischemic colitis and septic shock, the patient was transferred to our hospital for surgical treatment 18 days after the injury. Preoperative laboratory findings were as follows: hemoglobin, 9.0 g/dl; platelet, 169,000 μl; serum albumin, 3.28 g/dl (normal range 3.5–5.2 g/dl); C-reactive protein, 2.7 mg/dl; sodium, 139 mEq/L (normal range 136–145 mEq/L); arterial blood gas analysis, pH 7.55, pCO₂ 37 mmHg, PO₂ 63 mmHg, HCO₃⁻ 32.1 mmol/L, SaO₂ 94.1%; prothrombin time (PT), 14.8 s; international normalized ratio, 1.21; activated partial thromboplastin Time, 35.3 s; and D-dimer of 18.94 μg/ml (normal range < 0.5 μg/ ml). To evaluate COVID-19 pneumonia, we performed chest computed tomography (CT), which showed diffuse PTE in both the main and left upper lobar/segmental pulmonary arteries, consolidation in the right lower lobe, ground glass opacity in both lower lobes, a small amount of right pleural effusion, and left 4–9th, 11–12th rib fractures (Fig. 1A, B, C). Abdominopelvic CT scan revealed deep vein thrombus (DVT) in the left common iliac vein and left external iliac vein. Transthoracic echocardiography revealed a 65% ejection fraction, mild aortic stenosis, a thickened and calcified mitral valve with trivial mitral regurgitation, and visible echogenic material in the left atrium; however, electrocardiography showed no atrial fibrillation. Cardiology consultation recommended delayed surgery 2–3 days after heparinization as prophylaxis for the ongoing PTE and insertion of an inferior vena cava (IVC) filter (ALN Optional Vena Cava Filter with Hook, ALN) (Fig. 2). The patient was admitted to the operating room for planned right hip hemiarthroplasty. Preoperative vital signs were BP 165/78 mmHg, heart rate...
72 beats/min, body temperature 36.5°C, respiratory rate 20/min, and oxygen saturation 91% with two liters of O₂ through nasal prongs. During surgery, the continuous radial arterial pressure, train-of-four (TOF), and bispectral index (BIS) were monitored. Anesthesia was induced using remimazolam (5 mg/kg/h) and rocuronium (35 mg). After confirming a BIS of 40 and 0% TOF, tracheal intubation was performed. Anesthesia was maintained using remimazolam (1 mg/kg/h) and remifentanil (0.2 µg/kg/min). We chose remimazolam as the induction and maintenance agent to reduce hemodynamic instability. The cardiac surgery team judged it challenging to cannulate the patient and initiate extracorporeal membrane oxygenation (ECMO) immediately in case of a sudden cardiac arrest as the surgery was performed in the left lateral decubitus position. Therefore, the cardiac surgery team inserted an introducer sheath (Prelude® sheath introducers 5 Fr, Merit medical systems, Inc.) into the right femoral artery and vein, for performing ECMO, to be connected in case of an emergency. For intraoperative transesophageal echocardiography (TEE) monitoring, a TEE probe was inserted to evaluate the thrombus in the left atrium; however, no thrombus was observed. The patient’s mean arterial pressure was maintained at over 70 mmHg during surgery by administering an ephedrine bolus of 5 mg four times. The total amount of fluid administered to the patient was 1,400 ml of plasmalyte, the amount of bleeding was 300 ml, and the urine output was 90 ml. The total anesthetic time was 190 min and the total operating time was 170 min. At the end of the surgery, all anesthetics were stopped, and 0.2 mg of flumazenil was used to reverse remimazolam. The patient had a TOF of 100% and was administered pyridostigmine (10 mg) and glycopyrrolate (0.2 mg) to reverse muscle relaxation. The patient was able to breathe spontaneously and tracheal extubation was performed without any complications. The patient was transferred to the ICU. On postoperative day 2, the ECMO sheaths were removed, and the patient was transferred to the general ward without any specific events. The IVC filter was removed on postoperative day 8, and the patient was discharged without any complication.

**DISCUSSION**

The patient was diagnosed with COVID-19 and asymptomatic PTE, and was administered general anesthesia after inserting an IVC filter before surgery. The patient scored 88 points on the pulmonary embolism severity index (PESI), which is used as a risk stratification tool for PTE. The patient’s PESI was solely influenced by her advanced age of 88 years and not by the other ten clinical criteria used to calculate PESI score such as sex, history of cancer, respiratory rate, temperature, or history of heart failure. However, this score represents a moderate-risk group with an expected 30-day mortality rate of 3.2–7.1%, and higher levels of care are recommended [5]. Hip fracture surgery is recognized as a surgical procedure with a heightened risk of venous thromboembolism. Several factors, including advanced age, female sex, elevated body mass index, and surgical procedures lasting over two hours, have been identified as potential risk factors [6]. Delayed surgery in patients with hip fractures is also a risk factor for thromboembolism [2]. To reduce delirium and postoperative hospital stay, accelerated surgery, that is, surgery within 6 h after injury, has been proposed [1]. Therefore, even during the COVID-19 era, early surgery is advantageous for favorable patient outcomes. However, in this case, the patient stayed home for four days after the injury, and the operation was postponed because of sepsis.

Several studies have reported that COVID-19 infection itself is associated with PTE. According to a meta-analysis, the incidence of PTE in patients with COVID-19 is 14.7% in the general ward and 23.4% in the ICU [7]. This result represents a higher incidence compared to 2.1% in ICU patients during the pre-pandemic period [8]. In addition, the incidence of

**Fig. 2.** A fluoroscopic image was taken during the inferior vena cava filter insertion procedure.
PTE in COVID-19-infected patients was nine times higher than that in non-COVID-19 patients. The in-hospital mortality of COVID-19-infected patients with PTE was 16.6%, similar to 16.0% in COVID-19 patients without PTE; therefore, it seems that PTE does not make a big difference in COVID-19 mortality. However, compared with the in-hospital mortality of 6.5% in non-COVID-19 patients with PTE, the mortality rate of COVID-19 patients with PTE is more than twice as high [9].

The exact epidemiology and pathophysiological mechanisms related to COVID-19-associated PTE remain unknown. Several studies have reported that COVID-19 increases the probability of thromboembolism [4,10]. Several factors are associated with the mechanisms related to the hypercoagulable state in COVID-19 patients [4]. First, direct and indirect factors such as severe hypoxia, underlying diseases, and organ dysfunction caused by COVID-19 may be associated with various hemostatic abnormalities [10]. Second, complement activation and cytokine release may result in proinflammatory and procoagulant effects due to endothelial dysfunction, von Willebrand factor elevation, Toll-like receptor activation, and tissue-factor pathway activation. Dysregulation of the coagulation cascade leads to the formation of intraalveolar systemic fibrin clots [4]. Third, releasing proinflammatory cytokines called ‘Cytokine storm’ increases the risk of intravascular microthrombosis and induces secondary local consumption coagulopathy [10]. Fourth, the interactions between several blood cell types may be a critical factor in the pro-coagulant effect of viral infections [4]. Due to the hypercoagulable state, patients with COVID-19 present with higher levels of D-dimer, fibrinogen and fibrinogen degradation products, prolonged prothrombin time, international normalized ratio, and thrombin time [4]. These coagulation abnormalities are associated with a poor prognosis [8]. The patient, in this case, also showed an increase in D-dimer to 18.94 µg/ml, which indicated the presence of PTE.

Since the COVID-19 pandemic, there have been concerns regarding delays in transporting trauma patients to hospitals due to the collapse of the healthcare system. According to Jarvis et al. [11], after the COVID-19 pandemic, the time to visit the hospital after the injury (injury to hospital arrival time) required for patients undergoing hip surgery took an average of 11.5 min longer than that before the pandemic. Nevertheless, this was not clinically meaningful, and there was a significant difference in the injury-to-hospital arrival time only when the number of infections surged during the early stages of the pandemic. However, the in-hospital mortality rate was 3.4% after the pandemic compared to 1.1% before the pandemic. According to Kim et al. [3], there was no significant difference in the overall time to surgery before and after the pandemic; however, the proportion of cases in which surgery was delayed by more than 36 h increased significantly after the pandemic. The reason for the delay in surgery was the time needed for medical investigation and stabilization. Preoperative tests and examinations that should be performed outside the isolation room or in contact with other people, such as electrocardiography, pulmonary function tests, and imaging, were postponed, and the patient was quarantined until the COVID-19 test was negative. In this report, 30-day mortality did not differ before and after the COVID-19 pandemic.

According to a meta-analysis comparing the prognosis of patients who underwent hip surgery before and after COVID-19, there was no significant difference in the 30-day mortality [12]. However, a comparison between COVID-19-infected and non-infected patients revealed higher mortality rates in the former [12]. It is difficult to generalize the situation because of regional differences between the COVID-19 epidemic period and the medical system. However, except for some surges in COVID-19 infections, early hip surgery was performed similarly to that in the pre-pandemic period. Postoperative mortality was similar but increased in COVID-19-infected patients.

In patients who underwent total hip/knee arthroplasty in April 2020, when the lockdown was implemented due to COVID-19 in the United States, the incidence of PTE/DVT after surgery increased more than three-fold compared to the same period before the pandemic [13]. The authors suggested that the reasons for immobility were a decrease in activity during the initial lockdown of the pandemic and COVID-19. Although patient history of COVID-19 was not investigated, the authors noted that asymptomatic COVID-19 infection may have increased the incidence of PTE/DVT in unknown patients. Cuthbert et al. [14] reported that postoperative ICU admission was 27% in COVID-19-positive patients with hip fractures after the pandemic compared to 5% in COVID-19-negative patients. In addition, the length of hospital stay (median 23 days vs. 9 days, P < 0.001) and 30-day mortality (29% vs. 10%, P = 0.001) increased, and thromboembolic events occurred in 9.8% of COVID-19 positive patients.

An IVC filter was inserted to prevent additional thromboembolic events before surgery. IVC filters are recommended when a patient has venous thromboembolic disease, with an
absolute contraindication to anticoagulation, problems that require stopping anticoagulation, or recurrent venous thromboembolism after receiving appropriate anticoagulation [6]. Because surgery was planned for our patient, anticoagulation therapy could not be continued for a sufficient period. Therefore, an IVC filter was inserted. In our patient, an ECMO sheath was inserted in advance, along with an IVC filter, to prepare for cardiac arrest. Although there are no specific guidelines for ECMO preparation in stable patients, ECMO was necessary because of the patient’s advanced age and the lateral position required for surgery. Delaying ECMO initiation by more than 30 min in cases of acute pulmonary embolism can result in worse patient outcomes. [15].

In conclusion, this case report presents a geriatric patient diagnosed with a hip fracture, COVID-19, and asymptomatic PTE. Despite sepsis-related delays in hip surgery, general anesthesia was safely administered after heparinization and insertion of an IVC filter. Given the inevitability of delayed hip surgery in patients with COVID-19, the likelihood of developing PTE is significantly increased. Hence, the evaluation and prophylaxis for this condition are of utmost importance.

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None.

**CONFLICTS OF INTEREST**

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

**DATA AVAILABILITY STATEMENT**

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

**AUTHOR CONTRIBUTIONS**


**REFERENCES**


A pacemaker is a device that assists circulation by generating electrical impulses. An increasing number of arrhythmic patients are supported by pacemakers [1]. Pacemaker failure can be catastrophic for device-dependent patients. Patients with pacemakers or cardioverter/defibrillators who are scheduled to undergo surgery are vulnerable to device-related complications, including pacemaker malfunction. Cautious perioperative management, including magnet or reprogramming of the device to asynchronous mode, is required to prevent undesirable events [2]. Furthermore, the operation team should be aware of the current detailed status of pacemakers by reviewing medical documentation and cardiologist consultation. Here, we present the case of a patient with an unanticipated mode change of pacemaker during living donor liver transplantation. This case report was approved by our Institutional Review Board (no. 2022-11-075), and written informed consent was obtained from the patient for the publication of this case.

CASE REPORT

A 66-year-old, 82.4-kg, 167.5-cm man with alcohol-associated hepatocellular carcinoma underwent living-donor liver transplantation. He initially experienced intermittent chest discomfort after exercise one year before liver transplantation, and atrial fibrillation with a heart rate of 30 to 45 was
observed on electrocardiogram. After short-term follow-up, he was diagnosed with sick sinus syndrome and paroxysmal atrial fibrillation with slow ventricular response or junctional bradycardia. A pacemaker (DDDR, ACCOLADE Magnetic Resonance Imaging [MRI] EL DR L331, Boston) was inserted one month before the surgery in order to manage arrhythmia (Fig. 1). Ventricular and atrial endocardial pacing leads were inserted into the left subclavian vein. They were positioned in the right ventricle midseptum and right atrium appendage using fluoroscopic guidance, respectively. He had no pacemaker-related problems since its application. Cardiologic consultation showed that the pacemaker was functioning well and tolerable for liver transplantation after its mode change.

The initial laboratory results were 11.0 g/dl hemoglobin, 35.4% hematocrit, 118 × 10^3/μl platelet count, 14.0 s prothrombin time with an international normalized ratio of 1.10, and 38.5 s activated partial thromboplastin time. Preoperative electrocardiogram showed sinus bradycardia with a rate of 58 beats per minute and first degree atrioventricular block (Fig. 2). Diastolic dysfunction grade 1 with left atrial enlargement and minimal tricuspid regurgitation was found on echocardiography. The left ventricular ejection fraction was 70%, and no regional wall motion abnormalities were observed. The preoperative interrogation report showed that his pacemaker was programmed for synchronous dual-chamber pacing (DDD) at 50–130 beats per min. The patient’s intrinsic rhythm was a sinus with 60 beats per min. The sensitivity of the pacemaker electrode is defined as the minimum myocardial voltage required to be detected as a P-wave or R-wave. The original state of atrial sensitivity was 0.75 mV, and right ventricular sensitivity was 2.5 mV. The pacemaker output was the current delivered in a burst from the pulse generator. The initial atrial output was 3.5 V per 0.40 ms, and right ventricular output was 3.5 V per 0.40 ms.

**Fig. 1.** Chest radiography with pacemaker leads.

**Fig. 2.** Preoperative electrocardiogram with pacemaker. aVR: augmented vector right, aVL: augmented vector left, aVF: augmented vector foot.
The pacemaker mode was reprogrammed preoperatively. Since the pacemaker was capable of functioning during MRI scanning, a cardiac implantable electronic device (CIED) specialist selected MRI mode for reprogramming and protection mode time out; the time limitation that pacemaker mode automatically reverses to the original status was set to 24 h. Unfortunately, the anesthesiologist and surgeon were unaware of the detailed information on pacemaker interrogation. The pre-anesthetic visit notes did not include details pertaining to the pacemaker model, variables, and settings.

After standard monitoring including a 5-lead electrocardiogram, general anesthesia was induced with intravenous thiopental sodium 350 mg, vecuronium 8 mg and sevoflurane. Intubation was performed easily with a plain endotracheal tube. The patient was mechanically ventilated with a tidal volume of 6 ml/kg and a positive end-expiratory pressure of 6 cmH₂O. Invasive arterial blood pressure monitoring was performed with right radial artery and right femoral artery cannulation. The right femoral vein was catheterized to monitor compression of the inferior vena cava during the surgical procedure. A 9-Fr catheter (ARROW MAC 2 lumen, Teleflex) and pulmonary artery catheter (Swan-ganz CCOMbo V, Edwards Lifesciences) were inserted via the right internal jugular vein. Anesthesia was maintained with sevoflurane and continuous infusion of vecuronium (0.6 μg/kg/min). Intravenous dopamine (3–10 μg/kg/min) and norepinephrine (0.05–0.1 μg/kg/min) were continuously infused to maintain mean blood pressure above 70 mmHg. Intravenous dopamine (5 μg/kg/min) was administered during the reperfusion period. Epinephrine was not required during the whole period of liver transplantation, including the reperfusion period. Blood loss, calculated as lost red cell mass, was 1,341 ml [3] and total urine output was 770 ml. One unit of pre-leukocyte-reduced red blood cells, two units of fresh frozen plasma and 963 ml of autologous red cell mass acquired from Cell Saver was transfused during transplantation. The total anesthesia time was 8 h and 59 min.

Overall, liver transplantation was performed without adverse events. The pacing rhythm was maintained at 90 bpm. However, the pacemaker suddenly failed to provide a regular pacing rhythm during abdominal closure with staplers. The heart rate slowed at 70–80 bpm, and QT prolongation was observed on electrocardiography. ST-II was –0.3 and ST-V was –0.5 at the time of the event, and there was no abnormality in the PR interval. Arterial blood gas analysis showed normokalemia (K⁺ 5.3 mmol/L) and mild acidosis (pH 7.278, pCO₂ 42.4 mmHg, HCO₃⁻ 19.3 mmol/L, base excess –7.0 mmol/L). No additional antiarrhythmic drugs were infused during the operation. In summary, pacemaker malfunction was not likely caused by metabolic abnormalities or myocardial ischemia. Surgeons were immediately notified of pacing errors. There was no probable surgical procedure that might have deteriorated the pacemaker function. Intravenous atropine 0.25 mg was administered to prevent further delay in cardiac rhythm. CIED specialists were not available immediately after the unexpected pacemaker mode changes as it occurred outside their regular working hours. Fortunately, the native heart rate was maintained above 70 bpm, and the blood pressure did not fluctuate after pacing failure (Fig. 3). The risk of electromagnetic interference (EMI) was low because the additional use of monopolar electrocautery was not expected for residual operations. Since the operation was about to end, we decided to transfer the patient to the intensive care unit without additional medical management or interrogation of the pacemaker function. Moreover, on-call CIED specialists were urgently consulted for additional pacemaker interrogation because the attending anesthesiologists suspected a pacemaker mode change.

The patient was transferred to the intensive care unit (ICU) postoperatively with a continuous infusion of dopamine 10 μg/kg/min and norepinephrine 0.05 μg/kg/min. Norepinephrine was discontinued immediately after arrival due to high blood pressure, and intravenous remifentanil infusion was started for sedation. Dopamine was tapered off the day after surgery. The postoperative laboratory findings were as follows: hemoglobin 10.2 g/dl, hematocrit 33.2%, platelet count 98 × 10⁹/µl, prothrombin time 28.6 s with an international normalized ratio 2.81, and activated partial thromboplastin time 83.7 s. Pacemaker interrogation was performed by a cardiologist and on-call CIED specialist 24 min after arrival at the ICU, and the pacemaker was found to be in DDD mode, which implies automatic preset reversal. There were no technical issues regarding the pacemaker battery or lead position changes. Upon retrospective analysis, the preoperative pacemaker reprogramming duration setting of 24 h was revealed to be the cause of unexpected pacing failure. The pacemaker mode was reprogrammed from DDD to DOO with 90 beats per min, on the evening of the day before surgery by a CIED specialist to prevent EMI caused by intraoperative use of electrocautery. Both atrial and right ventricular outputs were converted to 5.0 V per 1.0 ms. Additional information on pacemaker interrogation is shown in Table 1. The CIED specialist did not consider 24 h to be insufficient for liver transplantation and reprogrammed the
pacemaker using a routine preoperative setting that was appropriate for short and simple surgical procedures. Postoperatively, the anesthesiologists provided feedback, including preoperative confirmation of pacemaker mode change and cooperation flow to handle emergent pacemaker crises, to the CIED specialist to prevent recurrent events.

The following day, the patient was referred for emergent surgical bleeding control. His pacemaker was rearranged to asynchronous mode (DOO mode) just before the operation to prevent repetitive errors (Table 1). During the second operation, a 4 × 4 cm hematoma was found in the subhepatic hilar portion. No active bleeding was found after hematoma evacuation, and additional ligation with bleeding control was performed. Five days after liver transplantation, the patient was transferred to the general ward with stable vital signs. On the day of the follow-up outpatient appointment, the anesthesiologist visited the patient and explained the cause of the intraoperative event and further possibilities for pacemaker mode change.

**DISCUSSION**

Cardiac pacemakers have rapidly evolved from simple electrical stimulators to advanced medical devices that can provide personalized anti-arrhythmic treatment. The first modern cardiac pacemaker was developed in 1932 by American physiologist Albert S. Hyman, who created an electromechanical device powered by a hand-cranked motor. Hyman attempted to provide electric impulses to the patient’s right atrium by connecting an external direct current gener-

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**Table 1. Timeline of Pacemaker Interrogation (Liver transplantation [22.06.21 08:37-17:36])**

<table>
<thead>
<tr>
<th>Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Self rhythm</td>
<td>Sinus with 69 bpm</td>
</tr>
<tr>
<td>Pacemaker mode</td>
<td>DDD</td>
</tr>
<tr>
<td>Rate (base/upper)</td>
<td>50/130 bpm</td>
</tr>
<tr>
<td>Paced/sensed AV delay</td>
<td>220-300/200-300 ms</td>
</tr>
<tr>
<td>Output/sensitivity (atrial)</td>
<td>3.5 V/0.40 ms (Bi), 0.75 mV (Bi)</td>
</tr>
<tr>
<td>Output/sensitivity (right ventricular)</td>
<td>3.5 V/0.40 ms (Bi), 2.5 mV (Bi)</td>
</tr>
</tbody>
</table>

DDD: atrial and ventricular sequential pacing with pacing impulses triggered only when programmed intervals are exceeded, DOO: dual asynchronous pacing at constant rate regardless of intrinsic cardiac activity, AV delay: atrioventricular delay.
ator and bipolar needle electrode inserted via an intercostal space [4,5]. The first totally implantable internal pacemaker was introduced by Elmqvist and Senning in 1958. It was implanted in a 43-year-old engineer named Arne Larsson who had suffered from a complete heart block [4]. The development of cardiac pacemakers was followed by detailed programming including rate responsiveness and multichamber pacing. Emerging techniques are focused on remote monitoring, leadless, and batteryless devices [6]. The pacemaker inserted in this patient was a dual-chamber pacemaker with rate responsibility, which is safe in MRI environments. Specifically, the pacemaker can be reprogrammed to AOO, VOO, or DOO modes, representing asynchronous atrial, ventricular, and dual pacing, respectively, prior to MRI scanning. MRI time-out mode can be used to automatically return the patient to the original pacemaker setting after the scan, and the duration can be customized depending on the type of procedure: off, 12, 24, and 48 h [7].

Although hemodynamic instability was not observed in this case, it could have led to catastrophic events considering the long surgical duration of liver transplantation. Preoperatively, preoperative assessment, including direct inquiry into any symptoms related to device malfunction, should be performed. Electrolyte abnormalities, acid-base disturbances, and blood gas analysis should be evaluated because they may influence pacemaker function. Lead fractures or migration may be identified using chest radiography. Recent electrocardiography should be performed, and spikes preceding all P-waves and the QRS complex may indicate pacemaker dependency [8]. Reprogramming of the cardiac pacemaker should be considered if the patient is highly pacemaker-dependent or if advanced functions such as rate responsibility or sleep/rest mode are in use [8].

A main shortcoming of the present case was that the duration of preoperative pacemaker reprogramming was too short and should have been evaluated to determine whether it was long enough until the end of liver transplantation. An unexpected pacemaker mode reversal to the original DDD setting can increase the risk of EMI. Common consequences of EMI are inappropriate inhibition or triggering of pacemaker signals, and reversal to asynchronous pacing. In particular, EMI oversensing by the atrial channel of the pacemaker in DDD mode can result in pacemaker-mediated tachycardia.

To prevent potential interference, bipolar electrical diathermy is considered safer than monopolar diathermy. If monopolar diathermy is required, it should be used in cutting rather than coagulation mode, and limited to 1–2 bursts after 10-s pauses. If EMI is likely to occur, the pacemaker should be set to asynchronous mode (ex. VOO, DOO) by reprogramming the device or using a magnet [2,8]. The major advantages of magnets are that they are reversible, easily available, and do not require specialists. However, the indiscriminate application of magnets can cause potential hazards [9]. The magnet cannot switch pacemaker mode if it is positioned incorrectly. Magnet may not alter pacemaker mode in patients who are obese or have abdominal or submuscular implants. In addition, magnet behavior can be unpredictable when applied to pacemakers with low battery voltage. To prevent fatal intraoperative arrhythmias, equipment should be available for external defibrillation and temporary pacing. If it is difficult to approach the chest wall during the procedure, an external patch should be attached before surgery. Defibrillator pads should be placed at least 10–15 cm away from the pacemaker to prevent damaging of the device. Postoperatively, the patient’s cardiac rate and rhythm should be monitored continuously, and pacemaker function should be immediately interrogated [2].

If a pacemaker fails to pace the ventricle, several causes of pacemaker malfunction should be considered. In recent devices, generator and lead failures are relatively rare. Additional conditions, such as acid-base or electrolyte imbalances, myocardial ischemia, or elevated plasma concentrations of antiarrhythmic drugs may contribute as possible causes [10]. In this case, acid-base and electrolyte imbalances were ruled out by performing arterial blood gas analysis. Additionally, the pacing threshold usually increases in cases of pacemaker malfunction caused by myocardial ischemia [11]. Myocardial ischemia can be confirmed using coronary angiography. To manage this situation, the patient’s escape rate and cardiac rhythm should be analyzed. If the rate is slow, intravenous atropine 0.5 mg or isoproterenol infusion (1–2 μg/min) may be considered as medical treatment [12]. Cardiopulmonary resuscitation and advanced cardiac life support are not contraindicated when hemodynamic instability occurs because of pacemaker malfunction. Defibrillation or cardioversion can be performed, but the current may damage the pacing and sensing circuits of the pacemaker. To minimize this risk, the defibrillation paddle should be located as far as possible from the generator. Additionally, external pacing should be considered for possible pacing failure after defibrillation or cardioversion [13]. Anesthesiologists should be alert when treating patients
with implantable pacemakers because minor errors may lead to inadvertent pacing failure or severe hemodynamic instability. In particular, the hemodynamics of cirrhotic patients should be monitored cautiously because increased arrhythmic risk and subsequent cardiovascular symptoms have been reported, including chronotropic incompetence, cardiomyopathy, prolonged QT intervals, hyperdynamic circulation, and impaired ventricular contractility [14]. As hemodynamic instability during liver transplantation is an independent predictor of recipient mortality and graft failure [15], cautious preoperative and intraoperative management is required to prevent unexpected pacing failure and surgical complications.

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**CONFLICTS OF INTEREST**

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

**DATA AVAILABILITY STATEMENT**

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

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The incidence and prevalence of coronary artery diseases have steadily increased over the past ten years. Pharmacological medications, percutaneous coronary intervention (PCI), and coronary artery bypass grafting (CABG) have been used to treat these diseases. Chronic severe chest pain caused by coronary artery disease, which does not improve with these treatments, is known as refractory angina pectoris (RAP). RAP reduces the quality of life and interferes with physical activity. However, reliable therapy for RAP has not yet been found [1,2].

Spinal cord stimulation (SCS) is a possible treatment approach [1,2]. Although the conventional SCS waveform shows remarkable potential for managing RAP [3], it can cause undesired paresthesia and may not be effective for centralized pain. The recently developed burst waveform of SCS is considered a good alternative for addressing these challenges. It can suppress nociceptive and neuropathic pain by modulating both the medial and lateral pain pathways. In addition, it has been reported to provide better pain relief with a lower incidence of undesired paresthesia [4].

However, to our knowledge, few case reports have applied the burst waveform of SCS to RAP worldwide [5]. Thus, we present a case where the burst waveform of SCS was successfully applied to RAP.

**CASE REPORT**

A 52-year-old male with hypertension and diabetes mellitus visited the Department of Cardiology complaining of chest pain. The pain started one month prior and was worsening, with the patient reporting 8 points on the numeric rating scale (NRS, 0 = no pain, 10 = maximum pain). Coronary angiography (CAG) revealed 90% stenosis of the distal right coronary artery (dRCA). PCI was successfully per-
formed on the dRCA, resulting in pain improvement.

However, despite the treatment, the patient revisited the hospital several times because of recurrent chest pain. As a result, CAGs were performed up to seven times over the following three years. Nevertheless, none of the CAG showed any significant interval changes. Moreover, none of the medications that had been administered thus far, including aspirin, clopidogrel, ticagrelor, trimetazidine, nicorandil, candesartan, bisoprolol, nebivolol, ezetimibe, and rosuvastatin, were effective. Thus, the cardiologist concluded that the pain was no longer of cardiac origin.

The patient was then referred to the Department of Anesthesiology and Pain Medicine. The pain was continuous, tightening, and dull, mainly in the left chest area, and radiated to the left shoulder (NRS, 3–4). However, he also had an irregular, intermittent episode of severe pain that lasted for 4–10 h, approximately twice a week (NRS, 10). No aggravating or alleviating factors were identified.

Despite administering painkillers, including acetaminophen, nonsteroidal anti-inflammatory drugs, tramadol, opioids, gabapentin, buprenorphine, and two stellate ganglion blocks, the pain did not subside. Thus, the pain was considered refractory to any treatment modality, including pharmacological medications, PCI, and nerve blocks. Therefore, we planned for SCS as a viable therapeutic alternative.

For trial stimulation, a 14-G epidural needle was inserted at the thoracic vertebra (T) 6–7 level under fluoroscopic guidance, through which an octa-lead was advanced until the electrode reached the T1–2 level (Fig. 1). The electrode was then connected to an external impulse generator, and the stimulus of the tonic waveform was applied to provoke symptoms at the pain site.

In the 14-day trial program, both tonic (frequency of 20 or 30 Hz, pulse width of 500 µs, and amplitude of 1.0–2.0 mA) and burst stimulation (five pulses at 500 Hz, 40 bursts/s, and amplitude of 0.3 mA) were tested. Although the patient reported similar reduction in background pain with both waveforms (NRS, 2–3), only the tonic waveform effectively alleviated the two episodes of breakthrough chest pain (NRS, 7–8). Therefore, he was more satisfied with the immediate response to the severe breakthrough chest pain.

Therefore, permanent implantation was performed. A permanent pulse generator (Proclaim XR, Abbott) was implanted subcutaneously into the left lower quadrant of the abdomen (Fig. 2).

However, the patient complained of a persistent tingling sensation. Thus, we decided to use the burst waveform for background pain and switch to the tonic waveform in the event of sudden severe pain (the patient was instructed to change the waveform on his own). The results of this treatment approach were successful.

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Fig. 1. Chest radiographs showing the tip of the electrode lead located in the thoracic vertebra 1–2 epidural space and slightly to the left (anteroposterior view).

Fig. 2. A permanent pulse generator is implanted subcutaneously in the lower quadrant of the patient’s abdomen (lateral view).
In contrast, when the amplitude of tonic stimulation was increased from 1.0–2.0 mA to 2.0–3.0 mA, breakthrough pain diminished substantially without notable side effects. However, when the amplitude of burst stimulation was increased from 0.3 mA to 0.4 mA, background pain decreased to near zero, but headache occurred. Therefore, with the amplitude of tonic stimulation increased to 2.0–3.0 mA and the amplitude of burst stimulation maintained at 0.3 mA, the patient’s pain could be managed effectively.

Three months after discharge, the two modes (tonic and burst) were appropriately applied as required, and both background and breakthrough pain were well controlled. The patient also reported that the incidence of sudden severe pain had decreased from approximately twice per week to approximately twice per month. In addition, even when the pain occurred, he reported that the intensity decreased to NRS 7–8 from the previous NRS 10. Even in this case, when tonic waveform was applied, the pain quickly disappeared; therefore, the patient did not require painkillers and did not revisit the emergency room after the treatment.

DISCUSSION

This case report is the first application of the burst waveform of SCS for RAP in South Korea. Although the successful application of the tonic waveform of SCS to RAP has been previously reported, only a few cases of successful application of the burst waveform of SCS have been reported worldwide.

SCS was developed based on the gate control theory of pain, which states that continuous stimulation of Aδ-fibers in the dorsal columns can inhibit C-fiber responses in the dorsal horn neurons [6]. SCS induces local alteration of the excitability of wide-dynamic-range (WDR) neurons, promotes physiological inhibitory mechanisms, alters the activity of several neurotransmitters, and decreases sympathetic activity [7,8].

The conventional waveform of SCS is the tonic waveform, in which a certain stimulus amplitude is repeatedly given at a fixed time interval (in this case, frequency, 20 or 30 Hz; pulse width, 500 μs; and amplitude, 2.0–3.0 mA). In contrast, in the newly developed burst waveform of SCS, a few consecutive stimuli of a relatively low amplitude are given, followed by a pause of no stimulus. Subsequently, the stimuli cluster is repeated as before (in this case, five pulses at 500 Hz, 40 bursts/s, and an amplitude of 0.3 mA). In the burst waveform of SCS, if the total energy of the stimuli is the same as that of stimuli in the tonic waveform, the amplitude of each stimulus becomes smaller (weaker energy) than that of the tonic waveform, and the number of stimuli increases. It may be hypothesized that a smaller amplitude of each stimulus accounts for the lower incidence of paresthesia and provocation in the burst waveforms.

Although burst stimulation affects the dorsal column and gamma-aminobutyric acid receptors less and induces less paresthesia, it can inhibit the firing of WDR neurons at the dorsal horn to a greater degree than the inhibition observed with tonic stimulation [9]. In addition, unlike tonic stimulation, which modulates only the lateral pain pathway, burst stimulation modulates both the medial and lateral pain pathways, affecting the neural activity in the somatosensory and anterior cingulate cortices. This implies that it affects the somatic aspect of pain and its emotional components, exerting a better pain-relief effect [10].

SCS is an effective treatment approach for relieving ischemic pain in angina. First, pain can be relieved by reducing the stimulation of the dorsal columns and transmission of nociceptive impulses through the spinothalamic tract. Additionally, SCS directly improves ischemic conditions, supposedly playing an important role in inducing vasodilation by releasing calcitonin gene-related peptides and reducing myocardial oxygen demand with lowered sympathetic tone. In addition, the imbalance between oxygen supply and demand can be adjusted by improving the coronary blood flow at the microvascular level. Thus, ischemia can be improved with subsequent pain relief. Finally, SCS exerts an anti-ischemic function by inhibiting excessive intrinsic cardiac nervous system activity, which increases the incidence of arrhythmia or ischemia, reduces sympathetic activity, and redistributes myocardial blood flow from the non-ischemic to ischemic areas [11].

The efficacy of SCS in patients with angina has also been reported. According to a study conducted on CABG and SCS in patients with high-risk angina, no significant difference between SCS and CABG in pain reduction was noted, and more favorable results were reported with SCS for postoperative mortality and cerebrovascular events [1]. Additionally, a small difference in the effectiveness of SCS and percutaneous myocardial laser revascularization was noted in patients with refractory angina [2]. Therefore, SCS is recommended as a treatment option for refractory angina by the European Society of Cardiology (class IIb) and American College of Cardiology and American Heart Association (class IIb) guidelines [12].

Since SCS was first used as a treatment approach for angi-
na in 1987, many successful applications have been reported [1,2,13]. However, most cases involve tonic stimulation, and burst stimulation has been reported in only one case [5]. In the abovementioned case, the pain-relief effect of tonic stimulation was approximately 30%; however, it increased to > 80% after burst stimulation.

As burst stimulation has been applied to refractory angina in only a few cases, it suggests that its efficacy and mechanism have limitations. However, for pain types other than breakthrough pain, burst stimulation that does not induce paresthesia may relieve pain without causing discomfort or a tingling sensation. Regarding pain relief, angina pain is thought to be caused by a combination of nociceptive and neuropathic pain. Tonic stimulation is primarily effective for neuropathic pain. However, burst stimulation has been reported to be additionally effective for nociceptive pain, rendering it superior to tonic stimulation. Further, burst stimulation modulates both the medial and lateral pathways of pain. Therefore, burst stimulation may be more effective in pain control in angina, as well as in the emotional and somatosensory aspects.

Studies have reported that burst stimulation has a better pain-relief effect than tonic stimulation in patients with failed back surgery syndrome and diabetic neuropathic pain [14]. However, previous studies have rarely addressed the difference between the efficacies of the burst and tonic modes in refractory angina. Therefore, further studies on applying burst stimulation for refractory angina are warranted.

In conclusion, SCS may be a promising treatment approach for patients with RAP without laboratory abnormalities. Additionally, as reported in this case, the appropriate use of tonic and burst stimulations according to symptoms is expected to maximize the effect of relieving chest pain induced by RAP and improve the patient’s quality of life.

FUNDING

None.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

Conceptualization: Jae Chul Koh. Writing - original draft: Daehun Yun. Writing - review & editing: JI Soo Kwak. Supervision: Kaehong Lee, Leegyeong Je, Taesan Kim, Yoon Sun Park.

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REFERENCES


INTRODUCTION

Ultrasound-guided interfascial plane blocks are commonly used to provide postoperative analgesia in different anatomical regions [1]. Among the interfascial blocks, the quadratus lumborum block (QLB) is a field block used for analgesia after abdominal surgery [2,3]. This block, which was later used in different anatomical regions (hip surgery, lower limb vascular surgery, total hip arthroplasty, etc.) for analgesia in addition to the abdominal area, is performed by injecting a local anesthetic (LA) between different fascial layers according to the anatomical position of the thoracolumbar fascia (TLF) and quadratus lumborum (QL) muscle [3]. In the anterior QLB (aQLB), the LA is injected between the psoas and QL muscles. Different mechanisms of action of the aQLB have been proposed in case reports and clinical

Background: The quadratus lumborum block (QLB) has recently been used frequently for postoperative analgesia after abdominal surgery. The aim of this study was to investigate the effect of pressure changes between the middle thoracolumbar fascia layers to which the anterior QLB (aQLB) is applied at the level of the sensory block.

Methods: A total of 67 patients planned to undergo laparoscopic cholecystectomy were evaluated in the context of this prospective study. Bilateral aQLBs were administered to all patients, and a peripheral nerve block catheter was placed between the psoas and quadratus lumborum muscles. The correlation of interfascial pressures (IFPs) during block application, 30 min intraoperatively, and 30 min postoperatively with the sensory block level was determined as the primary outcome measure. Secondary outcome measures were the sensory block levels 30 min after block application and 30 min postoperatively; visual analog scale scores 30 min and 6, 12, and 24 h postoperatively; and 24 h tramadol consumption.

Results: The preoperatively and intraoperatively measured IFPs differed significantly between the right and left sides (P < 0.05). The preoperative and postoperative block levels also differed significantly between the right and left sides (P < 0.05). The preoperative and postoperative block levels and preoperatively measured IFPs showed a weakly negative correlation (right: r = 0.374; left: r = 0.470).

Conclusions: The results of this study show that pressure changes between the fasciae may be effective in aQLB application.

Keywords: Laparoscopic surgery; Nerve block; Pain; Plane block; Ultrasonography.
trials. With aQLB, analgesia can be achieved between the 6th thoracic and 2nd lumbar dermatomes [2]. Although the primary goal is to block the thoracolumbar nerves, paravertebral spread of the LA and sensory innervation in the TLF may be involved in the mechanism of action [2,4]. TLF is an anatomical formation consisting of aponeurotic and fascial layers that separate the paraspinal muscles in the lumbar region from the muscles of the posterior abdominal wall. It is a part of the myofascial structure surrounding the erector spinae, QL, and psoas muscles in the posterior and lateral lumbar regions with aponeuroses of the abdominal wall muscles. It plays a major role in stabilizing the lumbar spine and load transfer. In addition, it carries both proprioceptive and nociceptive innervations and may be sensitive; however, the evidence is weak [5]. The relationship between the TLF and anterior abdominal wall muscles has been demonstrated in different studies. The intra-abdominal pressure and muscle structure may affect the TLF. The connection of the TLF with other anatomical structures may affect the outcomes of blocks administered in the TLF.

The aim of the present study was to test the hypothesis that pressure changes between the aQLB and middle TLF layers influenced the sensory block level.

**MATERIALS AND METHODS**

**Patient selection**

A total of 100 patients scheduled to undergo laparoscopic cholecystectomy were evaluated in this prospective observational study following Institutional Ethics Committee (IEC) approval and registration of the clinical trial records (IEC number: 2019-5/26; ClinicalTrials.gov identifier: NCT04094987). All patients provided written informed consent for participation in the study. This study was conducted in accordance with the principles of the Declaration of Helsinki. Inclusion criteria were: laparoscopic cholecystectomy, age of 18–65 years, American Society of Anesthesiologist grade I–III, and informed consent. Exclusion criteria were: allergy to LA, previous opioid use, uncontrolled diabetes mellitus, hypertension, and the presence of infection at the site of application. Finally, a total of 72 patients were included in this study (Fig. 1).

**Anesthetic management**

Propofol, rocuronium bromide, and fentanyl citrate were intravenously administered to induce anesthesia. A mixture of sevoflurane, air, and O₂ was used at a flow of 2.5–3 L/min to maintain anesthesia. Mechanical ventilation was applied, providing an 8 ml/kg tidal volume in a volume-controlled mode. The intraoperative CO₂ levels were monitored using the end-tidal CO₂ module values of the anesthesia machine. Rocuronium bromide (0.6 mg/kg) was used as the neuromuscular blocking agent. A train of four monitor was used for neuromuscular monitoring. When the TOF ratio had reached 25%, rocuronium bromide was added at the rate of 1/4 of the intubation dose. A single dose of a nonsteroidal

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**Fig. 1.** Flow diagram of patient enrollment.
anti-inflammatory drug (tenoxicam 20 mg, intravenously) was administered 15 min before the end of the operation, and a tramadol + saline solution (5 mg/ml) was prepared for the postoperative patient-controlled analgesia (PCA) protocol. The PCA device was set with no basal infusion, a lockout time of 30 min, and a demand dose of 25 mg.

**Anterior quadratus lumborum block**

The aQLB was applied preoperatively 30 min before induction of anesthesia in the lateral decubitus position bilaterally. A convex ultrasound probe (2–6 MHz MyLab30, ESAOTE) was placed on the iliac crest, transverse to the axillary line, and the shamrock sign was defined by the posterior guided probe at the level of the L4 vertebra, which comprises the L4 vertebral body, transverse process, and QL, psoas, and erector spinae muscles. A peripheral nerve block was administered with a 100-mm, 18-gauge Tuohy needle (SonoPlex Pajunk) directed to the anterior TLF between the QL and psoas muscles [2,6]. A 20-gauge catheter with a central opening was placed after the location had been confirmed by hydrodissection using 3 ml saline (Fig. 2). After the preoperative pressure measurement, a total of 50 ml of 0.25% bupivacaine was injected, with 25 ml on the right and left sides.

**Interfascial pressure (IFPs) measurement**

The transducer line of the disposable pressure measurement set was connected to a catheter using a T-connector. A pressure-measuring transducer was secured in the region of block application and connected to the monitor. The pressure transducer was fixed at the same height as the block application area and connected to a monitor. The transducer was set at this altitude at the zero level. IFPs was measured after a 5 ml saline injection, with the patient in the supine position. Changes in the respiratory pressure were also detected (Fig. 3). Over 1 min, three measurements (average inspiratory and expiratory values for each measurement) were made, and the average of these measurements was recorded. All measurements were performed according to the standard protocols. The level of bilateral sensory blockade was monitored using a cold test 30 min after the block application and 30 min after the end of the operation.

**Outcome measures**

The primary outcome measure was the correlations of the IFPs (mmHg) during block application, 30 min intraoperatively, and 30 min postoperatively with the level of the sensory block. The secondary outcome measure was the senso-
ry block level 30 min after block application and 30 min postoperatively determined using the cold test. Visual analog scale (VAS) scores were obtained 30 min and 6, 12, and 24 h postoperatively, and the amount of 24 h tramadol consumption was measured.

Statistical analysis

Descriptive statistical techniques and chi-square \( (\chi^2) \) tests were used to compare qualitative data. The Shapiro–Wilk test was used to evaluate the normality of data distribution. The data distribution was not normal. The Wilcoxon signed-rank test was used to analyze repetitive measurements. Spearman’s rho correlation test was used to evaluate correlations. An association was considered significant at a \( P \) value < 0.05. Statistical software SPSS Version 22.0 (IBM Co.) was used for the statistical analyses.

Power analysis

The correlation coefficient of the pressure and block level was an \( r \) of 0.335 in the pilot study, including 10 patients. The necessary sample size was determined as 64 patients in order to obtain an 85% \( (\alpha = 0.05) \) study power. A total of 72 patients were included in the study, considering the possible setbacks. \( G^* \) power (ver. 3.1.9.4, University of Kiel) was used for sample size calculation [7].

RESULTS

A total of 72 patients were included in the study. However, the study was completed with only 67 patients owing to conversion to open surgery in two patients, accidental catheter removal in two patients, and a problem with the pressure measuring device in one patient (Fig. 1). Table 1 shows the demographics of the patients who completed the study. Fig. 4 shows the distribution of the sensory blockade 30 min after block application as right- and left-sided block levels. In the interfascial area, the preoperatively and intraoperatively measured IFPs differed significantly between the right and left sides \( (P < 0.05; \) Table 2). The preoperative and postoperative block levels showed significant differences between the right and left sides \( (P < 0.05; \) Table 2). A weakly negative correlation (right: \( r = 0.374 \); left: \( r = 0.470 \)) was found between the block levels obtained preoperatively and postoperatively and the preoperatively measured IFPs, while no correlation was found with the intraoperative or postoperative IFPs (Table 3). The body mass index (BMI) values of the patients did not correlate with the measured block levels. A weakly positive correlation was found between BMI and IFPs measured during the preoperative, intraoperative, and postoperative periods (Table 3). In the multiple regression analysis applied to determine the effect of IFPs and BMI together on block levels, no relationship was found with BMI, which may be owing to regulatory factors and the block levels \( (B: -0.68; 95\% \) confidence interval: \(-0.258 \) to \(0.122; r^2 = 0.209; P = 0.477)\). The mean duration between the preoperative sensory block measurement time and the postoperative sensory block measurement time was 177.8 ± 11.1 min. The decrease in the sensory block level between the two measurement times was 4% \((\text{minimum: } -42.86; \text{maximum: } 0.00)\). A negligible correlation was found between the sensory block level change and baseline IFPs \((r = 0.114)\). The mean VAS scores measured at 2, 6, 12, and 24 h postoperatively were 1.14 ± 0.97, 1.07 ± 0.89, 1.28 ± 1.15, and 1.28 ± 1.15, respectively. The mean total tramadol consumption of 24 h was 59.39 ± 46.2 mg. A negligible correlation was found between preoperatively measured IFPs and block levels, VAS scores, and tramadol consumption amount \((r = 0.15)\). A negligible correlation was found between preoperative IFPs and block levels and tramadol consumption amount \((r = 0.093)\).

DISCUSSION

We investigated the effect of pressure values measured using a catheter placed between the QL and psoas muscles in the anterior layer of the TFL at the block level and found a weakly negative correlation between the pressure values obtained from the measurements and the sensory block levels obtained 30 min after the block.

Two possible mechanisms of fascial plane blocks have been proposed, although they are yet to be fully confirmed.
The first is a localized effect on the neurons and nociceptors at the injection site, which is mediated by bulk flow and diffusion processes. The second is the vascular absorption of LAs. Mass flow and diffusion are bulk flows in which the fluid is moved by pressure. The shape and limits of this mass flow are determined by the speed and direction of the injection, elastic recoil of the swollen fascial plane, and physical forces generated by muscle contraction and movement. This theory is supported by the finding of different levels of sensory blockade after block application at similar drug doses. Data are lacking in the literature regarding the exact definitions of these physical forces and their effectiveness. This study was aimed at quantifying the differences in pressure

Table 2. Comparison of IFPs and Block Levels Between the Right and Left Sides

<table>
<thead>
<tr>
<th>Side</th>
<th>IFPs (mmHg)</th>
<th>Block Level (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preoperative</td>
<td>Intraoperative</td>
</tr>
<tr>
<td>Right side</td>
<td>7.4 (1–17)</td>
<td>15 (5–28)</td>
</tr>
<tr>
<td>Left side</td>
<td>7.8 (2–16)</td>
<td>14.3 (6–28)</td>
</tr>
<tr>
<td>P value*</td>
<td>0.002</td>
<td>0.006</td>
</tr>
</tbody>
</table>

Values are presented as number only or median (range). IFPs: interfascial pressure. *Wilcoxon signed-rank test was used for statistical analyses.

Fig. 4. Preoperative and postoperative block levels.

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between the leaves of the TLF and their effects on the distribution of LAs. Therefore, the anatomical structure of the TLF is important [8].

The TLF contains three layers: posterior, middle, and anterior. While the posterior layer surrounds the erector spinae muscles, the middle layer is located between the erector spinae and the QL muscles. The anterior layer is located between the psoas and QL muscles [5]. QLB can be performed in four ways according to the anatomical structures defined in the three-layered model. If an LA is administered between the QL and psoas muscles, it is called QLB 3 (anterior); if it is administered between the psoas and QL muscles, it is called QLB 1 (lateral); and if it is administered into the QL muscle, it is called muscular QLB [2]. Studies have investigated using the QLB to provide analgesia after surgeries, such as abdominal surgery (urological and laparoscopic surgeries), hip surgery, and cesarean section [2,3]. Different views have been reported regarding the effectiveness and mechanism of action of QLB in different studies. The amount of LA used and injection points of the same block vary in the literature [9-12]. In their systematic review and meta-analysis of these studies, Uppal et al. [3] reported the requirement of more studies to better characterize the risks and benefits associated with QLB. Studies on the mechanism of action of QLB have attempted to determine the extent of spread of the administered LAs. Paravertebral spread, which is a mechanism of action of QLB, other than blocking the thoracolumbar nerves, has been explored [2,3]. The distribution of LAs determined in cadaver studies has yielded different results [13-16].

While paravertebral spread was not found in two studies using 20 ml of dye, a study by Dam et al. [15] found dye spread in the paravertebral region and at the T9-T10 level [13-15]. In addition to the paravertebral spread of the administered dye, another study found spread up to the 7th thoracic level [16]. Another study attempting to determine the correlation between dermatomal spread and a cadaveric study in a case series found that the contrast agent diffusion area in the cadaver was consistent with sensory block levels in the case series. This study found the possibility of thoracic spread of the contrast agent and reported that the injected LA might follow the path of least resistance and prefer the fascia transversalis and transversus abdominis paths instead of the tight fascial compartments in the psoas major muscle [17]. In their case reports, Diwan et al. evaluated the diffusion of a contrast agent administered via a catheter in patients who had received QLB and had a catheter in the same

### Table 3. Correlation Between the Preoperative and Postoperative IFPs and Preoperative and Postoperative Block Levels and BMI

<table>
<thead>
<tr>
<th></th>
<th>Preoperative IFPs (mmHg)</th>
<th>Intraoperative IFPs (mmHg)</th>
<th>Postoperative IFPs (mmHg)</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RIGHT side</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preoperative block level</td>
<td>7.4 (1–17)</td>
<td>15 (5–28)</td>
<td>8.8 (2–19)</td>
<td>25.7 (20.2–33.2)</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>-0.343</td>
<td></td>
<td></td>
<td>0.049</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
<td>0.700</td>
</tr>
<tr>
<td>Postoperative block level</td>
<td>5.64 (3–7)</td>
<td></td>
<td></td>
<td>0.035</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.151</td>
<td>0.086</td>
<td></td>
<td>0.785</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.7 (20.2–33.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.430</td>
<td>0.305</td>
<td>0.473</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td><strong>LEFT side</strong></td>
<td>7.8 (2–16)</td>
<td>14.3 (6–28)</td>
<td>8.3 (3–18)</td>
<td>25.7 (20.2–33.2)</td>
</tr>
<tr>
<td>Preoperative block level</td>
<td>5.53 (4–7)</td>
<td></td>
<td></td>
<td>-0.004</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>-0.470</td>
<td></td>
<td></td>
<td>0.974</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postoperative block level</td>
<td>5.13 (4–7)</td>
<td></td>
<td></td>
<td>-0.090</td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.103</td>
<td>0.150</td>
<td></td>
<td>0.480</td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.7 (20.2–33.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correlation coefficient</td>
<td>0.401</td>
<td>0.332</td>
<td>0.394</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.001</td>
<td>0.004</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as median (range). IFPs: interfascial pressure, BMI: body mass index. Spearman’s rho correlation test was performed.
area [18]. They reported that different blocks performed in the subcostal and iliac crest regions might change the paravertebral spread and that the resistance encountered during the procedure, injection rate, and LA volume might be associated with the block level [18]. In addition, they detected swelling in the anterior TLF layer on computed tomography after LA injection and stated that excessive pressure could damage the fascia [18].

Our results demonstrated a correlation between IFPs measured between the fasciae and sensory block levels, similar to previous studies. Our results suggest that IFPs between the fasciae may be a factor affecting the sensory level obtained after the QLB [17,18]. Various studies have found that the TLF is associated with the anterior abdominal wall muscles. A positive correlation was found between the increase in spinal stiffness and the extent of the increase in intra-abdominal pressure. Furthermore, they emphasized that it was impossible to determine whether the cause of the spinal stiffness was increased intra-abdominal pressure or abdominal muscle activity, although with inconsistent results [19,20]. IFPs during pneumoperitoneum creation for laparoscopy in the present study were higher than the initial measurements. This result is similar to that of other studies investigating the correlation of this change with increased intra-abdominal pressure, paraspinal muscles, and TLF [19,20].

This study has some limitations. First, intra-abdominal pressure was not measured during IFPs measurements. Second, sensory block levels were not monitored during the 24-h postoperative follow-up. Third, the injection pressure was not standardized during the drug injection in block application. Finally, we did not evaluate other pathologies (lumbosacral abnormalities or diseases that might cause back pain) that could alter the anatomical structure between the paraspinal muscles and fascia [21,22].

In conclusion, aQLB outcomes depend on multiple variables, such as needle direction, injection site, and the amount of LA [16,17]. The results of this study showed that IFPs changes between the fasciae might influence the outcome of the aQLB. Differences in IFPs and block levels between the right and left sides of the same patient suggest that other factors besides the relationship of the abdominal wall structures and BMI values with TLF may affect the IFPs. The results of this study may guide future studies on the mechanism of action of QLB and distribution of LA between the fasciae.

**FUNDING**

None.

**CONFLICTS OF INTEREST**

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

**DATA AVAILABILITY STATEMENT**

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

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INTRODUCTION

Epidural anesthesia is a widely used form of regional anesthesia with a high success rate and a low complication rate. In most cases, the removal of an epidural catheter is straightforward. However, anesthesiologists occasionally face difficulties in catheter removal owing to various factors, such as the anatomy of the epidural space; diameter, tensile strength, and flexibility of the catheter; as well as the depth, level, and difficulty of its insertion. Catheters can become entangled with the nerve roots, blood vessels, lumbar fascia, posterior vertebral arches, vertebral processes, and facet joints that may pose challenges during removal. Currently, standard procedures or treatments for blocked epidural catheters are either inaccessible or rely on individual preferences and expertise.

The primary objective of this systematic review was to answer the fundamental question, “how to remove an entrapment?”

Background: The knotting or in vivo entrapment of epidural catheters is an uncommon but challenging issue for anesthesiologists. This study aimed to identify the possible causes behind entrapped epidural catheters and the effective methods for their removal.

Methods: A systematic review of relevant case reports and series was conducted using the patient/population, intervention, comparison and outcome framework and keywords such as “epidural,” “catheter,” “knotting,” “stuck,” “entrapped,” and “entrapment.” The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement was followed, and the review protocol was registered with International Prospective Register for Systematic Reviews (CRD42021291266).

Results: The analysis included 59 cases with a mean depth of catheter insertion from the skin of 11.825 cm and an average duration of 8.17 h for the detection of non-functioning catheters. In 27 cases (45.8%), a radiological knot was found, with an average length of 2.59 cm from the tip. The chi-squared test revealed a significant difference between the initial and final positions of catheter insertion (P = 0.049).

Conclusions: Deep insertion was the primary cause of epidural catheter entrapment. To remove the entrapped catheters, the lateral decubitus position should be attempted first, followed by the position used during insertion. Based on these findings, recommendations for the prevention and removal of entrapped catheters have been formulated.

Keywords: Catheters; Device removal; Anesthesia, Epidural; Pain management; Patient positioning.
trapped epidural catheter?” The secondary objective was to identify the possible causes of entrapment and outcomes of entrapped catheters.

MATERIALS AND METHODS

In the absence of specific guidelines for conducting systematic review of case reports, we followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement, wherever applicable, for comprehensive reporting [1].

Protocol and registration

This study was registered in PROSPERO (registration number: CRD42021291266) and the International Prospective Register of Systematic Reviews.

To assess the eligibility of the research papers, we employed the PICo approach for qualitative studies, namely, Population: characteristics of the patient or population; Interest: the condition or disease of interested in; and Context: the phenomena of interest related to a defined event, activity, experience, or process.

1. Inclusion criteria

We included case reports or case series that described the insertion of an epidural catheter (population of interest), which got stuck or entrapped during removal, or in which a knot was identified after the removal or with radiological examination (the condition or disease of interested and the phenomena of interest related to a defined event, activity, experience, or process). All articles were screened to determine whether our primary question “how to remove an entrapped epidural catheter?” was addressed in this study. We limited our inclusion criteria to cases published in English before December 30, 2021.

2. Exclusion criteria

We excluded reports that did not provide an answer to the primary question, or reported the tip of the catheter to be missing after removal. Additionally, animal studies, letters to the editor, and retracted reports as well as articles without an available full text were excluded.

3. Information sources

We searched PubMed, Google Scholar, MEDLINE, and SCOPUS to find the relevant case reports or case series using keywords “epidural catheter” and one of the following terms: “knot,” “knotting,” “stuck,” “entrapped,” and “entrapment.”

Study selection process

The process for selection of case reports or series has been demonstrated in Fig. 1.

Screening of the title and abstract was conducted by two authors. All reports that did not meet the inclusion criteria were excluded. Subsequently, full text reports of the selected articles were retrieved. The two authors independently examined these reports for eligibility, and additional studies were searched within the references iteratively. The list of studies was then forwarded to principal author, who developed a list of all the included and excluded articles. In the event of a disagreement between the two authors regarding the inclusion or exclusion of a report, the dispute was resolved by the principal author. The references of the selected articles were reviewed to identify any additional related articles. In case of any missing information, the corresponding authors were contacted using email addresses provided in the respective report or professional networks of researchers and scientists such as ResearchGate. In addition to seeking missing information, the authors were asked if they were aware of any other similar studies that could be included in the analysis.

1. Data collection process

After identifying the studies meeting the inclusion criteria and having the full text available, the articles were distributed to all authors for data extraction using a standardized Google Spreadsheet.

2. Data items

The extracted data included information encompassing patient characteristics (age, sex, weight, primary condition necessitating epidural placement, and patient position during insertion), any difficulties encountered during insertion, from the time of insertion (in hours) to the diagnosis of entrapment, any issues with the functionality of the catheter before knotting was detected (completely functional, partially functional, or blocked), any additional radiological studies that was conducted to confirm the diagnosis, the actions taken when a catheter was identified to be stuck, the method(s) employed for catheter removal, operator’s attributes or qualifications and years of experience, and outcome of the stuck catheter.
3. Reducing the risk of bias

We used the Risk Of Bias in Systematic Reviews (ROBIS) tool to reduce the risk of bias in methodological quality [2]. Patient/population, intervention, comparison and outcome (PICO) was employed to assess effectiveness of the reviews. One of the authors independently used the tool to evaluate the preliminary completion of manuscript writing and recommended changes, to address any perceived bias. If the source of bias could not be addressed, it was identified as a study limitation. Since all the studies were case reports, phases 2 and 3 of the ROBIS tool were not used, while phase 1 tool was used to determine the study’s relevance.

Statistical tests

Statistical analyses were performed using the SPSS software, version 23.0 (IBM Co.). For missing values of a continuous variable, we adopted a specific policy of not making any inferences when the missing values exceeded 50%, and replacing them with the average when the missing values were lower. We employed the Cohen’s kappa coefficient to measure the inter-rater agreement between two independent case study reviewers, when selecting reports to be included in the study. The Spearman’s rank correlation coefficients were used to assess correlations between variables. Categorical variables were compared using the chi-squared test. A P value of < 0.05 was considered to indicate statistical significance.

RESULTS

None of the case reports described the total number of patients in whom the epidural catheter was placed before a knot was identified, except in one patient. Therefore, the event rate and odds ratio for knotting could not be calculated. The results have been presented only in a descriptively manner in this study.

The measurement of agreement for the selection of case reports between the two reviewers using the Cohen’s kappa correlation coefficient was 0.918 for the final case selection.

Demographic characteristics

Demographic characteristics have been summarized in Table 1.

Patient’s position during epidural insertion and the ana-
Table 1. Demographic Characteristics Including Age, Sex, Weight, Indications for Epidural Placement, and Type of Epidural Catheter Used

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>42.7</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>11 (18.6)/41 (69.5)</td>
</tr>
<tr>
<td>Weight</td>
<td>7 (11.9)</td>
</tr>
<tr>
<td>Indication for epidural</td>
<td></td>
</tr>
<tr>
<td>OBS/GYNAE</td>
<td>30 (50.8)</td>
</tr>
<tr>
<td>Orthopedics</td>
<td>10 (16.9)</td>
</tr>
<tr>
<td>GI surgery</td>
<td>9 (15.3)</td>
</tr>
<tr>
<td>Urology</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Pain management</td>
<td>6 (10.2)</td>
</tr>
<tr>
<td>Not mentioned</td>
<td>3 (5.1)</td>
</tr>
<tr>
<td>Catheter type</td>
<td></td>
</tr>
<tr>
<td>Arrow</td>
<td>9 (15.3)</td>
</tr>
<tr>
<td>B Braun</td>
<td>7 (11.9)</td>
</tr>
<tr>
<td>Portex</td>
<td>10 (16.9)</td>
</tr>
<tr>
<td>Others</td>
<td>7 (11.9)</td>
</tr>
<tr>
<td>Not mentioned</td>
<td>26 (44.1)</td>
</tr>
</tbody>
</table>

Values are presented as mean or number (%). M: male, F: female, OBS/GYNAE: obstetrics/gynaecology, GI: gastrointestinal.

Table 2. Patient Position during Epidural Insertion, and the Anatomical Level of Insertion

<table>
<thead>
<tr>
<th>Patient's position</th>
<th>Frequency (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting</td>
<td>19 (32.2)</td>
</tr>
<tr>
<td>Lateral</td>
<td>14 (23.7)</td>
</tr>
<tr>
<td>Prone</td>
<td>2 (3.4)</td>
</tr>
<tr>
<td>Not mentioned</td>
<td>24 (40.7)</td>
</tr>
<tr>
<td>Epidural insertion level</td>
<td></td>
</tr>
<tr>
<td>Cervical</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Thoracic T6 and above</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Thoracic below T6</td>
<td>3 (5.1)</td>
</tr>
<tr>
<td>Lumbar</td>
<td>38 (64.4)</td>
</tr>
<tr>
<td>Caudal</td>
<td>2 (3.4)</td>
</tr>
<tr>
<td>Not mentioned</td>
<td>14 (23.7)</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

Depth of catheter insertion

The mean depth of catheter insertion into the skin was 11.825 cm. However, in 12 cases, the depth of catheter insertion was not mentioned. In seven cases the distance from the tip of the catheter was excluded from this depth of insertion analysis.

Functionality of the catheter

Out of 59 cases, 32 (54.2%) exhibited good functionality after insertion of the catheter before it became stuck, 3 (5.1%) had difficulty in delivering the test dose, and 13 (22.0%) had difficulty with catheter withdrawal, while functionality was not mentioned in 11 cases (18.1%). The average duration for the detection of non-functioning catheters was 8.17 hrs with an inter quartile range of 9 and a median value of 2.

Table 3 summarizes the investigations performed for the detection of catheter entrapment and findings related to the catheter’s state.

Among the 40 case reports that were investigated, 9 of them (22.5%) failed to show the catheter position, 17 (42.5%) showed the level of catheter, 7 (17.5%) showed the level of catheter with a knot, 1 showed migration of catheter, and in 6 cases (15.0%) specific finding was not mentioned. Among the 9 cases where X-ray was the only investigation conducted, the catheter position or knot could not be revealed.

We conducted a search for positive results from radiological examinations. Among the cases examined, 27 (45.8%) exhibited the presence of a knot, 18 (30.5%) exhibited no knot, and in 14 (23.7%) cases the specific finding was not described in Table 2.

We evaluated whether a specific approach, such as middle or paramedian approach, was associated with catheter entrapment. However, we found that more than 50% of this data was missing (39 cases i.e., 66.1%) having no information on the approach used. The remaining data demonstrated that 23.7% of the entrapped catheters were placed via the midline approach, whereas 10.2% were placed via the paramedian approach.

Resistance during insertion

Almost 25.4% of the cases (15 out of 59) reported that they felt resistance during insertion of the catheter or needle.

Operator’s experience

The catheter insertion was performed by anesthesiologists in seven cases (11.9%), anesthesia residents in eight cases (13.6%), and a surgeon in one case (1.7%). The remaining 43 cases (72.9%) did not mention who performed the procedure.
Table 3. Investigations Performed for the Detection of Catheter Entrapment and Catheter States Observed

<table>
<thead>
<tr>
<th>Investigation category</th>
<th>Number of cases (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray of spine</td>
<td>9 (15.3)</td>
</tr>
<tr>
<td>USG</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>CT ccan</td>
<td>10 (16.9)</td>
</tr>
<tr>
<td>X-ray + CT scan</td>
<td>5 (8.5)</td>
</tr>
<tr>
<td>Epidurogram</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Fluoroscopy</td>
<td>7 (11.9)</td>
</tr>
<tr>
<td>MRI</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>No investigation done</td>
<td>19 (32.2)</td>
</tr>
<tr>
<td>Not mentioned</td>
<td>6 (10.2)</td>
</tr>
<tr>
<td>Catheter’s state/finding</td>
<td></td>
</tr>
<tr>
<td>Stretched</td>
<td>15 (25.4)</td>
</tr>
<tr>
<td>Trapped</td>
<td>3 (5.1)</td>
</tr>
<tr>
<td>Kink</td>
<td>2 (3.4)</td>
</tr>
<tr>
<td>Knot</td>
<td>3 (5.1)</td>
</tr>
<tr>
<td>Loop</td>
<td>4 (6.8)</td>
</tr>
<tr>
<td>Migration</td>
<td>4 (6.8)</td>
</tr>
<tr>
<td>Broken</td>
<td>13 (22.0)</td>
</tr>
<tr>
<td>Not mentioned</td>
<td>15 (25.4)</td>
</tr>
</tbody>
</table>

Values are presented as number (%). USG: ultrasonography, CT: computed tomography, MRI: magnetic resonance imaging.

clearly mentioned. For cases with knots, the average length of the knot from the tip was 2.59 cm.

Saline flush test

A saline flush test to check the patency of the catheter was performed in only 12 cases (20.3%), and in all reported cases, the operators were unable to push the saline. In the remaining 47 cases, a saline test to check the patency of the catheter was either not performed or not mentioned.

Table 4 summarizes different methods that were used for the removal for entrapped epidural catheter and the specific recommendation for its removal.

Among the 26 cases where both position of the catheter insertion and removal was mentioned, 13 cases (22.0%) reported that the removal procedure was performed at the same position as the insertion, while 13 cases (22.0%) reported that the removal position was different from that of the insertion. A chi-squared test was performed to analyze the initial position of catheter insertion and that of the catheter removal, which showed a P value of 0.049, indicating a likelihood of the position of removal being different from that of the insertion.

Additionally, position during catheter removal was not mentioned in 20 cases (39.2%). Among the reported cases, catheter removal was performed in the prone position in 13 cases (25.5%), in lateral position in 10 cases (19.6%), and in sitting position in 7 cases (13.7%). In eight cases, the catheters were left in situ following breakage. The fate of the broken catheters over time and their follow-up findings were not mentioned in any of the studies.

**DISCUSSION**

**Demographics of study population**

The event of epidural catheter knotting and entrapment has a rate of occurrence of 0.0015% [3]. Stuck epidural catheters have been reported more commonly in middle-aged and female patients, especially during labor and delivery. Mean age of the study population was 42 years, and almost 70% of the study population was female; thus, more probability of knotted or stuck epidural was seen among the middle-aged female patients. The usage of epidural for labor an-
algesia or cesarean section accounted for 50% of indications for epidural administration, which led to a higher incidence of epidural-related cases among females.

Factors affecting entrapment

The position of the patient during insertion, region of the vertebral column where the catheter is inserted, and operator’s experience do not seem to influence catheter entrapment; however, an insertion length of 11 cm or more suggests a higher likelihood of entrapment, indicating that a longer insertion depth of the catheter may be associated with an increased risk.

If the distance exceeds 4.5 cm in the lumbar epidural space, the catheter has a tendency to deviate in direction, forming a bend or loop, which may predispose it to knot formation [4]. If the catheter is inserted more than 5 cm above the level of the needle, it may curl back, leading to kinking, a turn 180° turn, and movement to opposite direction. This may result in the catheter passing out of an intervertebral foramen, wrapping around a nerve, or a combination of these complications [5]. Inserted the catheter beyond the triple mark increases likelihood for curling and knot formation, even if it is subsequently pulled back [5]. Considering the average depth of the epidural space to be 5–6 cm, the mean length of insertion of stuck catheters was approximately 12 cm; supporting the validity of the 5 cm rule [6]. Additionally, the median distance at which the knot was found was 2–3 centimeters, suggesting that not inserting a catheter beyond 5 cm from the needle tip may be the best approach to prevent possible knotting. However, many of the catheters did not have a knot, but were stretched, suggesting that other mechanisms might play a role in entrapment.

In our review, 64.4% of epidural placemts were at the lumbar region, and only 5 cases reported placement above the lumbar region, which is consistent with the high incidence of obstetric cases in our study population. Most knotted catheters are inserted at the lumbar level, especially in obstetric patients, and a knot is formed along the last 3 cm of the catheter [7]. Muneyuki et al. [8] reported that an indwelling thoracic epidural catheter was less likely to curl, bend, or kink in the epidural space than an indwelling lumbar epidural catheter, and a greater amount of the catheter could be inserted without coiling, which attributes to the difference in the angle of insertion of the needle. In the lumbar region, the epidural needle impinges on the dura at a right angle, whereas in the thoracic region, the needle is inserted at an obtuse angle to the epidural canal, making it easier to insert the catheter straight [9]. Nevertheless, the exact rates of stuck epidural catheters in the thoracic and lumbar regions could not be determined in this study.

Tunneling the epidural catheter by 5 cm in a cohort of 82 patients was associated with reduced catheter motion; however, the percentage of catheters maintaining the original position was not statistically different [10]. Nevertheless, it is important to note that our study did not evaluate whether tunneling reduces the possibility of knot formation as this has not been consistently reported in the included studies.

Knot formation

The mean position of knot formation in our study was 2.59 cm from the tip, which is consistent with the findings of a study by Lim et al. [11] In their study, 13% of lumbar catheters inserted in a group of 45 males were advanced more than 4 cm without coiling, and coiling occurred at a median length of 2.8 cm from the catheter tip [11]. Based on 18 case reports, the frequency of knotted catheters is estimated to be 1:2000–30,000 epidurals, with 87% of the knots occurring < 3 cm from the catheter tip and 28% of the knots associated with a loop in the catheter [12], which is consistent with our study findings.

In cadavers study using epiduroscopy, paramedian catheters were observed to cause less epidural tenting and pass cephalad more reliably than midline catheters [13]. In our study, we observed that 66.1% of data (39 cases) were missing regarding approach used for epidural catheter placement. Among the available data, 14 cases (23.7%), had catheter placement in the midline, and 6 cases (10.2%) underwent the paramedian approach. Since only a few cases underwent the paramedian approach, it is possible that less tenting or knots were observed with this approach. However, it is evident from our review that a knot formation during or after a paramedian insertion approach is not uncommon.

Techniques for catheter removal

A total of 47.5% cases underwent catheter removal with traction. Among them 13.6% had the catheter removed in the same position as that of insertion, whereas 8.5% had it removed in a different position. These findings align with the recommendation put forward by Morris et al. [14], which suggests that whenever the removal of catheter becomes difficult, the recommendation is to pull out softly and steadily,
with the patient in the same position as that during catheter insertion; if this approach fails, an alternative strategy is to attempt catheter removal with the patient placed in different positions and at various angles of lumbar flexion or extension. Another method, traction was recommended by Lala et al. [15], who suggested that steady traction would allow the catheter and knot to decrease in diameter and facilitate easy passage through ligaments.

Consistent with our study findings, previous studies have suggested that removal is the easiest if the patient is in the same position as that during insertion [16]. This observation is in line with a report by Morris et al. [14], where they found that significantly less force was required when the patient was placed in the same position for withdrawal as that for insertion.

Among the cases in which the catheter was removed, 13 reported removal in a prone position (25.5%), 10 (19.6%) in lateral, and only 7 (13.7%) in sitting position. Cases that reported removal in the prone position were performed under anesthesia, whereas the lateral position was most successful for catheter removal without anesthesia. We presume that all cases in which successful removal occurred in the prone position were probably planned for surgical removal and were kept in that position after administration of general anesthesia; however, the specific contribution of the prone position and general anesthesia in facilitating successful removal is unclear. The sitting position places more force on the spine, creating increased resistance to withdrawal. The force required to remove a lumbar catheter was 2.5 times more in the sitting position than that in the lateral position [17]. Blacksheer et al. [18] suggested that less tension is required to remove the catheter when the patient is in the lateral decubitus position as opposed to the sitting position. According to Boey and

Carrie, lateral positioning allowed a 2.5 N reduction in the force needed to withdraw the epidural catheter in the median and paramedian approaches [19].

Catheter characteristics

Arrow brand catheters (Arrow, USA) have been reported to stretch more than other catheter brands (Perifix, B Braun; Perisafe, Becton, Dickinson and Co., Portex) and break at lower forces than other brands of epidural catheters, especially at the 5 cm mark [20]. Our study findings did not show significant differences between the catheter brands used for knot formation. A study by Blum and Sosis showed that Abbott epidural catheters (nylon, Abbott Laboratories Inc.) were significantly stronger, whereas Baxter catheters (nylon, Baxter Healthcare Co.) were the weakest among the six different types of commercially available 20 G epidural catheters [21]. Spring wire-reinforced catheters are more resistant to kinking and more patent. An unconstrained tug on any epidural catheter (polyamide, polyurethane, or fluorinated ethylene propylene) should not be attempted as it could conceivably be around a nerve root or result in a piece of any manufacturer’s catheter breaking off [22]. Applying traction to the catheter resulted in its breakage in approximately 30% of cases [10]. The incidence of catheter breakage was not assessed in our study because patients with broken catheters were excluded.

During difficult catheter removal, normal saline can be injected through the catheter before making another removal attempt [23]. Injection of sterile saline and rotation of catheter was unsuccessful in catheter withdrawal as demonstrated in a study by Brenier et al. [24]. Our study reported similar findings, as all 12 cases (20.3%) in which a saline flush test was performed were unsuccessful. An unsuccessful saline flush test indicates the presence of a knotted catheter.

Investigations for entrapped catheters

In 32.2% of the case reports, no investigations were carried out, whereas 10.2% cases it was not specified if any investigation was done. Among the nine cases in which lumbosacral spine radiography was performed, five failed to reveal the catheter position or knot. A similar suggestion was made in a study by Asai et al. [20], in which even radiopaque catheters could not be visualized on a radiograph of the spine, especially when they were located in the epidural space. Fluoroscopy was done in only 11.9% of cases. If the epidural catheter is radio-opaque and patent, fluoroscopic examination with contrast may be useful, although they are not always successful. A total of 25.4% patients had undergone computed tomography (CT) scans to detect knot/catheter position with positive results. CT scans have been recommended for locating retained catheters because of their high resolution and ease of testing [25]. Two case reports by Bréget et al. [26] successfully visualized the epidural knot/loop on CT scans. CT scans may be helpful in identifying knots. However, it is important to note that not all entrapped catheters have a knot, as they may be stretched without forming a knot.

Breakage, hematoma formation, epidural site infection,
and neurological deficits are common complications of catheter entrapment. However, we did not study the complications associated with catheter entrapment, or some of the included studies did not report any complications.

**Outcomes and removal of entrapped catheters**

In our study, 18 cases (30.5%) underwent surgical removal, of which 25.4% were done under general anesthesia and 5.1% were under local anesthesia. It is important to note that 17 case reports (28.8%) recommended some form of traction for the removal of catheters. Surgical removal was recommended only in six case reports (10.2%). Surgical removal of a broken catheter is not mandatory if the patient remains asymptomatic [10]. It is reasonable to surgically remove the epidural catheter in children to reduce the possibility of neurological problems through growth and development or in adults with definite neurological symptoms, as well as in cases in which the catheter tip is in the dura [23]. During catheter removal, it is important to ensure that patients should not experience pain, which may indicate the possibility of the catheter being tangled around the nerve root. Owing to the possibility of nerve root avulsion, the catheter should be removed under direct visualization via laminectomy [17]. Five case studies (8.5%) recommended leaving the catheter in situ if no complications were observed.

**Recommendations**

1) To prevent knotting and entrapment, the length of the inserted catheter should be limited to less than 5 cm. A catheter with a greater tensile strength should be chosen.

2) If catheter entrapment is suspected, the saline flush test should be carried out to check the functionality. If the test fails, there is a high risk of catheter knotting.

3) What types of investigations should be conducted? Lumbarosacral CT scan should be the investigation of choice, as radiography of the lumbarosacral spine may not identify the knot. Radiological investigation is not always required.

4) A common method of removal is gentle traction on the catheter; thus, traction application should be the first choice. 5) Removal of the knotted epidural catheter in the lateral position should be attempted first. If this fails, a second attempt should be performed in the same position as that of the insertion. Avoid undue force during the removal process to minimize the risk of complications or further entanglement.

6) If the second attempt fails and the patient has neurological symptoms, surgical removal under Local anesthesia, Regional anesthesia, and/or General anesthesia should be considered.

7) Catheter removal by gentle traction can be performed by placing the patient in the prone position during surgical removal.

8) Following catheter breakage, if the patient is asymptomatic, the catheter can be left in situ after providing necessary counseling.

**Limitations**

This systematic review was unable to deliver quantitative data. It was not possible to prove a cause-and-effect relationship or allow generalizations. Furthermore, there is a risk of over-interpretation and publication bias as only cases with successful catheter removal may have been published. With the availability of comprehensive national-level data in some countries, this review will help to design new studies that may address such biases.

**Conclusion**

Our study highlights the potential for catheter entrapment in the epidural space, with deeper insertions significantly contributing to knotting and entrapment. When faced with an entrapped catheter, the initial attempt at removal should be in the lateral decubitus position, followed by the position used during insertion. CT scan may prove beneficial in identifying the presence of a knot.

Furthermore, our findings suggest that factors beyond deeper insertion and knotting may contribute to catheter entrapment, as evidenced by the instances of catheter stretching during challenging removal. In cases where the epidural catheter breaks during removal, the catheter may be left in situ under close monitoring in asymptomatic patients.

The results of this study have implications for clinical practice, emphasizing the importance of careful catheter insertion and management techniques. Further research is warranted to better understand the underlying factors contributing to epidural catheter entrapment and develop more effective preventive strategies.
FUNDING

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CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS


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Inter-transverse process blocks: caution about difference in methods

TO THE EDITOR: I read with great interest a recently published case report that described three cases wherein a bolus inter-transverse process block (ITPB) plus a continuous erector spinae plane block was provided for pain relief during video-assisted thoracoscopic surgery [1]. I greatly appreciate the authors for their innovative applications and excellent presentations of these cases.

I wish to present my clarifications on the difference between the two blocks, namely the costotransverse foramen block (CTFB) and mid-point transverse process to pleura block (MTPB), that are collectively named “ITPB” as per the recent nomenclature.

Yamamoto et al. [1] provided a CTFB for the first case. I am uncertain whether the description of this technique, as per Fig. 1 of Yamamoto et al. [1], is correct because the needle direction is from caudad to cephalad. This is in contrast to the original description by Nielsen et al. [2], wherein the needle trajectory was from cephalad to caudad, and the needle tip was placed at the neck of the rib attached to the cranial portion of the caudal transverse process for the local anesthetic injection. Furthermore, the needle tip was placed at the midpoint between the transverse process and pleura, as described by Yamamoto et al. [1], which is similar to the MTPB [3]. I believe that this confusion occurred because Yamamoto et al. [1] cited the study by Shibata et al. [4] as a reference for CTFB. Because of this change in the needle direction, it is also uncertain whether the description of the CTFB injection site, as per Fig. 3 of Yamamoto et al. [1], is correct. The CTFB injection site should be over the neck of the rib attached to the caudal transverse process, in accordance with the original description by Nielsen et al. [2], and not closer to the cranial transverse process. The site of the MTPB injection was described correctly in Fig. 3, although the ultrasound image describing the method of MTPB for cases 2 or 3, was not provided [1].

To conclude, many interfascial plane blocks have been described in the recent literature, and some of these, such as CTFB and MTPB, are in close proximity. Hence, we must carefully analyze each technique based on appropriate reference(s) to avoid confusion among the different techniques. A recently published article on the nomenclature of various regional techniques [5] will also help greatly in this regard. Nevertheless, a strong consensus on the nomenclature for ITPBs and a clear description of the CTFB technique is needed.

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REFERENCES
2. Nielsen MV, Morigg B, Hoermann R, Nielsen TD, Bendtsen TF, Berglund J. Are single-injection erector spinae plane block and multiple-injection costotransverse block equivalent to thoracic


An 18 years old girl presented to the preoperative anesthesia clinic for surgery of a distal phalanx fracture. She had a history of delayed milestones and irregular periods with easy fatigability. Physical examination revealed that the patient was short-statured with a webbed neck (Fig. 1A). Family history was not significant except for short-statured parents. Her heart rate was 70 beats/min, blood pressure was 100/66 mmHg, respiratory rate was 14 breaths per min and body temperature was 36.5ºC. Her preoperative investigations were normal except for an electrocardiogram, which showed low-voltage complexes (Fig. 1B), and chest radiographs, which showed a moneybag heart (Fig. 1C). Point-of-care ultrasound examination of the heart showed a swinging motion within the anechoic space (Fig. 2, video). In the four-chamber apical view, the anechoic space measured > 2 cm posterior and > 1 cm anterior to the heart, suggesting a large pericardial effusion (Fig. 2C). No collapse of the right atrium or ventricle was observed, which ruled out tamponade physiology and precluded the need for pericardiocentesis (video). A thyroid function test was also ordered, and its result showed severe hypothyroidism (thyroid stimulating hormone > 496 µIU/ml, T3 < 0.05 ng/ml, and T4 < 2 µg/dl). Other differential diagnoses included tuberculosis, autoimmune diseases, renal failure, and tumors, which were excluded based on biomarker and antibody measurements. Other routine hematological investigations were normal. A cardiologist’s opinion was sought, who advised only correction of the hypothyroid status for the management of the effusion. The patient was started on thyroxin therapy at 100 µg, which was increased to 150 µg. One week later, the patient underwent an uneventful surgery under a wrist block. The thyroid function test and echocardiography were repeated after 4 weeks, which showed a return to the euthyroid status with minimal pericardial effusion. Karyotyping results showed a mosaic variant of Turner Syndrome, for which she was advised to undergo gynecological and endocrinological follow-up.

Written informed consent was obtained from the patient to report this case without revealing her identity.
Fig. 1. (A–C) Patient profile, ECG, chest X-ray. ECG: electrocardiogram.

Fig. 2. (A–D) Parasternal long axis view, parasternal short axis view, apical 4-chamber view, subcostal 4-chamber view.
SUPPLEMENTARY MATERIALS

Supplementary video is available at https://doi.org/10.17085/apm.22255.

FUNDING

None.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS


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Garima Garg, https://orcid.org/0000-0003-0650-6144
1. Online manuscript review process and guidelines for submission

1) All manuscripts must be submitted through the online submission system (available at http://submit.anesth-pain-med.org). Any inquiries about the manuscripts should be posted on the “Contacting Author” page, which is available to the right upon logging in. Specify the manuscript number, author, and corresponding author when posting an inquiry.

2) The corresponding author should be a faculty. The corresponding author will be notified by e-mail whenever there is any change in the status of a submitted manuscript, and any resubmission can only be made by the corresponding author.

3) Once the manuscript has been submitted and placed under review, the content or author information cannot be changed.

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APM has made English editing mandatory for manuscripts submitted on or after September 1, 2013. Authors are responsible for the cost of editing. For English manuscripts, please submit them to a professional editing service after acceptance and upload the edited file and certificate of editing in the manuscript submission system. Manuscripts edited by an individual and not through a professional editing service will not be accepted. Manuscripts submitted in Korean will be translated into English by the Society after acceptance, and Korean version will be published only on the website (www.anesth-pain-med.org).
Instructions for Authors

Enacted: May 15, 2006
Recently revised (15th): January 16, 2023

Anesthesia and Pain Medicine (APM) is the official scientific journal of the Korean Society of Neuroscience in Anesthesiology and Critical Care (KSNACC), the Korean Society for Anesthetic Pharmacology (KSAP), the Korean Society of Obstetric Anesthesiologists (KSOA), the Korean Society of Pediatric Anesthesiologists (KSPA), the Korean Neuromuscular Research Society (KNRS), the Korean Society of Cardiothoracic and Vascular Anesthesiologists (KSCVA), the Korean Society of Transplantation Anesthesiologists (KSTA), the Korean Spinal Pain Society (KSPS), the Korean Society of Regional Anesthesia (KSRA), and the Korean Society for Airway Management (KSAM). The abbreviated title is “Anesth Pain Med”. It is published in English four times a year on the last day of January, April, July, and October.

I. Editorial Policy

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

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In addition to members of the Korean Society of Anesthesiologists, any researcher throughout the world can submit a manuscript if the scope of the manuscript is appropriate. Authors are requested to submit their papers electronically using the online manuscript submission system, available at: http://submit-apm.org. Authors, reviewers, and editors send and receive all correspondences through this system. Final revisions by authors should be submitted within 1 week of the request.

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All funding sources should be declared on the title page or in the Acknowledgements section at the end of the text. If an author’s disclosure of potential conflicts of interest is determined to be inaccurate or incomplete after publication, a correction will be published to rectify the originally published disclosure statement, and additional action may be taken as necessary.

If one or more editors are involved as authors, the authors should declare conflict of interest.

Ex) AAA has been an editor of the Anesthesia and Pain Medicine since 2017; however, he was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

2. Statement of informed consent

Copies of written informed consents and Institutional Review Board (IRB) approval for clinical research are recommended to
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CONSORT for reporting of randomized controlled trials (http://www.consort-statement.org)

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PRISMA for reporting of systematic reviews (http://www.prisma-statement.org)

MOOSE for reporting of Meta-analyses of observational studies (https://jamanetwork.com/journals/jamasurgery/article-abstract/2778476)

CARE for reporting of clinical cases (https://www.care-statement.org)

AGREE for reporting clinical practice guidelines (http://www.agreetrust.org/resource-centre/agree-reporting-checklist/)

ARRIVE for reporting of animal pre-clinical studies (https://arriveguidelines.org/arrive-guidelines)

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A manuscript must be written in proper and clear English or Korean. Our preferred file format is DOCX or DOC. Manuscripts should be typed double-spaced on A4-sized paper, using 12 point font in English, using 10 point font in Korean.

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Abbreviations should be avoided as much as possible. When they are used, a full expression of the abbreviated words should be provided at the first use, with the abbreviation following in parentheses.

Ex) target controlled infusion (TCI)

After that, “TCI” can be used instead of “target controlled infusion.”

Common abbreviations may be used, however, such as DNA. Abbreviations can be used if they are listed as a MeSH subject heading (https://www.ncbi.nlm.nih.gov/mesh).

3. Word spacing

1) Leave 1 space on each side when using arithmetic marks such as +, −, ×, etc.
   Ex) 24 ± 2.5

2) Leave no space when using a hyphen between words.
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2) When using parentheses, leave 1 space on each side in English, and leave no space in the Korean manuscript.

3) When using brackets in parentheses, apply square brackets.
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2) Citations should be applied after the last word.
Ex) It is said that hypertension can be induced [1] and the way to injure the brain [2] is...
Ex) Choi and Kim [1] reported...

3) Apply citations before a comma or period.
Ex) ....is reported [1],

4) Several or coupled superscripts can be written as [1–5] or [1,3,5].

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The manuscript should be organized in the order of title, abstract, introduction, methods, results, discussion, acknowledgments, references, tables, figures, and figure legends. Figures should be uploaded as separate files. The title of each new section should begin on a new page. The conclusion should be included in the discussion section. Number pages consecutively, beginning with the first page of the manuscript. Page numbers should be placed in the middle of the bottom of the 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 included as a supplement in an appendix.

6. Organization of manuscript

1) Clinical or experimental research

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Ex) Effect of smoking on bronchial mucus transport velocity under total intravenous anesthesia .......... [●]
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Disclosure of all financial support for the work, including departmental or institutional funding/support, is mandatory.

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All manuscripts should contain a structured abstract that is written only in English. Authors should provide an abstract of no more than 250 words. It should contain 4 subsections: Background, Methods, Results, and Conclusions. Citation of references is not permitted in the abstract. A list of key words at least 6, with a maximum of 10 items, should be included at the end of the abstract. Key words should be selected from MeSH (https://www.ncbi.nlm.nih.gov/mesh), and these should be written in small letters with the first letter capitalized. Separate each word with a semicolon (;), and include a period (.) at the end of the last word.
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Ex) 5%, 36 °C

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Ex) Premedicated Mg²⁺[O]

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Results should be presented in a logical sequence in the text, tables, and figures, giving the main or most important findings first. Do not repeat all the data provided in the tables or figures in the text; emphasize or summarize only the most important observations. Results can be sectioned by subsection titles but should not be numbered. The citation of tables and figures should be provided as Table 1 and Fig. 1.
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Precisely describe the methods of statistical analysis and computer programs used. Mean and standard deviation should be described as mean ± SD, and mean and standard error should be written as mean ± SEM. Median and interquartile should be described as median (1Q, 3Q). When displaying P values, use a capital P and do not put a “.” between “P” and “value”.
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D. When analyzing a categorical variable, an exact test or asymptotic method with appropriate adjustments should be used if the number of events and sample is small. The standard chi-squared test or difference-in-proportions test may be performed only when the sample size and the number of events are sufficiently large.

E. The APM strongly encourages authors to show confidence intervals, and it is not recommended to present the P value without showing the confidence interval. In addition, the uncertainty of estimated values, such as the confidence interval, should be described consistently in figures and tables.

F. Except for study designs that require a one-tailed test, for example, non-inferiority trials, the P values should be two-tailed. A P value should be expressed up to three decimal places (ex. P = 0.160, not as P = 0.16 or P < 0.05). If the value is less than 0.001, it should be described as “P < 0.001” but never as “P = 0.000.” For large P value greater than 0.1, the values can be rounded off to one decimal place, for example, P = 0.1, P = 0.9.

G. A priori 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. Usually, the mean difference and standard deviation (SD) are typical parameters in estimating the effect size. The power must be equal to or greater than 80 percent. In the case of multiple comparisions, an adjusted level of significance is acceptable.

H. When reporting a randomized clinical study, a CONSORT type flow diagram, as well as all the items in the CONSORT checklist, should be included. If limited in terms of the space of the manuscript, this information should be submitted as a separate file along with the manuscript.

I. 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 cardiac indices in patients measured on a scale that is accurate to 0.1 L/min/m² should be expressed as 2.42 (0.31) L/min/m².

J. Except when otherwise stated herein, authors should conform to the most recent edition of the American Medical Association Manual of Style.

Discussion

The discussion should be described to emphasize the new and important aspects of the study, including the conclusions. Do not repeat in detail the results or other information that is provided 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.

Funding

Financial support, including foundations, institutions, pharmaceutical and device manufacturers, private companies, intramural departmental sources, or any other support, should be described.

Acknowledgments

Persons or institutes that contributed to the manuscript but not sufficiently to be coauthors may be recognized.

References

- References should be obviously related to documents and should not exceed 50 in number. The number of references should not exceed 100 in reviews. However, the number of references has no limitation in systematic review and meta-analysis. References should be numbered consecutively in the order in which they are first mentioned in the
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- Only one table is to be drawn per page in the order cited in the text.
• The title of the table is to be in English and written at the top of the table in the form of a phrase.
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• For demographic data, gender is recorded as M/F, age as yr, (if necessary, use days or months in children) without decimal point. The “±” sign within the table is to be aligned with the rows above and below.
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• Significance marks are to conform to the Vancouver style (Uniform Requirements for Manuscripts Submitted to Biomedical Journals. JAMA 1997; 227: 927-34). In other words, these must be in the order of * , † , ‡ , § , ∥ , ¶ , ** , †† , ‡‡ and written as superscripts.

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The APM publishes supplemental video (movie) clip(s) that will be available online. Authors should submit videos according to our video submission guidelines.
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2 Video clips should contain succinct teaching points that must be supported by the current literature or standard reference texts, preferably those most accessible to the general reader. The adequacy of the teaching points will be evaluated during the review process and finally confirmed by the Editorial Board at the end of the review process.
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issues.

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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. Copies of written informed consents should be kept. If necessary, the editor or reviewers may request copies of these documents. If these steps are impossible, Institutional Review Board approval should be obtained prior to submission. The rarity of a disease condition is itself not an acceptable justification for a case report.

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(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 3 and maximum of 10 items, should be included at the end of the abstract.

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

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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 are invited only by editorial board. If authors want to submit an unsolicited review article, please contact editorial office (apm@anesthesia.or.kr). Review articles should include unstructured abstracts written in English equal to or less than 250 words. The organization should be in order of abstract, introduction, text following each title, conclusion and references. Figures and tables should be provided in English. Body text should not exceed 30 A4-sized pages, and the number of figures and tables should each be less than 6. However, if necessary, the number of pages, the number of figures, and tables can be added in accordance with the decision of the editorial committee.

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Book reviews as well as news of scientific societies and scientific meeting dates in Korea or abroad can be included.

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