Reduce complications. Improve patient outcomes.

3M™ Bair Hugger™ Normothermia System

When it comes to proactive temperature management, degrees matter. Even a small drop in core body temperature can result in inadvertent perioperative hypothermia, a complication associated with an increased risk of surgical site infection, longer length of stay, and other costly, potentially deadly consequences.

The 3M™ Bair Hugger™ Normothermia System allows clinicians to help maintain normothermia before, during, and after surgery. The system includes:

- Convective air warming units, blankets, and gowns
- Non-invasive core temperature monitoring

5. 3M, Bair Hugger and the Bair Hugger logo are trademarks of 3M. © 2019. All rights reserved.

Choice of neuromuscular block reversal agent to reduce postoperative pulmonary complications

Cardiovascular manifestation of end-stage liver disease and perioperative echocardiography for liver transplantation: anesthesiologist’s view

Anesthetic care for electroconvulsive therapy

http://anesth-pain-med.org
Aims and Scope

Anesthesia and Pain Medicine (APM) is the official journal of the following ten subsocieties of the Korean Society of Anesthesiologists: the 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 quality of care and the education 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 for operative delivery, pain relief in labor, care of the critically ill parturient, 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 anesthesia
- Pathophysiology, pharmacology, and all respects 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.

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

Vol.17 No.2 April 2022

**Reviews**

121  Choice of neuromuscular block reversal agent to reduce postoperative pulmonary complications
Sung-Ae Cho, Tae-Yun Sung

132  Cardiovascular manifestation of end-stage liver disease and perioperative echocardiography for liver transplantation: anesthesiologist’s view
Sangbin Han, Jaesik Park, Sang Hyun Hong, Chul Soo Park, Jongho Choi, Min Suk Chae

145  Anesthetic care for electroconvulsive therapy
Kyoung-Woon Joung, Dong Ho Park, Chang Young Jeong, Hong Seuk Yang

**Anesthetic Pharmacology**

Clinical Research

157  Effects of chlorpheniramine on emergence agitation after general anesthesia for ureteroscopic stone surgery: a retrospective cohort study
Choon-Kyu Cho, Minhye Chang, Seok-Jin Lee, Sung-Ae Cho, Tae-Yun Sung

**Obstetric Anesthesia**

Clinical Research

165  Association between anesthetic method and postpartum hemorrhage in Korea based on National Health Insurance Service data
Yongho Jee, Hyun Jung Lee, Youn Jin Kim, Dong Yeon Kim, Jae Hee Woo

**Pediatric Anesthesia**

Clinical Research

173  Comparison of nebulized dexmedetomidine and ketamine for premedication in pediatric patients undergoing hernia repair surgery: a randomized comparative trial
Geeta Singariya, Namita Malhotra, Manoj Kamal, Rishabh Jaju, Shruti Aggarwal, Pooja Bihani

**Neuromuscular Research**

Experimental research

182  Effects of hydrocortisone-presensitized sugammadex on recovery from neuromuscular blockade induced by rocuronium: a rodent in vivo study
Hey-Ran Choi, Hong-Seuk Yang, Jae-Moon Choi, Chungon Park, Junyong In, Yong Beom Kim

Clinical Research

191  Adverse events of sugammadex that occurred in a Korean population
Woong Han, Jong Min Lee, Dong Ho Park, Chia An Lee, Chang Yeong Jeong, Hong Seuk Yang
**Cardiothoracic and Vascular Anesthesia**

Clinical Research

199  Comparison of two-lung and one-lung ventilation in bilateral video-assisted thoracoscopic extended thymectomy in myasthenia gravis: a retrospective study  
Mijung Yun, Gunn Hee Kim, Sung-chul Ko, Yun Jae Han, Wooshik Kim

**Transplantation Anesthesia**

Clinical Research

206  Cause of postoperative mortality in patients with end-stage renal disease  
Sanghoon Song, Chaeyeon Cho, Sun Young Park, Ho Burn Cho, Jae Hwa Yoo, Mun Gyu Kim, Ji Won Chung, Sang Ho Kim

213  Intraoperative lactic acid concentration during liver transplantation and cutoff values to predict early mortality: a retrospective analysis of 3,338 cases  
Kyoung-Sun Kim, Sang-Ho Lee, Bo-Hyun Sang, Gyu-Sam Hwang

**Spinal Pain**

Case Report

221  Multispecialty perspective on intradural disc herniation: diagnosis and management  
Vinicius Tieppo Francio, Christopher S. Wie, Micheal T. Murphy, Matthew T. Neal, Mark K. Lyons, Wende N. Gibbs, Natalie H. Strand

**Regional Anesthesia**

Case Report

228  Two cases of late-onset cardiovascular toxicities after a single injection of local anesthetics during supraclavicular brachial plexus block  
Ji Yeon Kim, Beom Il Park, Min Hee Heo, Kyoung Woo Kim, Sang-II Lee, Kyung-Ta Kim, Won Joo Choe, Jang Su Park, Jun Hyun Kim

**Airway Management**

Case Report

235  An anesthetic experience of hereditary angioedema type I patient undertook total laparoscopic hysterectomy  
Yun-Sic Bang, Jaeho Cho, Chunghyun Park

239  Management of pulmonary aspiration due to undiagnosed achalasia during induction of general anesthesia  
Hee Jung Kim, Yong Seon Choi, Jeong Hyun Jin, Bora Lee
Letter to the Editor
245 High-flow nasal cannula oxygenation for awake craniotomy in patients with obesity: looking beyond oxygenation
Habib Md Reazaul Karim, Pradipta Bhakta, Antonio M Esquinas, Parmod Kumar Bithal

246 Authors’ reply
Ji-Hye Kwon, Jeong Jin Lee

247 Liver transplant and the sweet–bitter truth
Varun Suresh, Rohan Magoon, Shalvi Mahajan

Corrigendum
248 Corrigendum: Effect–site concentration of remifentanil for preventing propofol injection pain during induction of balanced anesthesia
Joungmin Kim, Daehoon Kim, Hyung Gon Lee
Silicone Elastomeric Pump
Neofuser+ Neofuser Plus+

SILICONE ELASTOMERIC PUMP FOR SYSTEMIC/REGIONAL PAIN

- Lightweight disposable design and silent operation
- Multiple choices in reservoir sizes and options
- Precise scales to monitor the infusion process

Distributor: KCPMED
KCPMED B/D, 54, Donggyo-ro 27 gil, Mapo-gu, SEOUL, KOREA
+82-2-3141-2070 / kcpmed@kcpmed.com

Manufacturer: S&S MED
67, Bongseong-ro, Gunpo-si, Gyuenggi-do, KOREA
+82-31-473-5171 / sorip@hotmail.com
Does PONV still Remain unsolved?

Feel the difference with Ramosetron
Because Every Kid is Special

Bridion®, that a neuromuscular blockade reversal agent can be used by children over 2 years of age.

Before prescribing BRIDION®, refer to the full prescribing information for further details.
INTRODUCTION

Postoperative pulmonary complications (PPCs) have been inconsistently defined in clinical trials, but they usually include pneumonia, atelectasis, respiratory failure, and reintubation [1]. The incidence of PPCs reportedly varies from less than 2% to 70%, depending on the type of surgery, surgical population, and definition of PPCs [2–6]. PPCs are the most important and independent determinants of 30-day mortality, and nearly 25% of the deaths occurring within 1 week after surgery are related to PPCs [3,7]. Additionally, because PPCs cause an increase in morbidity, medical costs, and duration of hospitalization, the identification of its risk factors and application of strategies to reduce PPCs are important clinically.

Many physicians struggle to reduce the risk of increased morbidity and mortality in patients undergoing surgery. Most factors that contribute to the occurrence of PPCs are related to surgery or the patients [8]. Moreover, as risk factors for PPCs, the strength of the evidence for anesthesia-related factors is weaker than that for surgery- or patient-related factors [3,8]. Nevertheless, strong evidence has shown...
that residual neuromuscular block (NMB) is associated with an increased risk of PPCs [1]. Therefore, it is important to understand the factors related to the field of anesthesia and make efforts to prevent them.

Among the anesthesia-related factors, the use of NMB agents (NMBAs) is known to be associated with increased PPCs as well as residual NMB, since the first report of its contribution to postoperative mortality in 1954. However, the relationship between PPCs and the type of reversal agents for NMB, such as conventional anticholinesterases and the relatively new sugammadex, remains debatable. This review discusses the important research findings on PPCs in the field of neuromuscular research.

**POSTOPERATIVE PULMONARY COMPLICATIONS: DEFINITION, RISK FACTORS, AND PREDICTION MODELS**

PPCs are not a new concept. They have existed since long and remain a subject of interest for all anesthesiologists, physicians, and surgeons involved in perioperative medicine [9–11]. Since there is no fixed definition for PPCs, various definitions have been used over time. The commonly accepted definitions of PPCs include the European Perioperative Clinical Outcome (EPCO) definitions published in 2015 and a new definition published in 2018 [12,13]. In the EPCO definitions, PPCs comprise respiratory infections, respiratory failure, pleural effusion, atelectasis, pneumothorax, and aspiration pneumonitis [12]. On the other hand, the new definition of PPCs announced in 2018 comprises atelectasis detected on computed tomography or chest radiography, pneumonia diagnosed according to the US Centers for Disease Control criteria, acute respiratory distress syndrome according to the Berlin consensus definition, and pulmonary aspiration with no clinical history or radiological evidence [13].

The causes of PPCs are multifactorial, and the related risk factors can be classified as preoperative or intraoperative.

Preoperative factors include advanced age, American Society of Anesthesiologists physical status (ASA PS) ≥ II, frailty, chronic obstructive pulmonary disease, recent upper respiratory tract infection, obstructive sleep apnea (OSA), serum albumin level < 30 g/L, alcohol use, delirium, and abnormal chest radiography findings [1,8]. Intraoperative factors include surgical factors such as surgical site (e.g., abdominal, thoracic, neurosurgery, head and neck, or vascular), duration of surgery (> 2 h), and emergency surgery- or anesthesia-related factors such as general anesthesia or regional anesthesia, use of NMBAs, neostigmine administration, residual NMB, sugammadex with supraglottic airway, and no use of peripheral nerve stimulator [1,8,14].

Several risk score models have been proposed to predict PPCs, but there is no “one-size-fits-all” model for the risk stratification for PPCs, and most of them have certain limitations [7,14]. To date, the Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) risk score is the only predictive model that has shown sufficient predictive power in external validation [14]. Notably, only few models among the independent variables of several predictive models for PPCs, including the ARISCAT model, include anesthesia-related factors such as the use and reversal of NMBAs and anesthesia techniques (Table 1) [15–21]. This is probably because surgical factors, such as surgical site, and emergency surgery- and patient-related factors, such as age and underlying diseases, have a greater effect on PPCs than do the anesthetic factors [8,22]. Nevertheless, since the anesthesia-related factors, such as residual NMB, are modifiable and preventable unlike other factors such as age, surgical site, emergency surgery conditions, and surgical duration, understanding the effects of NMB and its reversal on PPCs is clinically relevant.

**RESIDUAL NEUROMUSCULAR BLOCKADE AND POSTOPERATIVE PULMONARY COMPLICATIONS**

Residual NMB, often defined by a train-of-four (TOF) ratio < 0.9, is one of the well-known anesthesia-related risk factors for PPCs. It is almost clear that residual NMB is associated with postoperative upper airway muscle dysfunction [23–25]. The main mechanisms of PPCs induced by residual NMB due to the NMBAs used during general anesthesia are respiratory muscle dysfunction, impairment of the hypoxic ventilatory response, and inability to protect the airway during swallowing. These pathological mechanisms may lead to adverse respiratory events such as atelectasis, hypoxia, aspiration, pneumonia, and reintubation [24].

Two representative strategies that anesthesiologists implement to avoid this potentially dangerous residual NMB include quantitative neuromuscular monitoring and appropriate reversal of the NMB. Neuromuscular monitoring in the perioperative period is essential to determine the degree of recovery from NMB through quantitative evaluation and to confirm the presence of residual NMB. A minimal level of NMB (TOF ratio, 0.7–0.9) cannot be detected without quanti-
Table 1. Studies Evaluating the Risk of Postoperative Pulmonary Complications

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of surgery</th>
<th>Type of anesthesia</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Six-factor risk score; 1997 [15]</td>
<td>Elective non-laparoscopic abdominal surgery</td>
<td>General</td>
<td>Age ≥ 60 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Impaired preoperative cognitive function</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Smoking history within the past 8 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Body mass index ≥ 27 kg/m²</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>History of cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Incision site-upper abdominal or both upper/lower abdominal incision</td>
</tr>
<tr>
<td>Arozullah respiratory failure index; 2000</td>
<td>Noncardiac surgery</td>
<td>General</td>
<td>Type of surgery</td>
</tr>
<tr>
<td>[16]</td>
<td></td>
<td>Spinal</td>
<td>Albumin &lt; 30 g/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Epidural</td>
<td>Blood urea nitrogen &gt; 30 mg/dl</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Partially or fully dependent functional status</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Age ≥ 70 years</td>
</tr>
<tr>
<td>Clinical prediction rule; 2009 [17]</td>
<td>Open upper abdominal surgery</td>
<td>General</td>
<td>Duration of anesthesia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Surgical category</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Current smoking</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Respiratory co-morbidity</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Predicted maximal oxygen uptake</td>
</tr>
<tr>
<td>ARISCAT; 2010 [18]</td>
<td>Scheduled or emergency surgery</td>
<td>General</td>
<td>Low preoperative arterial oxygen saturation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuraxial</td>
<td>Acute respiratory infection during the previous month</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Regional</td>
<td>Age &gt; 50 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Preoperative anemia (hemoglobin ≤ 10 g/dl)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Upper abdominal or intrathoracic surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Surgical duration of at least 2 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Emergency surgery</td>
</tr>
<tr>
<td>SLIP; 2011 [19]</td>
<td>Procedures requiring &gt; 3 h under mechanical ventilation</td>
<td>General</td>
<td>High risk cardiac, vascular, or thoracic surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gastroesophageal reflux disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Alcohol abuse</td>
</tr>
<tr>
<td>Gupta postoperative respiratory failure;</td>
<td>Scheduled or emergency surgery</td>
<td>Not mentioned</td>
<td>Functional status</td>
</tr>
<tr>
<td>2011 [20]</td>
<td></td>
<td></td>
<td>ASA physical status</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sepsis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Emergency case</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Type of procedure</td>
</tr>
<tr>
<td>Gupta postoperative pneumonia risk; 2013</td>
<td>Scheduled surgery</td>
<td>Not mentioned</td>
<td>Age (increase per year)</td>
</tr>
<tr>
<td>[21]</td>
<td></td>
<td></td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Functional status</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ASA physical status</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sepsis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Smoking within last year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Type of procedure</td>
</tr>
</tbody>
</table>


tative monitoring of the TOF [24,26]. To exclude clinically significant residual NMB, the TOF ratio must exceed 0.9, when recorded with mechanomyography or electromyography, and exceed 1.0 when using acceleromyography (AMG) [27]. Additionally, appropriate NMB reversal requires the administration of a titrated dose of the reversal agent according
to the level of the block under quantitative neuromuscular monitoring [28]. Reversal agents for NMB are divided into the following two major categories: anticholinesterases (e.g., neostigmine and pyridostigmine) and sugammadex. Anticholinesterases bind to acetylcholinesterase, which can prolong the effects of acetylcholine and competitively antagonize NMBAs. However, it has a ceiling effect, with no effect above a certain dose, and NMB over a deep block cannot be reversed with anticholinesterases. In previous studies, proper administration of neostigmine under neuromuscular monitoring reduced the PPCs associated with the use of NMBAs; however, there were reports of inappropriate reversal using neostigmine, such as neostigmine administration not guided by the TOF ratio or administered dose > 60 μg/kg [29,30]. Thus, it should be used only when the twitch height is ≥ 20% of the control or when the minimum TOF count is two [31]. In contrast, sugammadex is a relatively new reversal agent approved in 2008 in Europe, 2012 in Korea, and 2015 in the United States, which can reverse the NMB at any stage by encapsulating only the aminosteroidal NMBAs [32]. Various studies have shown that sugammadex is associated with a lower incidence of residual NMB than that of neostigmine [33–35]. Hence, the question of whether PPCs can be reduced using sugammadex is raised.

**REVERSAL AGENTS AND PPCS**

Unlike anticholinesterases, which are traditional NMB reversal agents, sugammadex is the only reversal agent that can reverse deep and intense blocks. Moreover, various studies have confirmed that sugammadex can reduce the incidence of residual NMB [33–35]. Various meta-analyses performed for several randomized controlled studies comparing neostigmine and sugammadex reported that the incidence of respiratory events and residual curarization could be reduced with sugammadex [36–38]. However, it is difficult to use these studies as evidence that sugammadex reduces PPCs, because the PPCs in these studies were identified as one of the outcomes of various adverse events and not as the primary outcome. As an ideal condition of a randomized controlled trial (RCT) would minimize the overall incidence of PPCs and the difference between the two groups, the incidence of PPCs in the real world may be different from that in an RCT [39]. Therefore, it is important to investigate the relationship between reversal agents and PPCs through large-scale cohort studies.

A retrospective study published in 2014 with data from 1,444 patients reported that sugammadex could lower the risk of PPCs in high-risk patients with ASA PS ≥ III; however, this finding should be interpreted cautiously because the endpoints are mixed, including acute post-anesthetic care unit (PACU) complications, bronchospasm, airway intervention, cardiac arrhythmia, length of stay in the PACU, and pulmonary outcome within 7 days postoperatively [40]. The post-anesthesia pulmonary complications after use of muscle relaxants (POPULAR) study published in 2019, supported by the European Society of Anaesthesiology and Intensive Care, is the first multicenter cohort study providing prospective data for PPCs and analyzing 22,803 patients to identify PPCs related to NMBAs [41]. The incidence of PPCs in that study was 7.8%. Moreover, it showed that the use of NMBAs was associated with an increase in PPCs, although the use of NMBA had a lesser effect on the risk of PPCs than did the type and duration of surgery or the patient’s preoperative pulmonary function. In contrast, monitoring of NMB, use of reversal agents, extubation at TOF ratio ≥ 0.9, and the use of sugammadex instead of neostigmine were not associated with a reduction in PPCs. Some of these results have been refuted in later studies [42,43]; PPCs were reduced with TOF ratio > 0.95 before tracheal extubation than with TOF ratio > 0.9 [42], and the use of sugammadex instead of neostigmine was associated with a decrease in PPCs [43]. In an exploratory analysis of the POPULAR data, applying a TOF ratio threshold of 0.95 before extubation instead of 0.9 showed a decrease in PPCs [42]. This is presumed to be due to the property of the AMG, which overestimates neuromuscular recovery. In the POPULAR study, 87% of the neuromuscular monitoring devices used were AMG, which requires “normalization” of the TOF ratio to obtain an accurate TOF ratio of 0.9. However, normalization is rarely performed in clinical practice. Additionally, NMB reversal was achieved only in less than half of the patients who received NMBAs, and the number of patients receiving sugammadex was < 2,000. Furthermore, only 20% of the patients had complete data that allowed for the matching of patients and comparison of the treatment methods. Therefore, a more appropriate conclusion might be that NMBAs can cause serious outcomes if managed improperly.

Until the sugammadex versus neostigmine for reversal of neuromuscular blockade and postoperative pulmonary complications (STRONGER) study was published in 2020, no large-scale multicenter study had focused on the relationship between reversal agents and PPCs [43]. Although this study has limitations in collecting data retrospectively, its hypothe-
sis was that patients receiving sugammadex have fewer PPCs than those receiving neostigmine. PPCs were confirmed in 4.1% of the 45,712 patients. The incidence of PPCs was 3.5% in the sugammadex group and 4.8% in the neostigmine group, confirming that the use of sugammadex reduced the risk by 30%. Moreover, and pneumonia and respiratory failure were reduced by 47% and 55%, respectively. However, since the data collection period of 5 years was set retrospectively, and the definition of PPCs was established using the prescription codes of the International Classification of Diseases-9 and -10, the results should be interpreted considering these limitations compared to prospective studies.

However, unlike previous studies [40,43], in a retrospective registry study on the occurrence of PPCs related to the use of sugammadex and neostigmine published in 2021 [44], there was no significant difference in the incidence of PPCs between them. In this study, the absolute incidence of PPCs decreased over time (adjusted odds ratio, 0.91 [per year]), which may be a simple change due to the long data collection period (10 years). In addition to the difference between the use of neostigmine and sugammadex, because of the multiple quality improvement initiatives over time including enhanced recovery after surgery protocols, the use of objective criteria for ventilator-related pneumonia and of TOF monitoring were implemented in the hospital where this study was conducted. All these factors may have influenced the reduction of PPCs.

Among the studies published so far on the occurrence of PPCs with sugammadex and neostigmine, a recently published meta-analysis analyzed 14 RCTs and 1,478 patients [45]. In the main meta-analysis, the risk of overall PPCs was lower with sugammadex than with neostigmine. In the stratified subgroup analyses, sugammadex was associated with a reduced risk of respiratory failure as compared to neostigmine, but there was no statistical difference in the occurrence of pulmonary infection, atelectasis, or pneumothorax. This meta-analysis may have clinical heterogeneity due to differences in patient comorbidities and the type of surgery. Additionally, PPCs such as respiratory infections, atelectasis, and pneumothorax were included only in 1–3 studies. These limitations should also be clearly considered [45].

Despite the discussions in recent studies, it is difficult to determine the exact association between the choice of reversal agent and PPCs. Published retrospective studies were unable to control for several factors that affect PPCs. However, controlled situations do not accurately reflect the actual clinical environment. In a clinical environment, the individual patient characteristics and the condition according to the risk factors should be understood and considered.

**RECENT RESEARCHES IN SPECIFIC PATIENT POPULATIONS OR SURGERIES**

As mentioned earlier, there are limited studies on the relationship between reversal agents and PPCs, and studies on certain specific populations and situations are lacking (Table 2).

**Elderly patients**

Old age is a well-known risk factor for PPCs, and two studies were recently published on PPCs following NMB reversal in the elderly [46,47]. In one RCT published in 2020, elderly patients aged > 70 years with ASA PS I–IV and scheduled for surgeries lasting > 3 h were divided into two groups [46]. Although the decrease in PPCs was not significantly different between sugammadex and neostigmine, the residual NMB and 30-day readmission rates were lower with sugammadex than with neostigmine. The other study published in 2021 was conducted in five countries, including South Korea, and it was confirmed that the occurrence of postoperative pneumonia and residual NMB was significantly lesser with sugammadex than with neostigmine in high-risk patients aged ≥ 75 years [47]. The difference between the two studies could be attributed to differences in the patient characteristics included in each study. Participants of the latter study (2021) included only those with ASA PS ≥ III and those aged ≥ 75 years, thus representing high-risk patients. Furthermore, it supported another study showing that PPCs in high-risk patients could be reduced with sugammadex used for NMB reversal [40].

**Pediatric patients**

Owing to the several restrictions on the use of sugammadex in children, as its pediatric use was not approved in South Korea until October 2021 and has been not yet approved in the United States for children, studies directly related to PPCs in children are rare. However, it has been found that sugammadex can be used safely and efficiently to reverse rocuronium-induced NMB in pediatric patients. Furthermore, studies showed no difference between sugammadex and neostigmine, except for the lower incidence of bradycardia with the former than with the latter [48,49]. In addition, a recent study confirmed that incidence of postop-
Table 2. Details of Studies Investigating the Relationship between the Reversal Agents for Neuromuscular Blockade and Postoperative Pulmonary Complications for Specific Patient Populations and Surgeries

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients and surgeries</th>
<th>Sample size</th>
<th>Mean or median age (yr)</th>
<th>Neuromuscular blocking agent</th>
<th>Reversal agent</th>
<th>Outcomes with sugammadex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Togioka et al., 2020 [66]</td>
<td>RCT</td>
<td>Patients aged ≥ 70 yr</td>
<td>46</td>
<td>74.8 (sugammadex)</td>
<td>Rocuronium</td>
<td>Sugammadex</td>
<td>Reduced/no difference in PPCs</td>
</tr>
<tr>
<td>Ledowski et al., 2021 [47]</td>
<td>RCT</td>
<td>Patients aged ≥ 75 yr</td>
<td>168</td>
<td>80</td>
<td>Rocuronium</td>
<td>Sugammadex</td>
<td>Reduced acute PPCs, better pulmonary outcome scores on POD 7</td>
</tr>
<tr>
<td>Li et al., 2021 [50]</td>
<td>RCT</td>
<td>Patients aged 1–6 yr</td>
<td>60</td>
<td>3.2 (sugammadex)</td>
<td>Rocuronium</td>
<td>Sugammadex</td>
<td>Reduced atelectasis, ICU stay, and hospitalization stays</td>
</tr>
<tr>
<td>Xiaobing et al., 2020 [51]</td>
<td>RCT</td>
<td>Patients aged 2–6 yr</td>
<td>60</td>
<td>26.9 months (sugammadex)</td>
<td>Rocuronium</td>
<td>Sugammadex</td>
<td>Reduced C-reactive protein and procalcitonin levels</td>
</tr>
<tr>
<td>Paredes et al., 2020 [60]</td>
<td>Retrospective observational study</td>
<td>Patients aged ≥ 18 yr</td>
<td>219</td>
<td>61.5</td>
<td>Rocuronium</td>
<td>Sugammadex</td>
<td>Incidence of PPCs, 8.2%</td>
</tr>
<tr>
<td>Adams et al., 2020 [61]</td>
<td>Retrospective observational study</td>
<td>Patients aged ≥ 18 yr</td>
<td>158</td>
<td>56</td>
<td>Rocuronium</td>
<td>Sugammadex</td>
<td>Need for mechanical ventilation within 48 h in 6.2% cases</td>
</tr>
<tr>
<td>Llaurado et al., 2014 [68]</td>
<td>Prospective observational study</td>
<td>Laparoscopic bariatric surgery</td>
<td>320</td>
<td>44.5 (HG*)</td>
<td>Rocuronium</td>
<td>Sugammadex</td>
<td>Reduced postoperative pathological changes on chest radiography</td>
</tr>
<tr>
<td>Unal et al., 2015 [69]</td>
<td>RCT</td>
<td>Patients aged 19–65 yr</td>
<td>74</td>
<td>44.8 (sugammadex)</td>
<td>Rocuronium</td>
<td>Neostigmine</td>
<td>Reduced PPCs, reducing duration hospitalization costs</td>
</tr>
<tr>
<td>Song et al., 2021 [70]</td>
<td>RCT</td>
<td>Patients ≥ 19 yr</td>
<td>254</td>
<td>67.0 (sugammadex)</td>
<td>Rocuronium</td>
<td>Neostigmine</td>
<td>Reduced PPCs, reduced ICU admission, and postoperative atelectasis</td>
</tr>
<tr>
<td>Lee et al., 2020 [71]</td>
<td>RCT</td>
<td>Patients aged 19–65 yr</td>
<td>159</td>
<td>59.5 (sugammadex)</td>
<td>Rocuronium</td>
<td>Pyridostigmine</td>
<td>Reduced early postoperative atelectasis</td>
</tr>
<tr>
<td>Unal et al., 2015 [69]</td>
<td>RCT</td>
<td>Patients ≥ 19 yr</td>
<td>93</td>
<td>63.8 (sugammadex)</td>
<td>Rocuronium</td>
<td>Pyridostigmine</td>
<td>Reduced plena effusion</td>
</tr>
<tr>
<td>Song et al., 2021 [70]</td>
<td>RCT</td>
<td>Patients aged 19–65 yr</td>
<td>3464</td>
<td>58.9</td>
<td>Rocuronium</td>
<td>Pyridostigmine</td>
<td>Reduced 30-day unplanned readmission rates, duration hospitalization, and hospital costs</td>
</tr>
<tr>
<td>Han et al., 2020 [72]</td>
<td>RCT</td>
<td>Patients aged ≥ 18 yr</td>
<td>1,232</td>
<td>6.56 (neostigmine)</td>
<td>Maintenance drug: vecuronium</td>
<td>Neostigmine</td>
<td>No difference in pulmonary function</td>
</tr>
<tr>
<td>Oh et al., 2020 [73]</td>
<td>Retrospective observational study</td>
<td>Patients aged &gt; 19 yr</td>
<td>3464</td>
<td>5.89</td>
<td>Maintenance drug: vecuronium</td>
<td>Neostigmine</td>
<td>No difference in pulmonary function</td>
</tr>
<tr>
<td>Oh et al., 2020 [74]</td>
<td>Retrospective observational study</td>
<td>Laparoscopic gastrectomy</td>
<td>126</td>
<td>6.59 (neostigmine)</td>
<td>Maintenance drug: vecuronium</td>
<td>Neostigmine</td>
<td>No difference in pulmonary function</td>
</tr>
<tr>
<td>Lee et al., 2020 [75]</td>
<td>RCT</td>
<td>Patients aged ≥ 18 yr</td>
<td>62.9</td>
<td>6.59 (neostigmine)</td>
<td>Maintenance drug: vecuronium</td>
<td>Neostigmine</td>
<td>No difference in pulmonary function</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial; PPCs: postoperative pulmonary complications; ASA: American Society of Anesthesiologists physical status; POD: postoperative day; ICU: intensive care unit; OSA: obstructive sleep apnea; VATS: video-assisted thoracoscopic surgery; RCT: retrospective controlled trial; PDC: postdischarge complication; MDT: multidisciplinary team; IG: intervention group; HG: historical group; ASA PS: American Society of Anesthesiologists physical status.
Obesity causes various anatomical and physiological changes in the human body. This not only includes the anatomical changes caused by fat accumulation, but also physiologic changes in respiration, such as excessive tissue metabolic requirements, increase in respiratory workload, increased oxygen consumption and carbon dioxide production, and ventilation/perfusion mismatching, making the patients vulnerable to hypoxia and apnea [63–66]. These changes could be one of the factors increasing the incidence of respiratory complications postoperatively. However, the evidence and research showing that sugammadex reduces PPCs in patients with obesity or OSA are lacking. Therefore, the studies on obese patients mentioned below included the results of OSA patients representing obese patients. According to a systematic review published in 2018, it was expected that the use of sugammadex could reduce PPCs when compared to the use of neostigmine in patients with OSA, but the relevant evidence was limited [67]. Among the two studies analyzed in this systematic review, a prospective observational study of patients undergoing laparoscopic bariatric surgery showed that the requirement of mechanical ventilation did not differ significantly between sugammadex and neostigmine (1.25% vs. 3.1%) [68]. However, postoperative pathological findings, including atelectasis or pleural effusion on chest radiography, were significantly lesser with sugammadex than with neostigmine. Another study on patients with OSA in 2015 showed that desaturation, reintubation, and unplanned intensive care unit admissions were significantly lower with sugammadex than with neostigmine [69]. However, in both these studies, the primary outcome was not PPCs, the definition of PPCs was not clear, and it is uncertain whether the results are clinically relevant. Therefore, this target group requires further study.

Thoracic and abdominal surgery

The surgical site is the most important risk factor for PPCs [8]. PPCs are different from cardiac complications; even in healthy adult patients, the risk of PPCs is high if the surgical site is intrathoracic or in the upper abdomen [8,18].

Intrathoracic surgery is associated with increased incidence of atelectasis and other PPCs because of the need for one-lung ventilation during surgery [5]. In a retrospective observational study of patients undergoing open lung lobectomy, the primary outcomes of hospitalization duration and postoperative atelectasis were significantly lower with sugammadex than with pyridostigmine [70]. Similarly, in a retrospective study of patients undergoing single-port vidi-
eo-assisted lung lobectomy, early postoperative abnormalities on chest radiography were significantly lesser with sugammadex than with pyridostigmine [71]. However, according to an RCT conducted on patients undergoing video-assisted lung lobectomy in 2021, there was no difference in the incidence of PPCs between sugammadex and neostigmine [72]. The extubation criterion was set at TOF ratio ≥ 0.9 in the RCT study, suggesting the possibility that the complications were not different. Therefore, it was confirmed that PPCs may not simply differ depending on the choice of the reversal agent, and it is important to reverse the NMB completely. Additionally, abdominal surgery is one of the major factors increasing the risk of PPCs [1,8,14]. According to a retrospective study investigating PPCs in patients undergoing laparoscopic gastrectomy, the incidence of pleural effusion was significantly reduced with sugammadex, and the incidence of other PPCs (respiratory failure, pneumonia, aspiration pneumonitis, atelectasis, and pneumothorax) did not differ between sugammadex and neostigmine [73]. In a retrospective observational study that compared sugammadex and neostigmine with the 30-day readmission rate as the primary outcome in patients undergoing major abdominal surgery, the use of sugammadex reduced the 30-day readmission rate by 34% [74]. However, in an RCT comparing sugammadex and neostigmine, sugammadex did not significantly improve the change in the forced vital capacity, which was the primary outcome, nor did it reduce the incidence of atelectasis after major abdominal surgery [75]. Therefore, the effect of sugammadex on PPCs during abdominal surgery remains debatable.

CONCLUSION

Although several efforts are being made to reduce PPCs, it remains questionable whether the choice of the NMB reversal agent affects PPCs. To date, complete reversal of the NMB before extubation under neuromuscular function monitoring seems more important than choosing a reversal agent. Moreover, understanding and considering the characteristics of each patient and the surgery type are important to reduce PPCs. As mentioned in the beginning, because the strength of evidence regarding surgical or patient-related factors as risk factors for PPCs is greater than that for anesthesia-related factors, a multidisciplinary approach should be considered to reduce PPCs.

FUNDING

None.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

Conceptualization: Tae-Yun Sung. Writing - original draft: Sung-Ae Cho, Tae-Yun Sung. Writing - review & editing: Sung-Ae Cho, Tae-Yun Sung.

ORCID

Sung-Ae Cho, https://orcid.org/0000-0002-1519-3787
Tae-Yun Sung, https://orcid.org/0000-0002-0714-1477

REFERENCES

7. Chandler D, Mosieri C, Kallurkar A, Pham AD, Okada LK, Kaye

128 www.anesth-pain-med.org
Reversal agent and pulmonary event

53. Ebo DG, Baldo BA, Van Gasse AL, Mertens C, Elst J, Sermeus L,


68. Llauradó S, Sabaté A, Ferreres E, Camprubí I, Cabrera A. Postoperative respiratory outcomes in laparoscopic bariatric surgery: comparison of a prospective group of patients whose neuromuscular blockade was reverted with sugammadex and a historical one reverted with neostigmine. Rev Esp Anestesiol Reanim 2014; 61: 565-70.


Introduction

Liver transplantation (LT) is considered the only definitive therapy for decompensated cirrhosis or severe acute liver failure that can improve the expected lifespan and quality of life [1]. Despite improvements in hemodynamic monitoring devices and anesthetic techniques, LT remains an extremely challenging procedure for anesthesiologists. Not only does the procedure itself pose a high risk of massive blood loss [2], but patients with end-stage liver disease (ESLD) are fre-
Echocardiography and cirrhosis

Frequently accompanied by many conditions that contribute to hemodynamic instability, such as cirrhotic cardiomyopathy (CCM), pericardial effusion, coronary artery disease (CAD), portopulmonary hypertension (PoPH), electrolyte derangements, and large amounts of ascites [3–5].

Echocardiography is a powerful tool that directly visualizes the structural and functional status of the heart in real-time at the bedside [5]. Transthoracic echocardiography (TTE) is a non-invasive cardiology investigation technique that obtains images from the surface of the body through four acoustic windows: parasternal, apical, subcostal, and suprasternal notch [6]. Transesophageal echocardiography (TEE) is a semi-invasive imaging tool in which the probe is inserted into the esophagus, and images are obtained through the esophagus and stomach [7]. Moreover, echocardiography provides more reliable measures than traditional pressure-based indicators such as pulmonary artery occlusion pressure and central venous pressure. It also has a high diagnostic value for detecting systolic or diastolic dysfunction, wall motion abnormalities, valvular dysfunction, hypovolemia, volume overload, left ventricular outflow tract obstruction (LVOTO), pericardial abnormalities, intracardiac air, and thrombus [5,8]. Echocardiography is gaining popularity and is becoming more broadly adopted due to these advantages. TTE is recommended for all LT candidates by the American Association for the Study of Liver Diseases (AASLD) [1]. According to the American Society of Echocardiography (ASE) guidelines, the usefulness of intraoperative TEE during LT is supported by a grade B2 level of evidence [9], and TEE has already been widely utilized during LT in the United States [10]. In contrast, the use of pulmonary artery catheterization has decreased even though it is still recommended and useful [11].

Although anesthesiologists cannot fully play the role of cardiologists, perioperative echocardiography is still a feasible and useful option, considering that it provides additional accurate and detailed assessments that could affect patient management strategies with minimal or no risk to the patient. Perioperative echocardiography by anesthesiologists is especially helpful when performing emergency operations because the ability to complete a comprehensive preoperative evaluation of patients is unlikely [12,13]. As the majority of liver transplants are from deceased donors worldwide, most are likely to be emergency cases. Therefore, perioperative echocardiography by anesthesiologists seems a useful tool. Although in Korea, 75.2% of the LT were performed with livers from living donors in 2019, deceased donor LT still accounted for 24.8% of the cases, which is not a negligible number [14].

PATHOPHYSIOLOGIC CHANGES OF CIRRHOSIS AND EFFECTS ON CARDIAC FUNCTION

Cirrhosis results from hepatic inflammation, fibrogenesis, angiogenesis, and loss of parenchymal cells. Structural and functional abnormalities of the liver lead to increased hepatic resistance and portal hypertension, which underlie most of the complications and mortality in patients with cirrhosis [15]. Subsequently, systemic vasodilation occurs mainly in the splanchnic vasculature bed because of increased circulating endothelial vasodilators from enhanced release and impaired degradation [16]. Decreased peripheral vascular resistance is initially compensated for by increased cardiac output, forming a characteristic circulatory status in patients with ESLD known as hyperdynamic circulation [17]. Relative arterial underfilling also stimulates baroreceptors and causes expansion of plasma volume with activation of the neurohumoral axis, including the renin-angiotensin-aldosterone system (RAAS), sympathetic nerve system (SNS), and arginine vasopressin [18]. Prolonged alterations in hemodynamic status and subsequent structural and functional changes in the heart could contribute to the development of CCM [19].

Structural change of heart

Structural remodeling of the heart has been reported in cirrhotic patients, including left ventricular hypertrophy, especially in the interventricular septum, and increased left ventricular end-systolic diameter, end-diastolic diameter, and volume of the left atrium. However, the degree of change seems modest [20–23].

Systolic dysfunction

In cirrhotic patients, systolic dysfunction is related to mortality and severe complications, such as hepatorenal syndrome (HRS) [24]. Some of the suspected causes of dysfunction are diminished β-adrenergic signaling, altered membrane current, and upregulation of endogenous cannabinoïds and cardio-depressant substances [25–27]. Many cirrhotic patients are asymptomatic at rest and show normal or enhanced systolic function due to hyperkinetic circulatory...
abnormalities [28]. However, when physically or pharmaco logically challenged, they are unable to increase or even show decreased contractility, revealing dysfunction masked by hyperdynamic status [29–31]. This could be a plausible explanation for the deterioration of subclinical systolic dysfunction to overt heart failure under surgical stress or nor malized pulmonary vascular resistance after LT [32,33].

The left ventricular ejection fraction (LVEF) is the most frequently used parameter to assess systolic function. However, it is limited in that it can be strongly affected by the loading condition, which may mask systolic dysfunction when afterload is severely decreased, as in cirrhotic patients [34]. Global longitudinal strain (GLS) is an emerging parameter for systolic function evaluation that indicates the percentage of systolic myocardial shortening in the longitudinal direction derived from automated speckle tracking echocardiography. GLS has been shown to be superior in detecting subclinical systolic dysfunction when LVEF is still within the normal range [35,36].

**Diastolic dysfunction**

Diastolic dysfunction is quite common in cirrhotic patients, with a reported prevalence ranging from 25.7% to 81.4% [37]. However, it is associated with adverse outcomes such as higher allograft rejection, graft failure, and mortality [38]. Diverse mechanisms have been suggested, including hypertrophy of the myocardium, cardiomyocyte edema, and patchy fibrosis, and consequently, increased stiffness of the myocardial wall [25,39]. Sodium retention may also contribute to diastolic dysfunction in patients [40]. Enhanced RAAS seems to play a role in fibrotic changes in the heart [41].

Diastolic function can be easily assessed using Doppler echocardiographic parameters. Deceleration time, isovolumetric relaxation time, and the ratio of early and late trans mitral flow velocities (E/A) were included as diagnostic criteria for diastolic dysfunction in the 2005 Montreal guideline for CCM. The 2016 American Society of Echocardiography and European Association of Cardiovascular Imaging (ASE/EACVI) guidelines for diastolic dysfunction exploit the following parameters, which are also adopted in the updated diagnostic criteria for CCM by the Cirrhotic Cardiomyopathy Consortium (CCC): septal or lateral early diastolic mitral an nular velocity (e’), E/e’ ratio, tricuspid regurgitation (TR) velocity, and left atrial volume index (LAVI) [42,43].

**Rhythm disturbance**

There are two main abnormalities in rhythm disturbance: autonomic dysfunction and conduction abnormalities. Autonomic dysfunction is associated with increased SNS activity, reduced heart rate variability, baroreflex sensitivity, and chronotropic incompetence. Impaired autonomous nervous systems are thought to contribute to hemodynamic dysregulation in patients with cirrhosis [44]. Impaired function of the autonomous nervous system can be explained by altered lipid metabolism and disturbed nerve integrity, the influence of vasodilating substances, and inhibition of vagal function by increased angiotensin II [45,46]. Chronotropic incompetence refers to the inability to respond appropriately to physiological or pharmacological stimulation with an increased heart rate or contractility. Enhanced SNS activity and the resultant increased levels of circulating catechol amines and downregulation of β-adrenergic receptors are thought to be responsible for autonomic dysfunction. This is supported by evidence that abnormal cardiac distribution of sympathetic activity was observed in a study using meta-do benzylguanidine (mIBG), an analog of noradrenaline [44].

The prevalence is reported as high as 50% in cirrhotic pa tients, and the presence of chronotropic incompetence is related to adverse outcomes. Umphrey et al. [47] showed that cirrhotic patients who failed to achieve 82% of the maximum predicted heart rate on dobutamine stress echocardiography (DSE) were associated with increased perioperative complications after LT.

Prolonged QT interval is the most commonly observed conduction abnormality in patients with cirrhosis. The prevalence in cirrhotic patients is reported to be 30–60% when a rate-corrected QT (QTc) interval > 440 ms is applied as the cut-off value [48]. The degree of prolongation seems to be affected by the severity of liver disease, as seen in the correlation between the QT interval and Child-Pugh score [49]. The suspected mechanism for the abnormality includes potassium ion channel dysfunction, which can deteriorate by cytokine release during infection or bleeding [23,50]. QT prolongation has been associated with lethal ventricular arrhythmia, especially the type known as “torsades de pointes.” Some studies have demonstrated an association between QT prolongation and an increased risk of sudden death or reduced survival. However, sudden cardiac death is rare in cirrhotic patients, and the clinical significance of prolonged QT intervals in cirrhotic patients remains unclear [48,51]. Atrial fibrillation is frequently encountered in pa-
tients with cirrhosis. The model for end-stage liver disease (MELD) has been shown to be a risk factor for new-onset atrial fibrillation. Autonomic dysfunction, inflammatory mediators, cytokines, vasoactive substances, and fibrotic pathways seem to play a role [52]. Electromechanical uncoupling, asynchrony of electrical and mechanical activation, is another example of a conduction abnormality reported in cirrhosis [53].

Right heart dysfunction

Reddy et al. [54] demonstrated that a high output state in cirrhotic patients and increased preload could elevate left ventricular filling pressure and, subsequently, pulmonary artery pressure. A chronically sustained hyperdynamic state may cause enlargement of the right heart and even heart failure [43]. Underlying PoPH may also contribute to the occurrence of right heart failure [8].

CIRRHOTIC CARDIOMYOPATHY: UPDATED CRITERIA IN 2019

These cardiovascular abnormalities, typically accompanied by cirrhosis, can be diagnosed as cirrhotic cardiomyopathy when they are severe enough to meet certain criteria. CCM refers to a pathological cardiac condition in patients with ESLD in the absence of prior heart disease [43]. Initially believed to be the result of direct cardiac toxicity of alcohol in the 1950s, it was named for the first time in 1989 as ‘cirrhotic cardiomyopathy’ and started to be perceived as a syndrome of cardiac dysfunction in ESLD patients [55,56]. It was more clearly defined at the Montreal 2005 World Congress of Gastroenterology as an impaired contractile response to stress and/or diastolic dysfunction with electrophysiological abnormalities. In addition, diagnostic criteria for CCM have been proposed [40]. Recently, updated criteria with modern concepts of heart failure were proposed by a multidisciplinary expert group called the CCC in 2019 (Table 1) [43].

Heart failure is an important cause of death, accounting for 7–21% of post-LT mortality. Heart failure is also one of the leading causes of hospital admissions, accounting for 24% of admissions within 90 days of LT in the United States [57]. CCM is quite common and is believed to be present in approximately half of cirrhotic patients without symptoms at rest [58]. However, under conditions that impose physiological or pharmacological stress on the heart with CCM, such as infections, transjugular intrahepatic portosystemic shunt, and surgical stimuli during LT, cardiac dysfunction may be unmasked and progress to overt heart failure. Normalization of peripheral vasodilation in the post-LT period could also be a stressor in the heart with increased afterload and cause post-LT heart failure [32,33]. Moreover, the association between CCM and other conditions such as HRS and increased mortality and/or morbidity after therapeutic procedures has 

<table>
<thead>
<tr>
<th>Type of dysfunction</th>
<th>2005 Montreal criteria</th>
<th>2019 CCC criteria</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic dysfunction</td>
<td>Any of the following is met: - LV ejection fraction &lt; 55% - Blunted contractile response on stress testing</td>
<td>Any of the following is met: - LV ejection fraction &lt; 50% - Absolute GLS &lt; 18% or &gt; 22%</td>
<td>More sensitive for detecting subclinical systolic dysfunction Validity of the adjusted cut-off value for LV ejection fraction has been questioned</td>
</tr>
<tr>
<td>Diastolic dysfunction</td>
<td>Any of the following is met: - Deceleration time &gt; 200 ms - Isovolumetric relaxation time &gt; 80 ms - E/A &lt; 1</td>
<td>≥ 3 of the following is met:* - Septal e’ velocity &lt; 7 cm/s - E/e’ ratio ≥ 15 - LAVI &gt; 34 ml/m² - TR velocity &gt; 2.8 m/s²</td>
<td>Updated to detect advanced diastolic dysfunction with increased specificity Concern exists about the prevalence of advanced diastolic dysfunction being too low</td>
</tr>
<tr>
<td>Supportive criteria</td>
<td>Abnormal chronotropic response Electrophysiological abnormalities Prolonged QTc interval</td>
<td>Abnormal chronotropic/inotropic response Electrocadiographic changes Electromechanical uncoupling</td>
<td>Considered as potential additional markers, not diagnostic Prolonged QTc is no longer diagnostic New potential serum biomarkers included (i.e., galectin-3) CMRI is included for detecting subclinical myocardial dysfunction</td>
</tr>
</tbody>
</table>

CCC: Cirrhotic Cardiomyopathy Consortium, LV: left ventricle, GLS: global longitudinal strain, E: early transmitral flow velocity, A: late transmitral flow velocity, e’: early diastolic mitral annular velocity, LAVI: left atrial volume index, TR: tricuspid regurgitation, BNP: brain natriuretic peptide, proBNP: prohormone of BNP, CMRI: cardiac magnetic resonance imaging. *Diagnosed with advanced (grade II or III) diastolic dysfunction. †Primary pulmonary hypertension or portopulmonary hypertension should be ruled out.
been observed in several studies [51]. Considering its high prevalence and harmful effects, it is a noteworthy complication that should be investigated prior to LT surgery.

The diagnostic criteria for CCM consist of three categories: systolic dysfunction, diastolic dysfunction, and other supportive criteria. In the 2005 Montreal criteria, systolic dysfunction was diagnosed when any of the following criteria were met: blunted contractile response on stress testing or LVEF < 55%. However, the usefulness of these criteria has been questioned for several reasons. First, there is no universally accepted definition of blunted contractile response. Second, stress testing is often limited or possibly confounded by factors such as the common use of β-adrenergic antagonists and the inability to perform exercise stress tests. Third, subclinical systolic dysfunction can be masked by decreased afterload due to the vasodilatory state of patients with cirrhosis. Fourth, together with the reasons mentioned above, additional parameters other than LVEF have been used to evaluate cardiac functional reserve. Considering these, the 2019 CCC guideline re-defined systolic dysfunction as when any of the following is present: LVEF ≤ 50%, absolute GLS < 18%, or > 22% [43]. GLS was included as it seems to be a more sensitive parameter of systolic function and a superior predictor of cardiac events and mortality than LVEF. In addition, it is relatively less dependent on loading conditions than LVEF [59,60]. Although there are limitations in that GLS is affected by age, sex, and loading condition, and only limited and conflicting evidence for the use of GLS in detecting CCM with normal LVEF is present, it is still believed to play a role in detecting subclinical systolic dysfunction in cirrhotic patients. Downward adjustment of the LVEF cut-off value from 55% to 50% was made without any detailed description in the article but was seemingly done to reflect normal values in the general population [43]. However, some researchers have questioned the validity of adjusted LVEF cut-off values based on post-LT mortality [61].

According to the 2005 Montreal criteria, diastolic dysfunction was diagnosed when any of the following criteria were met: deceleration time > 200 ms, isovolumetric relaxation time > 80 ms, or E/A < 1. However, these parameters can be affected by loading conditions and heart rate. In addition, a U-shaped relationship with the degree of diastolic dysfunction renders it difficult to distinguish between advanced and normal function [43]. Relatively new guidelines for the assessment of diastolic dysfunction were issued in 2016 by the ASE/EACVI. These guidelines have two different algorithms for screening and grading. To screen for diastolic dysfunction, the guidelines recommend four parameters: septal e’, the ratio of E to e’ of the medial wall or average, TR velocity, and LAVI. For grading, E/A was used instead of septal e’ velocity [42]. To simplify and integrate the two algorithms, Oh et al. [62] proposed a revised unified version that was adopted in the 2019 CCC criteria. In the 2019 CCC criteria, patients who met more than three of the following criteria were diagnosed as having advanced (grade II or III) diastolic dysfunction: septal e’ velocity < 7 cm/s, E/e’ ratio ≥ 15, LAVI > 34 ml/m² and TR velocity > 2.8 m/s. Notably, primary pulmonary hypertension or PoPH should be ruled out before applying the TR velocity criterion [43]. Compared to previous guidelines, the 2016 ASE/EACVI is considered simpler and more specific, with a significantly lower prevalence of diastolic dysfunction. However, there is a concern about the possibility that updated guidelines can only detect advanced cases [63]. The increased specificity of the 2016 ASE/EACVI guidelines was also observed in cirrhotic patients undergoing LT [64].

A number of features not included in both the systolic and diastolic function sections were classified as supportive criteria in the 2005 Montreal criteria. In the 2019 CCC criteria, the supportive criteria section was replaced by ‘Area for Future Research Which Requires Further Validation.’ Although the names and classifications of features have changed, they seem to include roughly similar content, except for several updates. The blunted contractile response has moved from the systolic dysfunction section to an area for future research, which requires further validation because of the limitations mentioned above. Electrophysiological abnormalities, including prolonged QTc interval, are no longer considered to have significant diagnostic value for CCM, with prevalence as high as 50% in cirrhosis and suspicious predictive power for poor outcomes. Serum biomarkers are recommended to be helpful when used in conjunction with imaging studies. A variety of biomarkers, such as nitric oxide, endothelin, copeptin, endocannabinoids, interleukins, and galectin-3, have been proposed as potentially useful parameters in the future. However, further studies are required to confirm their clinical application. In addition, previously recommended biomarkers, brain natriuretic peptide, pro-peptide N-terminal prohormone of BNP, and T- and I-troponin, are still recognized for their clinical importance with their ability to reflect the severity of cirrhosis and cardiac dysfunction and predict morbidity and mortality. Cardiac magnetic resonance imaging is newly included in the criteria because it appears to have diagnostic value for
subclinical myocardial dysfunction and provides a comprehensive evaluation [43].

Studies on CCM reported its prevalence to be 46–63% in cirrhosis patients when the 2005 Montreal criteria were applied. Razpotnik et al. [58] conducted a study to compare the prevalence of CCM in 122 patients with cirrhosis using different criteria. They found that the overall prevalence was slightly higher with the 2005 Montreal criteria than the 2019 CCC criteria. However, the results differed remarkably between the two criteria when systolic and diastolic dysfunctions were analyzed separately. When the 2019 CCC criteria were applied, the prevalence of systolic dysfunction was higher (16.4% vs. 53.3%), while diagnostic dysfunction was lower (64.8% vs. 6.4%), reflecting the increased specificity of 2016 ASE/EACVI guidelines for diastolic dysfunction and more sensitive detection of subclinical systolic dysfunction by the implementation of GLS [58].

OTHER CLINICAL CONSIDERATIONS IN CIRRHOTIC PATIENTS

There are many pathological conditions accompanied by cirrhosis that can harmfully affect hemodynamic stability, as well as typical cardiovascular abnormalities, including CCM.

Coronary artery disease

The risk of ischemic heart disease is higher in patients with cirrhosis. Tiukinhoy-Laing et al. [65] evaluated the prevalence of CAD in LT candidates without known CAD and found that 26% of the patients had moderate to severe degree coronary stenosis. This result is consistent with another study that used multidetector computed tomographic angiography and found that only 9.2% of LT candidates showed normal coronary arteries, and 33.8% had moderate to severe stenosis [66]. Moreover, cirrhotic patients with non-alcoholic steatohepatitis, independent of traditional cardiac risk factors, have an increased perioperative risk of cardiovascular complications after LT [67,68]. Thus, it is not surprising that the incidence of ischemic events and cardiovascular mortality is as high as 2.5–3 times compared to the general population matched for cardiac risk factors [69]. However, the appropriate evaluation of CAD in patients with cirrhosis is limited for various reasons. Stress echocardiography, both exercise and pharmacological, is often limited because of physical constraints, chronotropic incompetence, common use of β-adrenergic antagonists, and a chronic state of vasodilation [8,70]. These limitations may contribute to the limited capability of DSE in LT patients. DSE in cirrhotic patients undergoing LT showed low sensitivity and moderate specificity for detecting CAD [71,72]. Invasive coronary angiography (CAG) is the gold standard for diagnosis and is recommended for patients at a high risk of CAD [73]. However, the invasiveness and risk of contrast-induced nephropathy have been concerns for CAG. Compared to CAG, coronary computed tomography angiography can be considered an acceptable non-invasive alternative with high sensitivity and negative predictive value [74]. Additional information about prognosis can be acquired with simple exercise testing, such as the 6-minute walk test, when available [75].

Dynamic left ventricular outflow tract obstruction

LVOTO is defined as a peak Doppler pressure gradient equal to or greater than 30 mmHg and is considered hemodynamically significant when the pressure gradient exceeds 50 mmHg [76]. Although typically related to hypertrophic cardiomyopathy or acute myocardial infarction, LVOTO can also occur under conditions such as decreased preload, afterload, increased heart rate, and contractility, which is similar to the pathophysiologic changes in cirrhotic patients. Substantial intraoperative blood loss, decrease in systemic vascular resistance during the reperfusion period, activation of the sympathetic nervous system by surgical stress, and intraoperative use of inotropic agents can induce LVOTO [77–79]. In some patients, LVOTO demonstrated during DSE was related to the occurrence of intraoperative hypotension [80]. Intraoperative TEE is useful for helping clinicians comprehend structural and functional abnormalities from real-time images and to guide the appropriate use of fluid and vasopressors [81].

Pulmonary vascular complications: portopulmonary hypertension and hepatopulmonary syndrome

Pulmonary vascular complications of cirrhosis occur mostly in two forms: PoPH and hepatopulmonary syndrome (HPS). PoPH is defined as pulmonary artery hypertension that occurs in association with portal hypertension irrespective of underlying liver cirrhosis [82]. It is related to increased mortality and morbidity, with a reported five-year survival of 14% when not treated and may lead to right heart failure if severe [83]. It is also associated with significant perioperative
morbidity and mortality [84]. The current diagnostic criteria for PoPH include identified portal hypertension with or without cirrhosis, mean pulmonary artery pressure > 25 mmHg, pulmonary artery occlusion pressure ≤ 15 mmHg, and pulmonary vascular resistance > 240 dyn·s·cm⁻⁵ or 3 Wood units [85]. The prevalence of PoPH was recently reported to be 6.3–8.5% in LT candidates and showed no association with MELD scores [86,87]. The proposed underlying mechanism for PoPH is that increased CO imposes shear stress on the pulmonary vascular wall and stimulates the release of vasoactive proliferative mediators. Moreover, the entrance of unfiltered vasoactive substances, bacteria, and endotoxins from the splanchnic circulation into the pulmonary circulation via the portosystemic shunt contributes to the pathologic change [85]. Echocardiography is considered the best screening tool for PoPH [88]. The right ventricular systolic pressure can be calculated from the measured peak TR velocity using the Bernoulli equation and used to estimate the pulmonary artery pressure. Different cut-off values are used depending on the purpose. A cut-off value of 30 mmHg is highly sensitive (97%) and adequate for screening PoPH, whereas a cut-off value of 50 mmHg can be used to detect moderate to severe PoPH that should proceed to right heart catheterization for diagnosis and further evaluation [89,90]. Medical treatments for PoPH include phosphodiesterase type-5 inhibitors, prostacyclins, and endothelial receptor antagonists [88]. Although severe PoPH is considered a contraindication for LT, PoPH that responds appropriately to medical therapy is indicated for LT, and postoperative reversal of PoPH has been reported [91]. Maintaining hemodynamic stability is a challenge in patients with PoPH. Physiological disturbances such as hypoxia, hypercarbia, hypothermia, and acidosis should be avoided because they can lead to the deterioration of pulmonary hypertension. Judicious fluid infusion is also required because hypovolemia and fluid overload can lead to right ventricular dysfunction. When right heart function is compromised, several inotropic agents or pulmonary vasodilators should be considered [84].

Hepatopulmonary syndrome is characterized by intrapulmonary vascular dilatation (IPVD) and resultant arterial hypoxia in patients with cirrhosis [92]. Excessive IPVD leads to ventilation/perfusion mismatch, insufficient transit time for the oxygenation of red blood cells, intrapulmonary shunting, and consequent arterial hypoxia [93]. Contrast-enhanced echocardiography can also be used to diagnose HPS. Microbubbles that appear in the left heart between 4–6 beats after their appearance in the right heart are considered evidence of IPVD [92]. The prevalence of HPS has been reported to be 15–30% in LT candidates, depending on the study population [94]. Cirrhotic patients with HPS show increased mortality and morbidity compared to non-HPS patients. However, HPS does not appear to be a direct cause of death. Rather, the progression of cirrhosis and associated complications are related to adverse outcomes [93]. LT is the only curative therapy available for HPS. Although perioperative mortality was increased compared to non-HPS patients, Arguedas et al. showed that most patients who survived surgery showed improvements or resolution of the abnormalities within six to 12 months after LT [95]. HPS can manifest as intraoperative and postoperative hypoxia in the perioperative period and frequently requires prolonged postoperative mechanical ventilation. However, an analysis of recent studies showed that perioperative mortality, which occurred as a direct consequence of HPS, did not increase [92].

**Pericardial effusion and cardiac tamponade**

Pericardial effusion is reported to be common in cirrhotic patients, with a prevalence of 4–10% and up to 63% in decompensated cirrhosis. The pathophysiology of cirrhosis, including fluid retention, seems to play a role, and effusion is reported to resolve after LT [96,97]. The estimated size of effusion and presence of hemodynamic compromise should be evaluated using echocardiography [98]. Hemodynamic compromise can be assessed by chamber collapse and characteristic alterations of mitral and tricuspid flow according to respiration [99]. Preemptive drainage can be considered when a large amount of effusion with a possible risk of hemodynamic compromise is identified [100]. Rarely, tense ascites can also compress the heart, causing hemodynamic compromise with a constrictive pathology [101].

**Patent foramen ovale**

Patent foramen ovale (PFO) is quite common in the general population, with a prevalence of PFO from autopsy studies of around 26% [102]. PFO has been associated with cryptogenic stroke, although its clinical significance and need for extensive closure are controversial [103]. The risk of paradoxical embolism in LT recipients is expected to increase further because remarkable hemodynamic changes and large fluid shifts might change intracardiac flow dynamics, and air emboli can be formed during surgery. Despite the theoretical possibility of paradoxical embolism and the
presence of several reported cases, data on perioperative stroke in cirrhotic patients with PFO is too rare to evaluate the incidence [104]. Furthermore, several studies have reported no increased adverse outcomes in patients with PFO following LT [105,106]. Hence, it is advised not to close the PFO in patients without a previous history of stroke before LT [104].

**Ascites**

Removal of large-volume ascites results in the faster reaccumulation of ascites and hypotension in patients with cirrhosis. Although not yet fully understood, suspected pathophysiology includes simple fluid shifting and, more importantly, mechanical decompression followed by a decrease in systemic vascular resistance in response to increased perfusion and shear stress [4,107]. Drainage of large-volume ascites is believed to contribute to fluid shift and intraoperative hypovolemia during the preanhepatic phase of LT [108].

**CLINICAL CONSIDERATIONS FOR INTRAOPERATIVE RISK OF LIVER TRANSPLANTATION**

Intraoperative hemodynamic instability during LT is associated with various contributing factors. Intraoperative blood loss is one of the most common and important risk factors. LT frequently results in massive blood loss. A recent study investigated 108 LT patients with an average intraoperative blood loss of 1,505.8 ml. Blood loss of more than 1,000 ml was observed in 72.2% of cases and more than 2,000 ml in 14.8% [109]. Although several possible predictors have been suggested, massive blood loss is still considered unpredictable with conflicting and inconsistent results. Therefore, sufficient intravenous access and blood products should be prepared before surgery [110]. The aforementioned abdominal decompression by drainage of ascites and opening of the abdomen may also contribute to decreased preload with vasodilation and reaccumulation of ascites [4,107]. Intraoperative manipulation of the inferior vena cava (IVC), including clamping of the IVC during the anhepatic phase and release for reperfusion, is another major contributor to abrupt changes in the preload during surgery. During clamping of the IVC, the significantly decreased preload should be replaced with fluid resuscitation to maintain hemodynamic stability. However, a decrease in preload is transient, and excessive fluid infusion may result in worsened hemodynamic instability, especially in the setting of right ventricular dysfunction [111]. Fluid overload is strongly associated with postoperative pulmonary complications [112]. In addition to fluid infusion, the transfusion of blood products is associated with pulmonary complications through transfusion-associated circulatory overload and transfusion-related acute lung injury [113]. Therefore, judicious fluid infusion and transfusion are required, and intraoperative TEE can be useful for guiding fluid infusion and transfusion when used in conjunction with hemodynamic parameters [114,115]. The reperfusion phase, which starts with unclamping of the IVC, is considered the most critical stage of LT in which major hemodynamic events are frequently encountered. Post-reperfusion syndrome (PRS) refers to an event that presents as severe hypotension, bradycardia, and low systemic vascular resistance within 5 min after unclamping. Cold, acidic, hyperkalemic blood that contains vasoactive inflammatory substances from ischemic grafts is thought to be responsible for PRS [116]. The relationship between PRS and CCM is not yet clear, with insufficient and inconsistent data. However, one study demonstrated a correlation between diastolic dysfunction and PRS, indicating a possible association [117]. These intraoperative hemodynamic instabilities and metabolic changes impose remarkable stress on the recipient’s heart. As shown by the association mentioned above between cardiac dysfunction and adverse outcomes, cirrhotic patients with cardiac dysfunction may be more vulnerable to such stress. Unfortunately, there is no reliable method for identifying LT candidates with a high risk of perioperative cardiac complications.

**CONCLUSIONS**

Cardiovascular abnormalities are frequently observed in patients with ESLD. Although LT is the only definitive therapy for ESLD, LT imposes remarkable stress on the heart, such as rapid hemodynamic changes and metabolic disturbances. As a result of underlying pathological conditions and acute stressful stimuli, cardiovascular complications account for a considerable portion of perioperative morbidity and mortality in LT recipients. Echocardiography is a powerful non- or semi-invasive tool that directly visualizes the structural and functional state of the heart, such as chamber sizes, systolic and diastolic function, valvular function, and pulmonary artery pressure. It can be used to evaluate the heart condition prior to surgery and intraoperatively to assess hemodynamic status. The usefulness of echocardiogra-
phy can be inferred from the fact that the AASLD recommends the preoperative use of TTE for all candidates, and the ASE recommends intraoperative TEE with a grade B level of evidence. We recommend the use of preoperative TTE and intraoperative TEE for LT, if not contraindicated. CAG or coronary computed tomography angiography should be considered in patients with a high risk of CAD, as stress echocardiography is often limited. Broader application of echocardiography and further research would be able to improve LT outcomes in the future.

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. This is a case report.

AUTHOR CONTRIBUTIONS

Conceptualization: Sangbin Han, Min Suk Chae. Formal analysis: Sangbin Han, Jaesik Park, Sang Hyun Hong, Chul Soo Park, Jongho Choi, Min Suk Chae. Methodology: Sangbin Han, Min Suk Chae. Writing - original draft: Sangbin Han, Min Suk Chae. Writing - review & editing: Sangbin Han, Jaesik Park, Sang Hyun Hong, Chul Soo Park, Jongho Choi, Min Suk Chae. Investigation: Sangbin Han, Jaesik Park, Sang Hyun Hong, Chul Soo Park, Jongho Choi, Min Suk Chae. Supervision: Min Suk Chae.

ORCID

Sangbin Han, https://orcid.org/0000-0002-0203-0751
Jaesik Park, https://orcid.org/0000-0001-5472-9567
Sang Hyun Hong, https://orcid.org/0000-0002-7091-8963
Chul Soo Park, https://orcid.org/0000-0003-3992-0309
Jongho Choi, https://orcid.org/0000-0001-9280-2737
Min Suk Chae, https://orcid.org/0000-0002-1426-4651

REFERENCES

12. Canty DJ, Roaye CE. Audit of anaesthetist-performed echocardiography on perioperative management decisions for non-car-


Echocardiography and cirrhosis

Counselling and medication are often thought of as the only interventions for psychiatric disorders, but electroconvulsive therapy (ECT) has also been applied in clinical practice for over 80 years. ECT refers to the application of an electric stimulus through the patient’s scalp to treat psychiatric disorders such as treatment-resistant depression, catatonia, and schizophrenia. It is a safe, effective, and evidence-based therapy performed under general anesthesia with muscle relaxation. An appropriate level of anesthesia is essential for safe and successful ECT; however, little is known about this because of the limited interest from anesthesiologists. As the incidence of ECT increases, more anesthesiologists will be required to better understand the physiological changes, complications, and pharmacological actions of anesthetics and adjuvant drugs. Therefore, this review focuses on the fundamental physiological changes, management, and pharmacological actions associated with various drugs, such as anesthetics and neuromuscular blocking agents, as well as the comorbidities, indications, contraindications, and complications of using these agents as part of an ECT procedure through a literature review and our own experiences.

Keywords: Anesthesia; Electroconvulsive therapy; Experience; Major psychiatric disorders.

INTRODUCTION

Electroconvulsive therapy (ECT), also known as electroshock therapy, is a unique treatment in patients with major depression, affective disorders, catatonia, schizophrenia, and other psychotic disorders for which pharmacological treatments do not produce adequate responses [1,2]. Historically, ECT was first described in 1938 by Italian doctors Ugo Cerletti and Luigi Bini and was performed without anesthesia for almost 30 years, being referred to as “Unmodified ECT” [3,4]. With the subsequent development of more advanced medications and their increased use in clinical applications, general anesthesia with an intravenous agent and neuromuscular blocking agent is now performed as an important part of the ECT protocol to improve patient safety, enhance treatment effects, and minimize complications.

Recently, ECT has been reported to produce symptom relief effects in 70–90% of cases, which is a superior outcome to the use of antidepressants and has a recurrence rate of approximately 20% [5]. Moreover, the United States Food and Drug Administration’s recent redesignation of ECT devices as Class II (from Class III) for certain indications may impact the application of this therapy, as this facilitates the continued availability of ECT devices worldwide and helps decrease the stigma associated with this procedure by acknowledging its safety and effectiveness [6]. Thus, the use of ECT is expected to increase.

The worldwide frequency of ECT interventions is approxi-
mately 4.9 (0.4–81.2) out of 10,000 people. In Asian countries, particularly China, Taiwan, and India, there has been a significant increase in the number of reported cases [7–9]. In Korea, some hospitals use ECT in both outpatient and inpatient settings; however, data on the overall clinical applications of this technique are currently lacking [10]. The incidence of ECT is increasing, and anesthesia is an essential component of its safe and successful use. Thus, more anesthesiologists will need to become familiar with the characteristics of this procedure. Our present review focuses on the clinical applications of ECT, anesthetic management during this procedure, pharmacological action of various drugs used in ECT, including anesthetics and neuromuscular blocking agents, possible complications, and postprocedural considerations. Evidence from a literature review and our own experiences are discussed.

**CLINICAL APPLICATIONS**

**Procedural aspects of ECT**

ECT involves the transmission of an electric current through the brain, causing generalized tonic-clonic seizures. During this procedure, the position of the electrode and the physical properties of the electrical stimulation affect the seizure threshold, which is related to the therapeutic effect and cognitive impairment. Three electrode positions (bitemporal, bifrontal, and right unilateral) are commonly adopted. Among these, the bitemporal position is the most widely used. In addition to the electrode positioning and physical properties of electrical stimulation, various factors can also affect the seizure threshold (Table 1).

The antidepressant effects of ECT are related to seizure duration, as measured using electroencephalography (EEG), electromyography, or muscle movement. Seizure duration assessment by muscle movement during general anesthesia is performed by placing a tourniquet on the arm or leg and blocking the blood flow to exclude the effect of muscle relaxants. The seizure duration on an EEG is approximately 5 s longer than the muscle movement [10]. The appropriate motor seizure duration was 25–50 s.

In the acute phase, the number of ECT treatments is not defined but must be performed until the symptoms are relieved or stabilized. Most patients who undergo ECT receive 6–12 treatments per course. However, patients with depression may require fewer patients, while patients with schizophrenia may require more treatment per course [11]. ECT is usually performed two or three times a week, but in certain urgent cases, such as patients with catatonia, daily courses may be used until symptoms improve [12,13]. In rare instances, ECT may need to be interrupted or discontinued due to tolerability issues, such as adverse cognitive effects, fear of anesthesia, headaches, or nausea.

Maintenance ECT (M-ECT) has been used for ongoing procedures to prevent the recurrence of a new episode of depression and can last for years, possibly indefinitely. In most cases, M-ECT has a schedule of 3–8 weeks, but some patients may require longer periods of weekly treatment [14].

**Indications for ECT**

Most guidelines recommend ECT as the first-line treatment for severe depressive episodes, such as the presence of psychotic features, catatonia, high suicide risk, and/or food or fluid refusal. A history of previous positive response and patient preference are also important considerations [15–17]. ECT is recommended as a second-line treatment for patients with severe major depressive episodes that are unresponsive to psychotherapeutic and/or pharmacological interventions. ECT is not recommended for personality disorders, drug abuse, or psychoneuroses. In children, the most common psychiatric indications are refractory depression, bipolar disorder, schizophrenia, catatonia, autism, and refractory status epilepticus [18].

According to the 2001 consensus statement of the American Psychiatric Association (APA), there are no absolute contraindications for ECT [19]. However, some conditions

<table>
<thead>
<tr>
<th>Table 1. Factors Affecting Seizure Thresholds</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Factors that increase the seizure threshold</strong></td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Skull thickness</td>
</tr>
<tr>
<td>Bilateral stimulation</td>
</tr>
<tr>
<td>Repeated stimulation</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Use of barbiturates, benzodiazepines, or anticonvulsants</td>
</tr>
<tr>
<td><strong>Factors that decrease the seizure threshold</strong></td>
</tr>
<tr>
<td>Genuine seizure</td>
</tr>
<tr>
<td>Hyperventilation/hypocapnia</td>
</tr>
<tr>
<td>Female sex</td>
</tr>
<tr>
<td>Hyperoxia</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
<tr>
<td>Use of caffeine, antidepressants, or clozapines</td>
</tr>
</tbody>
</table>
such as uncontrolled hypertension, coronary artery disease, congestive heart failure, aortic stenosis, implanted cardiac devices, atrial fibrillation, obstructive lung disease, asthma, and increased intracranial pressure with or without mass lesions pose a relatively high risk and may result in death during ECT [20,21]. The details of the indications for ECT are summarized in Table 2 [22,23].

Preoperative evaluations

The preoperative evaluation of ECT was comparable to that used in other general surgeries. Medical histories relevant to these assessments and important for a successful ECT include psychiatric history; drug history, including the type, dose, response, compliance, and side effects of any psychiatric drugs; and physical and laboratory examination results such as electrocardiography, chest radiography, serum creatine, and electrolytes [24]. Airway evaluations are also necessary because some conditions, such as difficulties with mask ventilation, a higher risk of pulmonary aspiration, and prolonged ventilation, may require unplanned intubation. In most cases, patients take their usual medications until the morning of the procedure, except for theophylline, herbal medications, or oral diabetes drugs [21].

Although ECT is a low-risk procedure, certain hemodynamic abnormalities may increase the risk of complications in patients with cardiovascular disease. Abrupt hemodynamic changes during ECT typically spontaneously recover a few minutes after a seizure. However, these changes can cause serious complications in patients with cardiovascular disease, and careful monitoring and preparation, including cardiopulmonary resuscitation, are needed in these patients [21,25].

As in adult patients, appropriate preoperative evaluations should be performed prior to ECT in pediatric patients. If a child has comorbidities, additional examinations and an increased planning time for anesthesia are required. In children with central nervous system malignancies, hydrocephalus, or cardiopulmonary diseases, the anesthesiologist should prepare for the interaction of anesthetics and any immediate negative effects of the procedure [18].

Pregnancy testing should be performed in all women of reproductive age. Although pregnancy is not a contraindication for ECT, fetal exposure to anesthetics must be minimized [26].

Physiologic changes during ECT

The physiology of the patient changes dramatically during the ECT. Between the electrical stimulation and the onset of seizure, conditions such as hypotension, bradycardia, and asystole can occur because the parasympathetic nervous system becomes dominant during this period. Tachycardia and hypertension occur during seizures because of rebound sympathetic activity [21,23,27]. In this period, the rate-pressure product (heart rate × blood pressure) increases 2–4 times with a 30–40% increase in systolic blood pressure, a > 20% increase in heart rate, and an increase in the index of myocardial oxygen consumption [28,29]. After seizures, the heart rate and blood pressure normalize within a few minutes, and any serious cardiovascular and complications that arise usually occur during this period [30]. Acute hemodynamic changes during ECT can cause pulmonary edema, ventricular tachycardia, myocardial infarction, and, in rare instances, cardiac shock [31–33].

Cerebral blood flow, intracranial pressure, cerebral metabolic rate, and cerebral oxygen consumption increase during seizures because of transient cerebral ischemia and cerebral hemorrhage [34,35]. Acute neurological and cardiovascular changes, fractures, dislocations, and muscle pain also occur due to generalized convulsions [36,37]. Intraocular pressure also increases during convulsions but normalizes after seizures in most cases [38].
GENERAL ANESTHESIA FOR ECT

Prior to ECT, patients should fast from solid food for more than 8 h. Clear liquids are permissible during this time to enable oral medications such as antihypertensive drugs to be taken up to 2 h before the procedure. To prevent post-ECT myalgia, patients can be pre-medicated with enteric-coated aspirin, acetaminophen, or intravenous ketorolac. Ventilation during ECT is assisted by a face mask with a standard simple bag-valve-mask system. Tracheal intubation is not recommended, except in very specific situations (e.g., late pregnancy or emergency treatments in which the patient has a full stomach), because ECT is typically performed frequently (two or three times a week for 3–4 weeks), and each procedure lasts only a few minutes. In obese patients with sleep apnea syndrome, an oral airway can be helpful in maintaining ventilation during the procedure.

Non-invasive blood pressure, pulse oximetry, electrocardiography, and capnography are recommended during an ECT procedure. A tourniquet technique or electromyographic monitoring should be employed to quantify the duration of the motor seizure activity. The tourniquet technique is used to isolate the distal circulation using a pressure of 160–200 mmHg before administering the muscle relaxant. Although sufficient muscle relaxation is necessary during ECT, forceful jaw clenching is still inevitable with this intervention because of the direct stimulation of the masticatory muscles, particularly the temporalis and masseter muscles, by electrical current. Hence, a bite block should be carefully placed before the application of the electrical stimulus to protect the patient’s teeth and minimize the risk of lacerating the tongue. Standard noninvasive hemodynamic variables and oxygen saturation should be monitored for 15–30 min after ECT [39]. Emergence agitation after ECT is usually treated by administering a small dose of midazolam or dexmedetomidine [40,41].

GENERAL ANESTHESIA DURING ECT FOR SPECIFIC PATIENT GROUPS

Children and adolescents

Although ECT is known to be safe in adults, it is not commonly used in children and adolescents because of the risk of damage to the nervous system at the early stages. However, the indications for ECT in the pediatric population have increased steadily over the past 20 years [18], the most common of which are refractory depression, bipolar disorder, schizophrenia, catatonia, autism, and pediatric refractory status epilepticus. Unique factors related to pediatric ECT include the potential need for a preoperative anxiolytic with dexmedetomidine, likely to be the most appropriate agent in this regard, as oral benzodiazepines are relatively contraindicated. Methohexital remains the gold standard anesthetic for pediatric ECT; although ketamine, propofol, and sevoflurane are becoming increasingly viable options [18,42,43].

Pregnant cases

ECT has been reported to be an effective and safe treatment for pregnancy-induced depression, unipolar depression, bipolar disorder, schizophrenia, and other psychiatric illnesses [44,45]. However, ECT can cause maternal complications such as aspiration and premature labor, as well as fetal complications such as spontaneous abortion and fetal death. Therefore, a multidisciplinary team approach is required to manage this treatment in pregnant cases [44,46].

When it is difficult to maintain the patient’s airway, or if fasting is insufficient, laryngeal mask airway or cricoid compression and endotracheal intubation can be helpful [47]. In addition, if there is a history of premature labor or uterine contractions following ECT, tocolytics can be used as prophylaxis. In addition, the use of inhaled anesthetics (e.g., sevoflurane) may reduce the risk of uterine contractions after ECT in late pregnancy [48]. Emergency cesarean section may be required in rare instances; therefore, treating clinicians should always be prepared for the possibility of premature delivery in relevant cases to ensure the child’s safety.

COVID-19 era

ECT units have faced certain challenges during the COVID-19 pandemic. These issues include screening, personal protective equipment, airway management, and maintenance of recovery rooms and facilities to prevent the spread and transmission of COVID-19 [49,50]. However, the most challenging of these issues is airway management. ECT requires close supervision by an anesthesiologist and the patient’s oral and airway secretions. Commonly administered mask ventilation and hyperventilation without reliable airway protection increase the risk of aerosolization, which poses a serious risk to health care staff [51]. To overcome this drawback, Luccarelli et al. [52] performed ECT without bag-mask ventilation by applying adequate preoxygenation. The
use of a second-generation supraglottic airway with a viral filter is also helpful in preventing viral transmission. In addition, Limoncelli et al. [53] reported the use of a Jackson–Rees circuit instead of an ambu-bag to provide leakage-free spontaneous ventilation, thus minimizing air emissions.

**DRUGS FOR ECT**

**Anesthetics**

The ideal characteristics of an anesthetic to be used for ECT include rapid onset, attenuation of ECT-induced physiological changes, minimal anticonvulsant effects, and rapid recovery. Although most of the currently available anesthetic agents can be used for ECT, seizure duration, hemodynamic stability, recovery time, antidepressant effect, and cognitive side effects must be considered when selecting this drug. Most anesthetics have a dose-dependent anticonvulsant effect; therefore, the minimum effective dose should be used during ECT [54]. The effects of commonly used anesthetics for ECT are summarized in Table 3.

1. **Methohexital**

Methohexital is the gold standard drug among the established anesthetics [55,56]. The routine dosage of this agent for ECT is 1.5 ± 0.3 mg/kg, but the Royal College of Psychiatrists (0.75–0.9 mg/kg) and APA (0.75–1.0 mg/kg) have recommended a dose reduction [56]. It remains the drug of choice for ECT except where there are barbiturate contraindications (e.g., acute intermittent porphyria) because they have few hemodynamic effects and low anticonvulsant properties [1,23]. However, methohexital is currently unavailable commercially in Korea.

2. **Thiopental sodium and thiamylal**

Thiopental sodium (1.5–2.5 mg/kg) and thiamylal (1.5–2.5 mg/kg) reduce the seizure duration and have a slower recovery compared to methohexital (0.5–1.0 mg/kg). Both of these agents also increase the incidence of arrhythmias such as sinus bradycardia and premature ventricular contraction, as well as increase the blood flow in the middle cerebral artery after ECT compared with propofol [57,58]. Moreover, they produce more hemodynamic changes than sevoflurane [59]. Hence, the use of thiopental and thiamylal as intravenous anesthetics for ECT is not advantageous.

3. **Etomidate**

Etomidate (0.15–0.3 mg/kg) is effective in patients with a short seizure duration (i.e., < 20 s) even under maximum stimulation because it prolongs this duration compared to methohexital, thiopental, or propofol [55,60]. However, etomidate also increases the incidence of confusion, delirium, nausea, and vomiting after ECT compared to other anesthetics such as propofol, methohexital, and thiopental [1,23,60]. Etomidate-induced myoclonic jerks should be differentiated from seizures after ECT, as long-term use of etomidate can cause adrenal insufficiency [61].

4. **Propofol**

Propofol is the most commonly used intravenous anesthetic owing to its rapid recovery and antiemetic mode of action. However, the seizure duration after ECT is shorter with this drug because it has stronger anticonvulsant effects than other intravenous anesthetics [61–63]. Propofol is thus preferred for use in adolescents and young adults receiving ECT because they typically have a lower seizure threshold and longer duration of seizures than adults [64]. The routine dosage of propofol is 1.0–1.5 mg/kg. If the minimum hyp-

---

**Table 3. Effects of Commonly Used Anesthetics in Electroconvulsive Therapy Protocols and Comparisons of the Physiologic Changes Before and After Electrical Stimulation (Before/After)**

<table>
<thead>
<tr>
<th>Anesthetic</th>
<th>Heart rate</th>
<th>Blood pressure</th>
<th>Cerebral blood flow</th>
<th>Seizure duration</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methohexital</td>
<td>↓ / ↑</td>
<td>↓ / ↑↑</td>
<td>NE</td>
<td>→</td>
<td>Standard anesthetics for ECT</td>
</tr>
<tr>
<td>Thiopental</td>
<td>↑ / ↑</td>
<td>↓ / ↑↑</td>
<td>↓ / ↑↑</td>
<td>↓</td>
<td>Histamine release</td>
</tr>
<tr>
<td>Etomidate</td>
<td>→ / ↓</td>
<td>− / ↑↑</td>
<td>NE</td>
<td>↑</td>
<td>Injection pain, slow recovery</td>
</tr>
<tr>
<td>Propofol</td>
<td>↓ / ↑−</td>
<td>↓ / ↑</td>
<td>↓ / ↑</td>
<td>↓</td>
<td>Injection pain</td>
</tr>
<tr>
<td>Ketamine</td>
<td>↑ / ↑</td>
<td>↓ / ↑↑</td>
<td>↓ / ↑</td>
<td>↑</td>
<td>Psychotic action</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>→ / ↑</td>
<td>↓ / ↑</td>
<td>NE</td>
<td>↓</td>
<td>Long acting</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>↑ / ↑</td>
<td>↓ / ↑</td>
<td>↓ / ↑↑</td>
<td>↓</td>
<td>Slow induction</td>
</tr>
</tbody>
</table>

ECT: electroconvulsive therapy, NE: not evaluated.
notic dose (0.75 mg/kg) is used, the seizure duration is similar from that seen with methohexital [62]. Although propofol produces a shorter duration of seizures, analysis of the antidepressant effects of ECT, such as the Hamilton rating efficiency and Beck Depression Inventory score, show that the use of propofol has similar outcomes to those achieved with methohexital [65]. As propofol has cardiovascular inhibitory properties, it can suppress acute hemodynamic changes immediately after ECT. Hence, it is preferred in patients with hypertension, tachycardia, or expected hemodynamic changes after ECT [64].

5. Ketamine
Ketamine is an intravenous anesthetic with both hypnotic and analgesic effects. The recommended dose of ketamine (1–2 mg/kg) can help achieve the desired ECT effects, but a low dose of this drug (0.4–0.8 mg/kg) leads to a shorter seizure duration on an EEG compared to methohexital. Because ketamine can also increase blood pressure, heart rate, and intracranial pressure, it is not generally preferred over methohexital or propofol for use in ECT procedures [54,66]. Moreover, it can induce psychiatric side effects such as agitation, confusion, delirium, and disorientation [64,67]. However, as ketamine has antidepressant properties, it is preferred in patients with depression [66].

6. Benzodiazepine
Benzodiazepines, such as midazolam and lorazepam, can alter the threshold and duration of seizures after ECT. In patients who have been taking benzodiazepine over the long term, seizures may not occur owing to its anticonvulsant effects [68]. Recently, remimazolam, a novel ultra-short-acting benzodiazepine, has been approved in many countries. Although there are no published reports on the effects of remimazolam as part of an ECT protocol, it may have anticonvulsant effects similar to those of other benzodiazepine drugs [69].

7. Dexmedetomidine
Dexmedetomidine is rarely used alone; in combination with other intravenous anesthetics, it can reduce the acute hemodynamic changes that are possible after ECT. Moreover, if dexmedetomidine at a 1 µg/kg dose is administered 10 min prior to ECT, it can reduce the extent of post-ECT agitation without affecting seizure duration or patient recovery time [70,71].

8. Inhalation anesthetics
Most ECT procedures are performed outside the operating theatre, and intravenous anesthesia is generally preferred over inhalational anesthesia. However, as possible inhalation anesthetics, sevoflurane (1.7%) and nitrous oxide (50%) can more potently reduce acute hemodynamic changes following ECT than thiopental [59]. The seizure duration and recovery times with these drugs were similar to those with thiopental. Inhalation anesthetics require a longer induction time than intravenous agents but can reduce the risk of uterine contractions after ECT in late pregnancy cases [72].

Neuromuscular blocking agents
Neuromuscular blocking agents are necessary to prevent possible musculoskeletal complications of ECT, such as myalgia, dislocation, and fracture, and are effective because they typically have a fast onset and a short duration of action [36,37].

1. Succinylcholine
Succinylcholine is the oldest and most commonly used neuromuscular blocking agent in ECT protocols [56,73]. The recommended dosage is 0.5 mg/kg, but higher doses (0.75–1.5 mg/kg) are also used in clinical practice [74]. Therefore, higher doses of succinylcholine should be avoided in patients with bradycardia [75]. Even at low concentrations, there is a risk of side effects (e.g., myalgia, malignant hyperthermia, hyperkalemia) in patients who are susceptible to malignant hyperthermia, neuroleptic malignant syndrome, catatonic schizophrenia, or organophosphate poisoning [76–78]. Because its duration of action may be prolonged, it must be used cautiously in patients with pseudocholinesterase deficiency or any kind of muscular dystrophy [54].

2. Atracurium and cisatracurium
In patients receiving intravenous atracurium, a 0.3 mg/kg pretreatment leads to significantly more ECT-induced moderate and vigorous convulsions (86 vs. 16%) and a shorter recovery time (4.2 ± 0.4 min vs. 9.2 ± 0.8 min) when compared with patients receiving 0.3 mg/kg [79]. Therefore, a low dose of atracurium is recommended when succinylcholine cannot be used. However, even small doses of atracurium (10–15 mg) can cause delayed recovery in patients with atypical plasma cholinesterase [80]. Clinically, cisatracurium is now starting to replace atracurium, but few studies have addressed its effectiveness using ECT.
3. Vecuronium and rocuronium

Vecuronium and rocuronium are non-depolarizing neuromuscular blocking agents with an aminosteroid structure that can also be used as part of the ECT protocol. Although the long duration of action has been a problem with these treatments, the development of sugammadex could make them useful in ECT. Sugammadex is a cyclodextrin-based compound with an antagonistic mode of action against aminosteroid nondepolarizing neuromuscular blockers. If sugammadex was used in conjunction with rocuronium during ECT, rapid onset of action and recovery could be expected. Hence, this potential drug combination has attracted attention as a possible alternative to succinylcholine [81,82]. In addition, calabadiol, a new antagonist of benzyli-soquinoline-based neuromuscular blocking agent, and a combination of gantacurium (CW002) and L-cysteine are anticipated to become part of future ECT procedures [83].

Drugs for the treatment of cardiovascular reactions during ECT

As acute cardiovascular reactions following ECT can cause serious complications, cardiovascular drugs are used to relieve acute parasympathetic and sympathetic reactions [29,84]. Some of these agents may affect the duration of seizures; however, the choice of drug should be made carefully [85].

1. Anti-cholinergics

Pretreatment with anticholinergics as part of the ECT protocol has been reported to reduce the incidence of premature atrial contracture, bradycardia, and asystole, as well as decrease secretion and salivation [57]. Glycopyrrolate (0.1–0.3 mg, i.v.) is the preferred agent in this regard because it can reduce salivation and bradycardia after ECT without side effects such as cognitive impairment [86].

2. β-blockers

β-blockers, such as esmolol and labetalol, attenuate the sympathetic and cardiovascular responses following ECT. Pretreatments of ECT patients with esmolol (1.0 mg/kg) or labetalol (0.3 mg/kg) are more effective than those with fentanyl (1.5 mg/kg) or lidocaine (1.0 mg/kg) [27]. Because esmolol can also decrease the duration of seizures, it is recommended to be administered immediately before or immediately after ECT [1,23].

3. Calcium channel blocker

Nicardipine (1.25–5 mg, i.v.) has a rapid hemodynamic control effect without impact on the cardiovascular inhibitory action of methohexital due to its rapid onset. Moreover, small doses of nicardipine have little effect on the duration of seizures [85]. Rebound tachycardia can occur after bolus administration of this drug, but intravenous administration of labetalol can attenuate this. A nicardipine and labetalol combination has also been reported to lower the mean arterial pressure immediately after ECT in comparison to labetalol alone [87].

4. Vasodilators

Nitroglycerin (NTG, 3 μg/kg, i.v.) can reduce hemodynamic changes after ECT compared to esmolol (2 mg/kg, i.v.) [27]. NTG has no effect on the duration of seizures [88]. In addition to the intravenous administration of this drug, a sublingual, patch, and ointment delivery method also reduces the onset of hemodynamic changes after ECT [89,90]. Nitroprusside is preferred in patients with intracranial aneurysms, dissecting aortic aneurysms, or aortic stenosis [91–93]. A β-blocker combined with nitroprusside lowers the incidence of tachycardia and hypertension and increases the blood flow velocity in the middle cerebral artery [34]. Nitroprusside also has no effect on seizure duration in ECT [94].

5. Ganglionic blocking agents

Although trimethaphan is not currently the preferred drug in clinical practice, its bolus administration at 5–15 mg can control hemodynamic changes after ECT without affecting the duration of the seizure [95]. Moreover, there were no side effects after ECT, such as rebound hypertension, arrhythmia, or hypotension [1,85].

6. Local anesthetics

Lidocaine can also attenuate the onset of hemodynamic changes after ECT, but it also decreases seizure duration in a dose-dependent manner [27,96].

7. Opioids

Opioids can act as a “seizure enhancers” by reducing the required hypnotic dose. Hence, short-acting opioids are effective in patients with an insufficient duration of seizures following ECT [1]. However, the effects of ECT have not been reported to be greater than those of hypnagogic alone [97]. Fentanyl (1.5 μg/kg, i.v.) shortens the seizure duration and does not alleviate ECT-induced hemodynamic changes [27].
Remifentanil (0.05–1.0 μg/kg/min) can prolong the duration of seizure by 27–38 s without impact on hemodynamic changes or recovery time [98,99]. Pethidine and tramadol are not recommended for use with ECT because they may interact with other antidepressants (e.g., monoamine oxidase inhibitors or selective serotonin reuptake inhibitors), potentially leading to hypertensive crises and/or serotonin syndromes [100].

8. Magnesium sulfates
Magnesium sulfates can reduce ECT-related hypertension and have no effect on seizure duration. The combined use of these compounds with remifentanil may delay the recovery of spontaneous respiration but can also prevent tachycardia and hypertension in elderly patients with ischemic heart disease [101].

**Postprocedural considerations**
ECT is a safe procedure in patients with minimal comorbidities. However, cardiovascular changes and psychiatric complications may occur following treatment. Pulmonary aspiration, respiratory failure, and residual neuromuscular blockade must be considered as possible complications of ECT interventions because neuromuscular blocking agents are used [102]. Although cognitive impairment is common after ECT, it is not permanent. Osler et al. [103] reported that ECT is not associated with dementia. Postictal delirium or agitation may also occur after ECT but should respond to small amounts of midazolam or propofol [104]. An extreme increase in cerebral blood flow due to sympathetic stimulation is also associated with intracranial hemorrhage. Succinylcholine-related myalgia responds well to nonsteroidal anti-inflammatory drugs such as ketorolac [18]. Prophylactic antiemetics may be recommended for high-risk patients or drugs such as sevoflurane and etomidate. Typical physiological changes and adverse events associated with ECT are summarized in Table 4.

**CONCLUSION**
ECT is a safe and effective treatment for various psychiatric disorders, and accepted indications for its use has steadily increased over time. Anesthesia during ECT should ideally provide deep hypnosis, ensure muscle relaxation to reduce injury, have minimal effects on seizure duration, and allow for rapid recovery to a baseline neurological and cardiopulmonary status. Multiple anesthetic agents are acceptable for use during ECT, and the choice of this drug should be considered for any underlying comorbidities that the patient has.

**FUNDING**
None.

**CONFLICTS OF INTEREST**
No potential conflict of interest relevant to this article was reported.

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

**AUTHOR CONTRIBUTIONS**
Anesthetic care for ECT

ORCID

Kyoung-Woon Joung, https://orcid.org/0000-0002-0626-4424
Dong Ho Park, https://orcid.org/0000-0002-6587-3756
Chang Young Jeong, https://orcid.org/0000-0003-3951-1222
Hong Seuk Yang, https://orcid.org/0000-0003-2023-8705

REFERENCES


54. MacPherson RD. Which anesthetic agents for ambulatory electro-convulsive therapy? Curr Opin Anaesthesiol 2015; 28: 656-
61.
76. Cooper RC, Baumann PL, McDonald WM. An unexpected hyperkalemic response to succinylcholine during electroconvulsive therapy for catatonic schizophrenia. Anesthesiology 1999; 91: 574-5.


Effects of chlorpheniramine on emergence agitation after general anesthesia for ureteroscopic stone surgery: a retrospective cohort study

Choon-Kyu Cho, Minhye Chang, Seok-Jin Lee, Sung-Ae Cho, and Tae-Yun Sung

Department of Anesthesiology and Pain Medicine, Konyang University Hospital, Konyang University College of Medicine, Daejeon, Korea

Background: The presence of a urinary catheter, postoperative pain, and postoperative nausea and vomiting are risk factors for emergence agitation (EA). Antimuscarinic agents are primary agents used in the prevention and treatment of urinary catheter-related bladder discomfort. Chlorpheniramine has antimuscarinic, antinociceptive, and antiemetic effects. This retrospective study investigated the role of chlorpheniramine in EA prevention following ureteroscopic stone surgery.

Methods: Of 110 adult patients who underwent ureteroscopic stone surgery under general anesthesia between January and December 2019, the medical records of 93 patients were analyzed retrospectively. The patients were divided into control (n = 52) and chlorpheniramine (n = 41) groups according to the receipt of intravenous chlorpheniramine before the induction of anesthesia. The incidence and severity of EA were compared between the groups as primary and secondary endpoints, respectively. The effects of chlorpheniramine on the requirement for inhalation anesthetic (desflurane) during surgery, changes in mean blood pressure and heart rate during emergence, and adverse events were also compared.

Results: The incidence (21.2% in the control group, 24.4% in the chlorpheniramine group) and severity of EA did not differ between groups. The intraoperative requirement for desflurane, changes in mean blood pressure and heart rate during emergence, and adverse events were also similar between groups.

Conclusions: Chlorpheniramine was not associated with a decrease in EA incidence or severity in patients who underwent ureteroscopic stone surgery.

Keywords: Anesthesia; Chlorpheniramine; Emergence agitation; Incidence; Urinary catheter.

INTRODUCTION

Emergence agitation (EA) is characterized by restless, excited, disoriented, and non-purposeful movement that can have clinical consequences, such as accidental removal of intravenous or drainage catheters, unintended extubation, bleeding at surgical sites, or injury of patients’ selves or medical staff, resulting in increased patient care burden and medical care costs [1,2]. The incidence of EA varies with the type of surgery, and increases up to 63.5% in patients with...
urinary catheters, compared to 9.8–13.6% in patients undergoing urological surgery [3,4]. Presence of a urinary catheter is a known risk factor for EA [1–4]. Therefore, antimuscarinic agents are often used to prevent and treat catheter-related bladder discomfort (CRBD) [5].

Chlorpheniramine is an alkylamine first-generation potent H₁ antihistamine generally used to prevent and treat hypersensitivity and allergic disorders [6,7], but also has sedative, local anesthetic, and antimuscarinic effects [6–8]. In addition, chlorpheniramine has an antiemetic effect and can be used to prevent and treat postoperative nausea and vomiting (PONV) [9]. These effects of chlorpheniramine are expected to attenuate EA by reducing PONV, postoperative pain, and CRBD [1–4], but at the same time, anticholinergic use is also a risk factor for EA [10]. Therefore, the effects of chlorpheniramine on EA are difficult to predict. Furthermore, no studies have evaluated the effect of chlorpheniramine in patients undergoing urological surgery and requiring urinary catheterization, with a high risk of EA. Thus, we aimed to evaluate the association between a single bolus dose (8 mg) of chlorpheniramine administered before the induction of anesthesia and EA in patients undergoing ureteroscopic stone surgery.

MATERIALS AND METHODS

This retrospective cohort study was approved by the Institutional Review Board (no. KYUH2020-01-005), and was registered with the Korea Clinical Research Information Service (http://cris.nih.go.kr) (no. KCT0004879). This study adhered to the STROBE checklist (https://www.strobe-statement.org/checklists/). Written informed consent was not obtained from patients due to the retrospective nature of the study. The medical records of patients who underwent elective ureteroscopic stone surgery under general anesthesia were reviewed retrospectively. Two anesthesiologists were in charge of anesthesia for the urological surgeries; they used the same anesthetic agents and patient monitoring and extubation criteria, according to our institutional protocols. However, only one anesthesiologist intravenously administered 8 mg chlorpheniramine (Pheniramine inj®, Yuhan Co., Korea) 5–10 min before the induction of anesthesia, in the absence of contraindication, to provide a sedative effect before anesthesia induction, to reduce PONV, and to help prevent perioperative hypersensitivity reactions [11,12]. According to this procedural difference, the patients were divided into chlorpheniramine and control groups. The inclusion criteria for this study were age 19–65 years and American Society of Anesthesiologists physical status classification I–III. All patients underwent elective ureteroscopic stone surgery under general anesthesia. The exclusion criteria were: the presence of a urinary catheter before anesthesia induction, induction of general anesthesia using a supraglottic airway device, cognitive or neuropsychological disorder, combined operation, contraindication to chlorpheniramine (e.g., prostatic hyperplasia, irritable bladder symptoms, bladder outlet obstruction, or glaucoma), and concomitant administration of steroids (e.g., dexamethasone or hydrocortisone) to prevent or treat an allergic reaction or anaphylaxis.

All patients were fasted for at least 8 h and arrived in the operating room without premedication. Patients in the chlorpheniramine group received intravenous 8 mg chlorpheniramine 5–10 min before the induction of anesthesia, whereas patients in the control group did not. All subsequent anesthesia care and surgical procedures were the same in the two groups. Routine monitoring included electrocardiography, noninvasive blood pressure measurement, pulse oximetry, end-tidal carbon dioxide (EtCO₂) measurement, Patient State Index (PSI) (SedLine®, Masimo Corp., USA) determination, and neuromuscular train-of-four (TOF) stimulation by acceleromyography (TOF-Watch SX®, Organon Ltd., Ireland) on the adductor pollicis muscle. Anesthesia was induced with intravenous propofol (1.5–2 mg/kg) and fentanyl (1–2 μg/kg).

Endotracheal intubation was facilitated by rocuronium (0.6 mg/kg). Volume-controlled mechanical ventilation was initiated at a tidal volume of 8 ml/kg and a respiratory rate of 12 breaths/min. During the maintenance of anesthesia, the EtCO₂ was maintained at 30–40 mmHg by adjusting the respiratory rate. Anesthesia was maintained with an oxygen/nitrous oxide mixture (50:50) and 3–8 vol% of the end-tidal concentration of desflurane to maintain the PSI at 25–50. All operations were performed in a lithotomy position. After surgery, each patient was catheterized with a Foley catheter, and the balloon was inflated with 5 ml normal saline by the urologist. After urinary catheterization, the patient was moved to the supine position. Desflurane and nitrous oxide were stopped, and manual ventilation was performed with 100% oxygen at 6 L/min. The neuromuscular block was reversed with 50 μg/kg neostigmine and 10 μg/kg glycopyrrolate. The extubation criteria were: PSI > 75, tidal volume ≥ 5 ml/kg, spontaneous respiratory breathing rate 10–25/min,
TOF ratio ≥ 0.9, and response to verbal commands. All patients were transferred to the post-anesthesia care unit (PACU) 5 min after extubation.

**Measurements**

Emergence was defined as the time interval between the discontinuation of all anesthetics (desflurane and nitrous oxide) and 5 min after extubation. The attending anesthetist (nurse), who has assessed agitation during emergence in all patients in our hospital since 2017, recorded the results on the patients’ electronic medical charts [13]. EA was assessed using the Ricker Sedation-Agitation Scale (RSAS, 7 points; 1 = unarousable, 2 = very sedated, 3 = sedated, 4 = calm and cooperative, 5 = agitated but responding calmly to verbal instructions, 6 = very agitated requiring restraint, 7 = pulling at the tracheal tube, trying to remove catheter or striking the staff) [14], and the highest RSAS score during emergence was recorded. RSAS scores > 5 were considered to reflect EA and were included in the EA incidence. RSAS was used to classify EA according to severity. The incidence of EA was analyzed as the primary endpoint, and the severity of EA was analyzed as the secondary endpoint. We also analyzed the time to extubation, defined as the time between turning off the inhalation anesthetics and extubation.

Data on hemodynamic parameters (mean blood pressure and heart rate) before the induction of anesthesia, at the end of surgery, at extubation, and 5 min after extubation were collected and analyzed. In addition, the highest and lowest concentrations of desflurane administered during the maintenance of anesthesia were determined and compared to exclude the effect of a difference in the concentration of inhalation anesthetic on EA.

Among the PACU data, the severity of postoperative pain (evaluated using an 11-point numerical rating scale [NRS; 0 = no pain, 10 = worst pain imaginable]), requirements for analgesics and antiemetics, and all adverse events were analyzed.

**Statistical analyses**

The primary endpoint of this study was the incidence of EA. In a previous study [3], the incidence of EA was 63.5% in patients who received urinary catheters. Assuming that a 50% reduction in the incidence of EA after administration of chlorpheniramine would be clinically relevant, a sample of 38 patients per group was required, with a power of 0.8 and a two-sided a value of 0.05.

The statistical analyses were performed using SPSS Statistics software (ver. 18.0 for Windows, IBM Corp., USA). Continuous variables were analyzed using Student’s t-test or the Mann–Whitney U test, depending on the Kolmogorov–Smirnov normality test result. Categorical variables were analyzed with the χ² test, the χ² test for trends (linear-by-linear association), or Fisher’s exact test, as appropriate. After obtaining the results of normality and Mauchly’s sphericity tests, changes in mean blood pressure and heart rate were analyzed using repeated-measures analysis of variance, followed by t-test with Bonferroni correction. P values < 0.05 were considered to be significant.

**RESULTS**

A total of 110 patients among those who received elective ureteroscopic stone surgery under general anesthesia in our hospital between January and December 2019 satisfied the inclusion criteria. Of these, 17 patients were excluded; thus, 93 patients were included in the final analysis (control group, n = 52; chlorpheniramine group, n = 41; Fig. 1).

The patient characteristics and operative data were comparable between the groups (Table 1). The intraoperative and recovery data are presented in Table 2. The incidence of EA was similar in the two groups (21.2% [11/52] in the control group and 24.4% [10/41] in the chlorpheniramine group; odds ratio, 0.832; 95% confidence interval: 0.3–2.2; P = 0.711). EA severity did not differ between groups (RSAS 3–7: control group, n = 2, 39, 8, 3, 1; chlorpheniramine group, n = 4, 27, 5, 3, 2, respectively; P =
Changes in mean blood pressure and heart rate were comparable between the two groups (P = 0.237 and 0.733, respectively; \( \text{Fig. 2A, B} \)). In addition, the highest and lowest intraoperative concentrations of desflurane, time to extubation, NRS scores for postoperative pain, and numbers of patients requiring analgesics or antiemetics in the PACU were similar in the two groups (Table 2).

All adverse events are presented in Table 3; no difference was detected between groups.

**DISCUSSION**

In this retrospective cohort study, a single dose of chlorpheniramine administered before the induction of anesthesia was not associated with a decrease in the incidence or severity of EA in adult patients undergoing ureteroscopic stone surgery under desflurane anesthesia.

The etiology of EA is not known. EA has been reported more often in the context of the use of newer, short-acting

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 52)</th>
<th>Chlorpheniramine (n = 41)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>49.7 ± 10.3</td>
<td>48.0 ± 12.0</td>
<td>0.485</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>34/18</td>
<td>23/18</td>
<td>0.361</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.3 ± 9.4</td>
<td>165.1 ± 8.7</td>
<td>0.147</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.6 ± 15.1</td>
<td>70.8 ± 14.9</td>
<td>0.961</td>
</tr>
<tr>
<td>Body mass index (kg/m(^2))</td>
<td>26.7 ± 4.5</td>
<td>25.8 ± 4.4</td>
<td>0.378</td>
</tr>
<tr>
<td>ASA classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I/II/III</td>
<td>11/36/5</td>
<td>9/31/1</td>
<td>0.454</td>
</tr>
<tr>
<td>Position of stone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney/ureter/both</td>
<td>17/25/10</td>
<td>13/15/3</td>
<td>0.427</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>69.7 ± 50.9</td>
<td>53.2 ± 32.2</td>
<td>0.059</td>
</tr>
<tr>
<td>Duration of anesthesia (min)</td>
<td>97.5 ± 52.0</td>
<td>81.1 ± 32.6</td>
<td>0.093</td>
</tr>
<tr>
<td>Fluids (ml)</td>
<td>200 (150, 300)</td>
<td>200 (150, 300)</td>
<td>0.715</td>
</tr>
<tr>
<td>Urinary catheter size (Fr)</td>
<td>14/16/18</td>
<td>10/40/2</td>
<td>0.229</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, number, or median (1Q, 3Q). ASA: American Society of Anesthesiologists.
Effect of chlorpheniramine on emergence agitation

### Table 2. Intraoperative and Recovery Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 52)</th>
<th>Chlorpheniramine (n = 41)</th>
<th>Mean difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desflurane</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest concentration (vol%)</td>
<td>5.8 (5.0, 6.0)</td>
<td>5.0 (5.0, 6.0)</td>
<td>0.2 (−0.2, 0.6)</td>
<td>0.361</td>
</tr>
<tr>
<td>Highest concentration (vol%)</td>
<td>6.0 (5.0, 6.0)</td>
<td>6.0 (5.0, 6.0)</td>
<td>0.2 (−0.1, 0.6)</td>
<td>0.149</td>
</tr>
<tr>
<td>Time to extubation (min)</td>
<td>8.0 (6.3, 9.0)</td>
<td>7.3 (5.5, 8.6)</td>
<td>0.4 (−0.8, 1.6)</td>
<td>0.210</td>
</tr>
<tr>
<td>RSAS (3/4/5/6/7)</td>
<td>2/39/8/2/1</td>
<td>4/27/5/3/2</td>
<td>NA</td>
<td>0.688</td>
</tr>
<tr>
<td>Emergence agitation</td>
<td>11 (2.1)</td>
<td>10 (2.4)</td>
<td>−3.2 (−20.6, 13.4)</td>
<td>0.711</td>
</tr>
<tr>
<td>NRS for pain</td>
<td>2.0 (1.0, 3.0)</td>
<td>1.0 (0.2, 5)</td>
<td>0.7 (−0.05, 1.4)</td>
<td>0.055</td>
</tr>
<tr>
<td>Analgesics</td>
<td>3 (5.8)</td>
<td>1 (2.4)</td>
<td>3.3 (−7.5, 13.4)</td>
<td>0.628</td>
</tr>
<tr>
<td>Antiemetics</td>
<td>2 (3.8)</td>
<td>0 (0)</td>
<td>3.8 (−5.1, 13.0)</td>
<td>0.502</td>
</tr>
</tbody>
</table>

Values are presented as median (1Q, 3Q), number, or number (%). Time to extubation was defined as the interval between turning off the inhalation anesthetics and extubation. Emergence agitation was defined as RSAS ≥ 5. CI: confidential interval, RSAS: Ricker Sedation-Agitation Scale. *3 = sedated, 4 = calm and cooperative, 5 = agitated but responding calmly to verbal instructions, 6 = very agitated and requiring restraint, 7 = pulling at the tracheal tube, trying to remove catheter or striking staff. †0 = no pain, 10 = worst imaginable pain.

### Table 3. Adverse Events in the Post-anesthesia Care Unit

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 52)</th>
<th>Chlorpheniramine (n = 41)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sore throat</td>
<td>8 (15.4)</td>
<td>11 (26.8)</td>
<td>0.174</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>1 (1.9)</td>
<td>0 (0)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2 (3.8)</td>
<td>1 (2.4)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (5.8)</td>
<td>0 (0)</td>
<td>0.252</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (3.8)</td>
<td>0 (0)</td>
<td>0.502</td>
</tr>
<tr>
<td>Headache</td>
<td>0 (0)</td>
<td>2 (4.9)</td>
<td>0.192</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0 (0)</td>
<td>1 (2.4)</td>
<td>0.441</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1 (1.9)</td>
<td>0 (0)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (1.9)</td>
<td>0 (0)</td>
<td>&gt; 0.999</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

halogenated compounds, such as desflurane and sevoflu- rane, than with the use of other inhaled anesthetics [15]. Proposed hypotheses for EA seen with desflurane use include rapid emergence with insufficient time to adjust to the strange environment, late recovery of cognitive function compared to other brain functions resulting in altered cognitive perception, increased pain sensation, and activation of the sympathetic nervous system [16].

Although the etiology of EA remains unknown, extended duration of surgery, CRBD, PONV, anticholinergics, type of surgery (e.g., otolaryngological and oral cavity surgeries), pain, and the presence of invasive devices (e.g., urinary catheter, tracheal tube, or chest tube) contributed to EA in adult patients undergoing general anesthesia [1–4]. Drugs that prevent EA include propofol, N-methyl-D-aspartate receptor antagonists (e.g., magnesium sulfate, ketamine, and tramadol), α1-adrenergic agonists (clonidine and dexmedetomidine), and μ-opioid agonists (e.g., fentanyl and remifentanil); these drugs have sedative and/or analgesic effects in common [13].

Antihistamines are among the drugs used most commonly during the perioperative period [17], and some researchers have recommended routine prophylaxis with an antihista- mine to prevent life-threatening histamine-related conse- quences after the induction of anesthesia [18]. Depending on their impacts on the central nervous system, H1 antihista- mines are classified into first-generation sedating antihista- mines and second-generation antihistamines that provide less or no sedation [6].

Chlorpheniramine is a first-generation H1 receptor antag- onist (H1 antihistamine) and one of the most potent antial- lergic agents in the alkylamine group; thus, it is commonly used to prevent or treat hypersensitivity and allergic reac- tions [8]. In addition, chlorpheniramine has sedating, antinociceptive, antiemetic, anti-inflammatory, and antimuscar-inic effects [9,19]. These effects were expected to have a positive influence on EA, but chlorpheniramine was not as- sociated with EA attenuation in this study. Possible explana- tions are as follows. First, although chlorpheniramine pro- vides a sedative effect by penetrating the blood–brain barrier and acting on central H1 receptors, it can impair cognitive and psychomotor performance, cause problems with coor- dination, and, paradoxically, cause excitability and restless- ness, even at therapeutic doses [6]. These effects may con- tribute to EA by further delaying the recovery of cognitive function after desflurane anesthesia. Second, previous studies have shown that anti-inflammatory and antimuscarinic agents (e.g., paracetamol, oxybutynin, tolterodine, glycopyr-
rolate, and butyrscolopamine) reduce CRBD [20,21]. However, in a recent study [22], chlorpheniramine decreased rescue tramadol usage to relieve postoperative CRBD, but did not reduce the incidence or severity of CRBD. The authors speculated that an 8 mg dose of chlorpheniramine is insufficient to reduce CRBD incidence and severity because of its weak antimuscarinic effects [7,22]. In addition, chlorpheniramine acts on serotonergic and cholinergic receptors, which can cause adverse effects, such as dizziness, tinnitus, anxiety, blurred vision, problems with concentration, dry mouth, and difficulty urinating [23]. These effects may have influenced the results of this study. Third, in this study, postoperative NRS scores for pain were low (medians = 1 and 2) in both groups, and only a few patients in the control group complained of PONV. These findings suggest that postoperative pain and PONV may not be important risk factors for EA in patients undergoing ureteroscopic stone surgery. Consequently, the antinociceptive and antiemetic effects of chlorpheniramine may not contribute to the attenuation of EA. On the other hand, a recent study [24] demonstrated a reduction in EA severity after functional endoscopic sinus surgery with a single preoperative dose (5 mg) of chlorpheniramine. The discrepancy between these results may be attributed to differences in the anesthetic agents (desflurane vs. sevoflurane), types of surgery (urological vs. nasal), EA assessment tool (RSAS vs. the Richmond Agitation-Sedation Scale), and assessment period [2].

The incidence of EA in this study was lower than the 63.5% reported in patients with urinary catheters [3]. This difference may reflect the evaluation of EA only in patients undergoing ureteroscopic stone surgery, which causes less postoperative pain, in this study, whereas previous studies included patients undergoing various types of surgery known to be associated with high risks of EA, such as oral cavity, otolaryngological, and orthopedic and abdominal surgeries [2,3]. In contrast, the incidence of EA in our study was more than double that of 9.8% reported in patients undergoing urological surgery [4]. However, not all patients in that study had urinary catheters, and some patients had surgery under general anesthesia comprising total intravenous anesthesia and/or induced with a supraglottic airway device [4]. Total intravenous anesthesia is protective against EA [25], and supraglottic airway devices may have induced less EA compared to endotracheal tubes [26].

In a previous study, intravenous chlorpheniramine (8 mg) caused no significant hemodynamic change during anesthesia [17]. However, EA itself can cause hemodynamic changes (e.g., hypertension and tachycardia) by increasing the sympathetic tone during emergence [13]. In this study, the mean blood pressure and heart rate during emergence did not differ between groups, supporting the lack of a significant difference in EA between groups.

The effect of the difference in anesthesia depth according to differences in inhalation anesthetic concentrations on EA is controversial [27,28]. In this study, desflurane concentrations were adjusted under PSI monitoring in both groups, and the highest and lowest desflurane doses during anesthesia were comparable between groups. Therefore, effects of the depth of anesthesia on EA could be excluded.

This study has some limitations. First, all patients received 1–2 μg/kg fentanyl during the induction of anesthesia. In a meta-analysis of data from 3,172 children, fentanyl showed a prophylactic effect against desflurane-related EA [29]. Thus, fentanyl may have contributed to the reduction of EA in both groups in this study. Second, in this study, the duration in PACU was not included in the emergence period. Considering that all patients were urinary-catheterized and that chlorpheniramine had little effect on CRBD incidence or severity [22], it is likely that we underestimated EA incidence and severity in both groups. Third, even though the anesthesia protocols and types of surgery were uniform, individual differences in practice among anesthesiologists and surgeons may have influenced the results. Finally, this study had a retrospective design, and chlorpheniramine was not administered for EA prevention. The effects of the drugs on EA may depend on the dose and timing of administration [2]. Therefore, prospective studies are needed with controlled dosages and timing of chlorpheniramine administration.

In conclusion, a single 8-mg bolus dose of chlorpheniramine administered before anesthesia induction was not associated with a decrease in EA incidence or severity following ureteroscopic stone surgery.

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


ORCID

Choon-Kyu Cho, https://orcid.org/0000-0001-9906-1396
Minhye Chang, https://orcid.org/0000-0002-1257-4533
Seok-Jin Lee, https://orcid.org/0000-0001-7894-8510
Sung-Ae Cho, https://orcid.org/0000-0002-1519-3787
Tae-Yun Sung, https://orcid.org/0000-0002-0714-1477

REFERENCES

22. In CB, Lee SJ, Sung TY, Cho CK, Jee YS. Effects of chlorpheniramine maleate on catheter-related bladder discomfort in pa-


Association between anesthetic method and postpartum hemorrhage in Korea based on National Health Insurance Service data

Yongho Jee¹, Hyun Jung Lee², Youn Jin Kim², Dong Yeon Kim², and Jae Hee Woo²

¹Advanced Biomedical Research Institute, Ewha Womans University Seoul Hospital, ²Department of Anesthesiology and Pain Medicine, Ewha Womans University College of Medicine, Seoul, Korea

Background: Postpartum hemorrhage (PPH) is a major cause of maternal mortality and the risk factors for PPH differ among studies. In this large-scale study, we investigated whether the anesthetic method used was associated with PPH after cesarean section.

Methods: We extracted data on cesarean sections performed between January 2008 and June 2013 from the National Health Insurance Service database. The anesthetic methods were categorized into general, spinal and epidural anesthesia. To compare the likelihood of PPH among deliveries using different anesthetic methods, crude and adjusted odds ratios (ORs) and 95% confidence intervals were calculated using logistic regression analysis.

Results: Data from 330,324 cesarean sections were analyzed, and 21,636 cases of PPH were identified. Univariate analysis showed that general and epidural anesthesia increased the risk of PPH compared to spinal anesthesia. The OR for PPH was highest for morbidly adherent placenta, followed by placenta previa, placental abruption, and hypertension. When other clinical covariates were controlled for, general and epidural anesthesia still remained significant risk factors for PPH compared to spinal anesthesia.

Conclusions: This study showed that general and epidural anesthesia elevated the risk of PPH compared to spinal anesthesia during cesarean section. Since we could not consider the potential bias of group differences in indications, more in-depth clinical trials are needed to validate our findings. Obstetric factors such as placental abnormalities had high odds ratios and thus are more important than the choice of anesthetic method, which should be based on the patient’s clinical condition and institutional resources.

Keywords: Anesthesia, epidural; Anesthesia, general; Anesthesia, spinal; Postpartum hemorrhage.

INTRODUCTION

Postpartum hemorrhage (PPH) is a major cause of maternal mortality. An increasing incidence of PPH has been reported in many countries, possibly related to older maternal age, obesity, multiple pregnancies, previous cesarean deliveries, labor induction and augmentation, and better detection methods [1,2]. However, the causes are still not fully understood. General anesthesia is a risk factor for PPH after cesarean delivery, since volatile anesthetic agents inhibit
spontaneous contractility of uterine muscle in a dose-dependent manner [1,3–5].

Neuraxial anesthesia is generally preferred over general anesthesia for cesarean section [6,7]. The main reason is the difficult airway management associated with general anesthesia, but other factors also influence the decision, including intraoperative awareness, postoperative bleeding, neonatal safety, postoperative pain management, and maternal bonding with the newborn following delivery [7]. According to previous reports, general anesthesia is used in about 6% of planned cesarean deliveries in the United States [8]. A study of the anesthetic methods used for cesarean delivery in Korea between 2013 and 2018 reported that general and regional anesthesia were used in 27.4% and 72.6% of cesarean deliveries, respectively [6]. While the use of general anesthesia has declined significantly, it is still used much more frequently in Korea compared to other countries [9]. In this large-scale study using National Health Insurance Service (NHIS) data, we investigated whether the anesthetic method was associated with PPH after cesarean section.

**MATERIALS AND METHODS**

**Data source and subjects**

This study was approved by the Institutional Review Board. We analyzed data from an NHIS database (no. NHIS-2020-1-274). Cesarean sections have been under the diagnosis-related group (DRG) payment system since July 2013 in Korea, so for almost all cases after that date we could not identify the mode of anesthesia from the NHIS database. Therefore, data on cesarean sections performed between January 2008 and June 2013 were extracted. Clinical characteristics and comorbidities were identified using the Korean Classification of Diseases (KCD), which is based on the International Classification of Diseases, 10th edition. Cesarean section was defined by codes O82 and O842. The exclusion criteria were malignancies (C00-97), diseases of the blood and blood-forming organs, immune-system disorders (D50-89), obstetric trauma causing rupture of the uterus (O71), and antepartum hemorrhage (O46). The anesthetic methods were categorized into general anesthesia (L1211, L1221), spinal anesthesia (L1213, L1223), and epidural anesthesia (L1214, L1224), based on a previous study reporting trends in anesthetic methods in Korea [6]. Cases in which the anesthetic method could not be verified were excluded from the analysis.

**Outcomes and statistical analysis**

SAS software (version 9.4, SAS Inc., USA) was used for the statistical analysis. The main outcome measure was the occurrence of PPH after cesarean section, corresponding to codes O721 (hemorrhage following delivery of placenta and uterine inertia), within 1 month of cesarean delivery. To compare patient characteristics among groups, continuous variables were assessed by analysis of variance and are presented as the mean ± SD. Categorical variables were analyzed using the chi-square test. To assess risk factors for PPH, and its likelihood of occurrence according to different anesthetic methods, crude and adjusted odds ratios (ORs), and 95% confidence intervals (CIs), were estimated using logistic regression analysis with forward selection. Initially, 19 variables were identified as possible covariates based on a literature review. Variables with high rates of missing data and a high Pearson correlation coefficient (> 0.8) were excluded. Finally, covariates adjusted for in the multivariate logistic regression models included maternal age, emergency operation (O821), previous PPH (O721, O622 during a previous delivery), multiple pregnancy (O30), placenta previa (O44), placental abruption (O45), morbidly adherent placenta (O432), preeclampsia (O11, O14), eclampsia (O15), hypertension (O10: preexisting gestational hypertension, O13: gestational hypertension, or O16: unspecified maternal hypertension), diabetes mellitus (O24), and the level of care. The diagnostic codes did not change during the study period. The hospitals where the cesarean sections were performed were classified according to the Korean Medical Care Act (tertiary, general, hospital, or clinic). Our logistic regression model was assessed using the Hosmer–Lemeshow goodness-of-fit test, which was not significant. P values < 0.05 were considered statistically significant.

**RESULTS**

A total of 899,284 cesarean sections performed between January 2008 and June 2013 were identified in the NHIS database after applying the exclusion criteria. The method of anesthesia could not be confirmed in 568,960 cases. Finally, the data from 330,324 cesarean sections were analyzed, revealing the use of general anesthesia in 57.17%, spinal anesthesia in 29.34%, and epidural anesthesia in 13.50% (Fig. 1). The patient characteristics are shown in Table 1. In emergency cases, the proportion of epidural anesthesia was high-
er than that of spinal and general anesthesia. The data also revealed that 42.56% of cesarean sections were conducted in clinics, 25.83% in hospitals, 17.38% in tertiary care hospitals and 14.24% in general hospitals.

Table 2 summarizes the characteristics of women according to anesthetic methods used for cesarean delivery. In total, 21,636 cases of PPH (6.55%) were identified from among the 330,324 cesarean sections. Univariate analysis showed that general anesthesia

![Flow diagram of participants who underwent cesarean section.](image)

Table 1. Characteristics of women according to anesthetic methods used for cesarean delivery

<table>
<thead>
<tr>
<th>Variable</th>
<th>Spinal (n = 96,909)</th>
<th>General (n = 188,830)</th>
<th>Epidural (n = 44,585)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>32.31 ± 4.10</td>
<td>31.95 ± 4.30</td>
<td>31.84 ± 4.02</td>
</tr>
<tr>
<td>Emergency</td>
<td>No</td>
<td>65,245 (67.33)</td>
<td>120,381 (63.75)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>31,664 (32.67)</td>
<td>68,449 (36.25)</td>
</tr>
<tr>
<td>Previous PPH</td>
<td>No</td>
<td>86,356 (89.11)</td>
<td>168,314 (89.14)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>10,553 (10.89)</td>
<td>20,516 (10.86)</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td>No</td>
<td>93,145 (96.12)</td>
<td>183,437 (97.14)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>3,764 (3.88)</td>
<td>5,393 (2.86)</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>No</td>
<td>96,215 (99.28)</td>
<td>186,611 (98.82)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>694 (0.72)</td>
<td>2,219 (1.18)</td>
</tr>
<tr>
<td>Placenta previa</td>
<td>No</td>
<td>94,788 (97.81)</td>
<td>181,558 (96.15)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>2,121 (2.19)</td>
<td>7,272 (3.85)</td>
</tr>
<tr>
<td>MAP</td>
<td>No</td>
<td>96,756 (99.84)</td>
<td>188,517 (99.83)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>153 (0.16)</td>
<td>313 (0.17)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>No</td>
<td>94,693 (97.71)</td>
<td>184,821 (97.88)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>2,216 (2.29)</td>
<td>4,009 (2.12)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>No</td>
<td>93,022 (95.99)</td>
<td>182,230 (96.5)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>3,887 (4.01)</td>
<td>6,600 (3.5)</td>
</tr>
<tr>
<td>Preeclampsia/eclampsia</td>
<td>No</td>
<td>93,851 (96.84)</td>
<td>183,299 (97.07)</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>3,058 (3.16)</td>
<td>5,531 (2.93)</td>
</tr>
<tr>
<td>Level of care</td>
<td>Tertiary</td>
<td>20,370 (21.02)</td>
<td>32,951 (17.45)</td>
</tr>
<tr>
<td></td>
<td>General</td>
<td>14,730 (15.20)</td>
<td>27,399 (14.51)</td>
</tr>
<tr>
<td></td>
<td>Hospital</td>
<td>23,384 (24.13)</td>
<td>46,150 (24.44)</td>
</tr>
<tr>
<td></td>
<td>Clinic</td>
<td>38,424 (39.65)</td>
<td>82,330 (43.60)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number (%). PPH: postpartum hemorrhage, MAP: morbidly adherent placenta.
and epidural anesthesia increased the risk of PPH 1.10-fold (95% CI 1.06–1.13) and 1.41-fold (95% CI 1.36–1.46), respectively, compared to spinal anesthesia. The highest OR for PPH was observed for morbidly adherent placenta (OR 3.84, 95% CI 3.09–4.77), followed by placenta previa (OR 1.45, 95% CI 1.35–1.55), placental abruption (OR 1.36, 95% CI 1.20–1.55), and hypertension (OR 1.24, 95% CI 1.14–1.35). Table 3 shows the associations between anesthesia types and PPH, while controlling for clinical covariates. When placental abruption, placenta previa, morbidly adherent placenta, hypertension, preeclampsia, eclampsia, and diabetes mellitus were controlled for, general (OR 1.06, 95% CI 1.03–1.10) and epidural anesthesia (OR 1.47, 95% CI 1.41–1.53) remained significant risk factors for PPH compared to spinal anesthesia.

**DISCUSSION**

This study showed that compared to spinal anesthesia, general and epidural anesthesia increased the risk of PPH in women undergoing cesarean section. However, we could not consider all of the important clinical factors that might have influenced the results. The obstetric factors still had higher odds ratios, implying that obstetric factors such as placental abnormalities were more important than the choice of anesthetic method.

Animal and experimental studies have demonstrated that volatile anesthetics can cause significant uterine relaxation [3,10]. In a rat model, Dogru et al. [10] showed that desflurane at a minimum alveolar concentration (MAC) of 0.5 did not affect the duration or amplitude of spontaneous uterine contractions, but decreased their frequency. At 1 and 2 MAC, desflurane significantly decreased the duration, amplitude and frequency of uterine contractions. Similarly, sevoflurane at 2 MAC significantly decreased the duration, amplitude and frequency of uterine contractions, whereas it did not at 0.5 MAC. In oxytocin-stimulated human myometrial fibers, exposure to 0.5, 1, and 2 MAC of desflurane and sevoflurane reduced the frequency and amplitude of contractions in a dose-dependent manner. The authors suggested that 0.5 MAC of both agents, and 1 MAC of desflurane, might be safe in the presence of oxytocin during cesarean section.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No PPH (n = 308,688)</th>
<th>PPH (n = 21,636)</th>
<th>Unadjusted odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>32.06 ± 4.21</td>
<td>31.98 ± 4.19</td>
<td>1.00 (1.00–1.00)</td>
</tr>
<tr>
<td>Anesthetic method</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal</td>
<td>91,191 (94.10)</td>
<td>5,718 (5.9)</td>
<td>1.00</td>
</tr>
<tr>
<td>General</td>
<td>176,713 (93.58)</td>
<td>12,117 (6.42)</td>
<td>1.10 (1.06–1.13)*</td>
</tr>
<tr>
<td>Epidural</td>
<td>40,769 (91.44)</td>
<td>3,801 (8.56)</td>
<td>1.41 (1.36–1.46)*</td>
</tr>
<tr>
<td>Emergency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>199,101 (93.99)</td>
<td>12,720 (6.01)</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>106,833 (92.46)</td>
<td>8,718 (7.54)</td>
<td>1.28 (1.24–1.31)*</td>
</tr>
<tr>
<td>Previous PPH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>272,775 (93.29)</td>
<td>18,980 (6.71)</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>33,159 (93.10)</td>
<td>2,458 (6.90)</td>
<td>1.07 (1.02–1.11)*</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>296,686 (93.47)</td>
<td>20,731 (6.53)</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>9,248 (92.9)</td>
<td>707 (7.1)</td>
<td>1.09 (1.01–1.18)*</td>
</tr>
<tr>
<td>Placental abruption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>305,845 (93.47)</td>
<td>21,360 (6.53)</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>2,842 (91.32)</td>
<td>270 (8.68)</td>
<td>1.36 (1.20–1.55)*</td>
</tr>
<tr>
<td>Placenta previa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>299,685 (93.53)</td>
<td>20,731 (6.47)</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>9,007 (90.91)</td>
<td>901 (9.09)</td>
<td>1.45 (1.35–1.55)*</td>
</tr>
<tr>
<td>MAP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>308,288 (93.47)</td>
<td>21,531 (6.53)</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>393 (78.86)</td>
<td>105 (21.14)</td>
<td>3.84 (3.00–4.77)*</td>
</tr>
<tr>
<td>Preeclampsia/eclampsia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>296,995 (93.46)</td>
<td>20,783 (6.54)</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>8,944 (93.22)</td>
<td>650 (6.78)</td>
<td>1.04 (0.96–1.13)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>302,187 (93.48)</td>
<td>21,070 (6.52)</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>6,498 (92.04)</td>
<td>562 (7.96)</td>
<td>1.24 (1.14–1.35)*</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>299,784 (93.49)</td>
<td>20,876 (6.51)</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>8,904 (92.32)</td>
<td>741 (7.68)</td>
<td>1.20 (1.12–1.28)*</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number (%). CI: confidence interval, PPH: postpartum hemorrhage, MAP: morbidly adherent placenta. *P < 0.05.
section [3]. Given the evidence above, questions arise as to whether regional versus general anesthesia really affects the risk of PPH and whether regional anesthesia should be preferred in PPH cases [11]. Studies have reported that general anesthesia is a risk factor for PPH, with ORs ranging from 1.87 to 22.25 depending on the study design, population and definition of PPH [1,5,12]. It has also been reported that various surgeries, including cesarean deliveries, performed under general anesthesia resulted in greater blood loss compared to neuraxial anesthesia [13,14]. A retrospective study comparing general and spinal anesthesia for cesarean section in Korea reported lower blood loss in a spinal anesthesia group (819.9 ± 81.9 ml) than in a general anesthesia group (856.7 ± 117.9 ml). The difference, however, was not considered clinically significant [15]. Generally, obstetric anesthesiologists use low concentrations of volatile anesthetics during cesarean section to minimize their negative effects on uterine muscle contraction [16]. Given that our results imply an OR of 1.06 for general anesthesia, concerns about postoperative bleeding do not seem to be a major factor when considering the method of anesthesia for cesarean section. Instead, the choice of anesthetic method should be made on the basis of clinical conditions and institutional resources [17]. Beilin [11] reported that general anesthesia is preferable if massive hemorrhage is likely, because the patients may become hypovolemic and airway edema may result from large-volume fluid resuscitation.

Interestingly, we also found that epidural anesthesia carried a significantly greater risk of PPH than spinal anesthesia. A previous case-control study exploring risk factors for PPH showed that the risk was greater for epidural and combined spinal epidural (CSE) anesthesia compared to spinal anesthesia alone. The adjusted OR of CSE during cesarean section without labor was 3.13 (95% CI 1.71–5.71), while the unadjusted OR of CSE and epidural anesthesia during intrapartum cesarean delivery was 2.59 (95% CI 1.45–4.62) and 1.65 (95% CI 1.11–2.44), respectively [5]. However, there were group differences in indications according to the anesthetic method. In another study, patient-controlled epidural analgesia suppressed uterine and abdominal muscle electromyographic activity during the second stage of labor [18]. Other studies of cesarean section have reported signifi-

---

**Table 3. Multivariate Logistic Model of Postpartum Hemorrhage**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anesthetic method</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>General</td>
<td>1.08 (1.05–1.11)*</td>
<td>1.07 (1.04–1.11)*</td>
<td>1.06 (1.03–1.10)*</td>
</tr>
<tr>
<td>Epidural</td>
<td>1.48 (1.42–1.54)*</td>
<td>1.49 (1.43–1.56)*</td>
<td>1.47 (1.41–1.53)*</td>
</tr>
<tr>
<td>Age</td>
<td>1.00 (1.00–1.00)</td>
<td>1.00 (1.00–1.00)</td>
<td>1.00 (1.00–1.00)</td>
</tr>
<tr>
<td>Multiple pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>1.13 (1.04–1.22)*</td>
<td>1.15 (1.06–1.24)*</td>
<td></td>
</tr>
<tr>
<td>Previous PPH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>1.07 (1.02–1.12)*</td>
<td>1.07 (1.02–1.11)*</td>
<td></td>
</tr>
<tr>
<td>Placental abruption</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>1.35 (1.19–1.53)*</td>
<td>1.22 (1.08–1.39)*</td>
<td></td>
</tr>
<tr>
<td>Placenta previa</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>1.44 (1.35–1.55)*</td>
<td>1.45 (1.35–1.56)*</td>
<td></td>
</tr>
<tr>
<td>MAP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>3.46 (2.78–4.31)*</td>
<td>3.44 (2.76–4.28)*</td>
<td></td>
</tr>
<tr>
<td>Emergency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>1.27 (1.23–1.30)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preeclampsia/eclampsia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.96 (0.89–1.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.22 (1.12–1.33)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.22 (1.13–1.31)*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: confidence interval, PPH: postpartum hemorrhage, MAP: morbidly adherent placenta. *P < 0.05.
significant hypotension, deeper surgical anesthesia, better postoperative pain control, and decreased use of additional analgesics with spinal compared to epidural anesthesia [19,20]. Since uterine blood flow is not autoregulated, uteroplacental perfusion is directly dependent on maternal perfusion pressure. However, these explanations are not sufficient to answer why epidural anesthesia may be a higher risk factor for PPH compared to spinal anesthesia. Confounders might have influenced our results; for example, epidural anesthesia is preferred in emergency situations if the patient already has a functioning epidural catheter in place for controlling labor pain. The frequency of emergency cases in our data was higher in the epidural group than in the other groups; 67.32% of spinal anesthesia cases were elective and 39.98% of epidural anesthesia cases were considered emergency. Cesarean section after labor onset can increase the risk of PPH. Desensitization due to large doses of oxytocin for labor induction, uterine muscle fatigue, and intrapartum factors such as chorioamnionitis may explain the higher risk of PPH after labor induction. [5,21–24]. In the current study, we did not have information about the dosage or timing of uterotonic use for labor induction, and whether the patients underwent cesarean section after labor was not known, which might have influenced our results.

The obstetric risk factors for PPH identified in this analysis are well-recognized and consistent with previous studies [23,25]. Multiple gestations are associated with impaired uterine contractility. Magnesium sulfate, used in patients with preeclampsia and eclampsia, can compromise uterine contractility and often causes platelet dysfunction [22]. Risk factors reported in the literature are mostly related to uterine activity. However, in a study investigating uterine contractile waves during the 2 hours after placental delivery, no correlation was found between uterine activity and blood loss, indicating that other factors are involved in hemostasis, such as coagulation factors [26]. A large US study using nationwide data showed that more than 60% of patients who hemorrhaged from atony and required transfusion did not have any identifiable antepartum risk factors [22]. Although recognition of PPH risk factors is crucial, measures to deal with unexpected PPH are also needed because uterine atony is difficult to predict before delivery in the absence of well-recognized causes.

The study period began in January 2008 so that any changes in the diagnostic codes could be tracked based on the fifth revision of the KCD. Due to difficulty in identifying the anesthetic method used for cases under the DRG payment system, data were extracted up to July 2013. Caution should be taken when interpreting our results because we could not include all cesarean sections performed during the study period. First of all, data of patients who had malignancies, diseases of the blood or blood-forming organs, and obstetric trauma were excluded. Moreover, the DRG payment system was applied in some centers on a trial basis during this study period, and we could not identify the anesthetic method in such cases. As a result, our data included only about 40% of all cesarean sections performed during the study period and the results may not reflect the actual population. As such, we were concerned about the possibility of selection bias. Literature data on the relative proportions of anesthetic methods used for cesarean deliveries are available only from 2013 to 2018 [6]. Analysis thereof showed that the rate of spinal anesthesia increased from 40.0% in 2013 to 53.7% in 2018, while the opposite trend was observed in general anesthesia, which decreased from 37.1% in 2013 to 22.2% in 2018. Considering this trend, general anesthesia might have been performed more frequently in the period between 2008 and 2013, in line with our results. Nonetheless, the rates of use of each anesthetic method and incidence of PPH in this study might not reflect the actual rates for the general population.

Our study was subject to the inherent limitations of a retrospective analysis. We could not consider several clinically relevant variables, such as body mass index, types and concentrations of volatile anesthetics used, uterotonic use, spontaneous labor and labor augmentation before cesarean delivery, parity, fetal birth weight, postpartum blood loss volume, volume of transfused blood and hemoglobin level, which might influence our results. Misclassification of cases may also have occurred due to coding errors.

In conclusion, analyzing a nationwide dataset, general and epidural anesthesia during cesarean section increased the risk of PPH compared to spinal anesthesia. As we could not consider the potential influence of confounders, future studies analyzing more detailed clinical datasets are needed to validate these findings. Obstetric risk factors such as placental abnormalities had high odds ratios; as such, they are more important than the choice of anesthetic method, which should be based on the patient’s clinical condition and institutional resources.

FUNDING

This research was supported by Research Grant 2019 funded by the Korean Society of Obstetric Anesthesiologists.
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


ORCID

Yongho Jee, https://orcid.org/0000-0003-0365-8302
Hyun Jung Lee, https://orcid.org/0000-0003-4255-8937
Youn Jin Kim, https://orcid.org/0000-0001-9189-5839
Dong Yeon Kim, https://orcid.org/0000-0002-4414-5653
Jae Hee Woo, https://orcid.org/0000-0002-1993-1687

REFERENCES

18. Qian X, Li P, Shi SQ, Garfield RE, Liu H. Uterine and abdominal muscle electromyographic activities in control and PCEA-treated nulliparous women during the second stage of labor. Reprod


Comparison of nebulized dexmedetomidine and ketamine for premedication in pediatric patients undergoing hernia repair surgery: a randomized comparative trial

Geeta Singariya1, Namita Malhotra1, Manoj Kamal2, Rishabh Jaju3, Shruti Aggarwal1, and Pooja Bihani1

1Department of Anesthesiology & Critical Care, Dr S N Medical College, Jodhpur, 2Department of Anesthesiology & Critical Care, All India Institute of Medical Sciences, Jodhpur, 3Department of Anesthesiology & Critical Care, Andaman Nicobar Island Institute of Medical Sciences, Port Blair, India

Background: Allaying anxiety and providing calm children in the operating room is a challenging task for anesthesiologists. This study was designed to compare the use of nebulized dexmedetomidine and ketamine for premedication in pediatric patients under general anesthesia.

Methods: Seventy patients, aged 2 to 8 years of both sexes, with American Society of Anesthesiologists physical status I/II scheduled for hernia repair surgery under general anesthesia, were randomized to two equal groups using a computer-generated random number table. Patients in group D received dexmedetomidine (2 µg/kg), and patients in group K received ketamine (2 mg/kg) by a jet nebulizer before the induction of anesthesia. The study’s primary objective was comparing the level of sedation, which was achieved at 30 min after a study drug administration using the Ramsay sedation scale, between the two groups. The secondary objectives were the two-group comparison of parental separation anxiety scale, acceptance of the mask, hemodynamic variables, recovery time, incidence of emergence agitation, and adverse events.

Results: The median Ramsay sedation scale at 30 min was 3 (1–4) in group D and 3 (1–3) in group K (P = 0.002). Patients in group D had a more acceptable parental separation anxiety scale (P = 0.001) and a satisfactory mask acceptance scale (P = 0.042).

Conclusions: Nebulized dexmedetomidine (2 µg/kg) provided better sedation along with smooth parental separation and satisfactory mask acceptance during induction of anesthesia with a similar emergence agitation profile and adverse reactions compared to nebulized ketamine in pediatric patients.

Keywords: Conscious sedation; Dexmedetomidine; Ketamine; Nebulization; Pediatrics; Premedication.
INTRODUCTION

For decades, there has been a quest to look out for a reliable and efficacious premedication to allay anxiety and fear of the stressful preoperative period. The leading factors contributing to preoperative anxiety in pediatric patients are parental separation, fear of doctors, needle injections, limited understanding of the nature of the illness, and the need for surgery [1]. Preoperative anxiety and stress responses are responsible for the activation of the sympathetic, parasympathetic, and endocrine systems. Children are likely to develop adverse clinical outcomes such as postoperative psychological trauma, emergence delirium, changes in sleep patterns, and aggression [2,3]. The reduction in preoperative anxiety and distress in children is not only an ethical imperative but also helpful in minimizing postoperative behavioral problems with the aid of a suitable premedication.

An ideal premedication drug should result in a sedated child to allow easy separation of a child from the parents, facilitating smooth induction of anesthesia and a pleasant perioperative experience for both children and parents. Although many studies have reported the effects of benzodiazepines, α-2 agonists, opioids, and ketamine as premedication drugs via various routes, there is no widely accepted drug or route of choice [4–6]. Most of these drugs produce variable sedation, with a risk of respiratory depression. Studies have reported higher bioavailability and fewer adverse events with the nebulized route than with oral or intranasal administration [7–10].

A few studies were available in the literature that compared the nebulized dexmedetomidine and ketamine as a premedication in pediatric patients undergoing inguinal hernia surgery under general anesthesia [11–13]. The hypothesis of this study was that nebulized dexmedetomidine and ketamine as premedications are equally effective in terms of sedation at 30 min in pediatric patients. The primary objective of this study was to assess the level of sedation achieved after 30 min of nebulization and to compare between the two groups, and the secondary objectives were parental separation anxiety scale, mask acceptance scale, recovery time, emergence agitation, hemodynamic changes, and adverse effects.

MATERIALS AND METHODS

Study design

The study was approved by the Institutional Ethical Committee (no. SNMC/IEC/2019/Plan/180) and registered at the Clinical Trial Registry of India (no. CTRI/2019/11/022270) before the commencement of the study. This clinical study was performed in accordance with the ethical principles for medical research involving human subjects outlined in the Helsinki Declaration of 1975 (revised 2013). This prospective, randomized study was conducted at a tertiary care teaching hospital between December 2019 and November 2020, after obtaining written informed consent from the parents or guardians. Preoperative evaluation of all patients was carried out one day before the scheduled surgery.

Study population and interventions

1. Participants and eligibility

A total of 70 patients, aged 2–8 years of both sexes, American Society of Anesthesiologists physical status I and II, who underwent hernia repair surgery under general anesthesia (surgical duration less than 60 min), were enrolled in this study.

2. Exclusion criteria

Patients with known allergy to the study drug, upper respiratory tract infection, any nasal disorders such as recurrent nasal bleed or nasal masses, or congenital heart disease, children with increased intracranial pressure/intraocular pressure, and children with any psychiatric illness were excluded from the study.

3. Primary objective

The primary objective of the study was to examine the level of sedation achieved at 30 min using the Ramsay sedation scale (RSS).

4. Secondary objectives

The secondary objectives were parental separation anxiety scale, acceptance of the mask, hemodynamic variables, recovery time, incidence of emergence agitation, and adverse events.

5. Randomization

Patients were randomly divided into group D (nebulized
dexmedetomidine 2 µg/kg, 35 patients) and group K (nebulized ketamine, 2 mg/kg, 35 patients) using a computer-generated random number table.

6. Allocation concealment
The group concealment was performed with a sealed opaque envelope by an independent investigator who was not involved in the study. The envelope was opened immediately after the arrival of a child in the preoperative holding area. The drug solution was prepared by an anesthesiologist, who was not involved in the observation or administration of the drug in identical syringes with matching random codes. The study drug was diluted in 4 ml by adding 0.9% normal saline in both groups.

7. Blinding
The observers, attending anesthesiologists, and data collectors were blinded to the drug being administered.

8. Monitoring
Standard American Society of Anesthesiologists monitors such as an electrocardiogram, non-invasive blood pressure, and pulse oximetry were applied, and baseline heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure, mean arterial blood pressure, respiratory rate, and peripheral oxygen saturation were recorded.

9. Intervention
The study drug was administered by a standard hospital jet nebulizer (Romsons Aero Neb nebulizer cup and mask set, Romsons Scientific & Surgical Pvt. Ltd., India) with an oxygen flow of 6 L/min over 10 to 15 min. Nebulization was stopped when the nebulizer started to sputter.

Outcomes
The sedation scale was assessed using the RSS immediately after completion of drug administration (0 min) and every 5 min for 30 min. A score of 3 or 4 was considered acceptable for sedation (Table 1) [14].

Parental separation was assessed 30 min after completion of study drug administration using a four-point parental separation anxiety scale (PSAS) (1 = excellent, easy separation; 2 = good, whimpers, but is easily reassured, not clinging; 3 = fair, cries and cannot be easily reassured, but not clinging to parents; and 4 = poor, crying, and clinging to parents) [15]. PSAS scores of 1 and 2 were considered acceptable separation, while scores of 3 and 4 were considered difficult separation.

Patients’ acceptance was assessed 30 min after completion of study drug administration by mask acceptance scale (MAS) (1 = excellent, unafraid, cooperative, accepts mask easily; 2 = good, slight fear of mask, easily assured; 3 = fair, moderate fear of mask, not calmed with reassurance; 4 = poor, terrified, crying, or combative) [15]. The MAS scores of 1 and 2 denote “satisfactory” mask acceptance, whereas scores of 3 and 4 were considered “unsatisfactory.”

Hemodynamic parameters were recorded after completion of drug administration (0 min) and every 5 min for 30 min.

Anesthesia technique
Anesthesia was induced with 100% oxygen and sevoflurane 8% with the help of a face mask. After loss of consciousness, an intravenous line was secured on the dorsum of the hand, and fentanyl 2 µg/kg intravenously (IV) was administered. The airway was secured using an appropriately sized laryngeal mask airway (LMA). Anesthesia was maintained by a minimum alveolar concentration of 1–1.2% of sevoflurane in a 50% oxygen/air mixture. Paracetamol (15 mg/kg IV) was administered to all patients before the completion of surgery. Upon regaining consciousness, the LMA was removed, and the patient shifted to the post-anesthesia care unit. Emergence agitation (EA) was assessed immediately after removal of LMA (0 min) and every 5 min thereafter until 30 min using the Watcha scale [16].

Anesthesia time (from the time of the start of induction to the time of discontinuation of sevoflurane), surgical time (from the time of incision to the application of last skin suture), and recovery time (from the time of discontinuation of sevoflurane to the time the patient opened his/her eyes on verbal command) were recorded. A fall in HR < 70 beats/min and a fall in SBP > 20% from basal level were considered bradycardia and hypotension, respectively, and man-

Table 1. Ramsay Sedation Scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Patient is anxious and agitated or restless, or both</td>
</tr>
<tr>
<td>2</td>
<td>Patient is cooperative, oriented, and tranquil</td>
</tr>
<tr>
<td>3</td>
<td>Patient responds to commands only</td>
</tr>
<tr>
<td>4</td>
<td>Patient exhibits brisk response to light glabellar tap or loud auditory stimulus</td>
</tr>
<tr>
<td>5</td>
<td>Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus</td>
</tr>
<tr>
<td>6</td>
<td>Patient exhibits no response</td>
</tr>
</tbody>
</table>
aged accordingly.

Other adverse effects, such as nausea, vomiting, and hypersalivation, were documented and managed according to the standard protocol.

Sample size calculation

The sample size was calculated based on a previous study [11]. The proportion of patients who achieved adequate sedation at 30 min after drug administration was 46% in the dexmedetomidine group and 13% in the ketamine group. Considering 80% power and 95% confidence intervals, a minimum sample size of 30 children per study group was estimated. To round off and cover the possible dropouts, 35 children in each group were included.

Statistical analysis

The data obtained were entered into a Microsoft spreadsheet and analyzed using Statistical Package for Social Science (SPSS) version 24.0 (IBM Co., USA). The normal distribution of data was confirmed using the Shapiro–Wilk test. It showed that our data were normally distributed, and thus, parametric tests have been used for statistical analysis. The unpaired Student t-test was used for quantitative variables (hemodynamic parameters), and the chi-square test (sedation level, PSAS) and Fisher exact test (emergence agitation, MAS) were used for qualitative variables. Continuous variables are expressed as mean ± SD, and categorical data are presented as numbers and frequencies. A one-way repeated measures ANOVA was conducted to identify significant changes in vital parameters at different time periods. Statistical significance was set at P < 0.05.

RESULTS

A total of 75 children were recruited for the trial. The parents of two patients did not provide consent for participation in the study, and three patients with upper respiratory tract infection were excluded from the study. The remaining 70 patients were randomly divided into two equal groups of 35 patients each (Fig. 1). The demographic data, surgical time, anesthesia time, and recovery time were not statistically significant between the two groups (Table 2).

The median Ramsay sedation scale at 30 min was 3 (1–4) in group D and 3 (1–3) in group K (P = 0.002) (Table 3). At 30 min, 16 (45.7%) patients in group D and 8 (22.8%) patients in group K achieved an RSS of 3 (P = 0.002), whereas RSS 4 was achieved in 6 (17.1%) patients in group D and none in group K (Fig. 2). The parental separation anxiety was within the acceptable range, and mask acceptance was satisfactory in group D compared to group K (Table 4).

Baseline hemodynamic parameters were comparable between the groups. At 25 min and 30 min after premedication, there was a statistically significant difference in the mean HR (P = 0.028, 0.011) between the two groups. Repeated measures ANOVA showed a significant time effect in HR (Wilks’ Lambda = 0.395, P < 0.001) between groups (Fig. 3). At 25 min and 30 min after premedication, there was a statistically significant difference in mean SBP (P = 0.025, 0.015). Repeated measures ANOVA showed no significant time effect in SBP (Wilks’ Lambda = 0.844, P < 0.384) between groups.

Intraoperative and postoperative hemodynamic parameters were comparable in both groups. None of the patients reported an episode of bradycardia or hypotension requiring intervention in either group after premedication. Thirty minutes after removal of LMA, 2.8% of children in the dexmedetomidine group and 8.5% of children in the ketamine group had EA. One patient in group D and two patients in group K complained of vomiting, and one patient in group K reported hypersalivation in the postoperative period.

DISCUSSION

The findings of this study were higher sedation scales achieved at 30 min, satisfactory parent child separation, and better mask acceptance in children premedicated with nebulized dexmedetomidine compared to nebulized ketamine. Moreover, both drugs had comparable hemodynamics and incidence of postoperative agitation.

Anxiolysis and smooth parental separation are important components of pediatric preoperative preparation. Various drugs, alone and in combination, via different routes were used. The nasal route of drug administration bypasses the enterohepatic circulation, which leads to better bioavailability and avoids the bitter taste of the drug compared to orally administered drugs. The atomizer used for nebulization creates small particulate forms of the drug, creating a thin layer around the buccal, nasal, and respiratory mucosa [9]. The inhaled drugs administered through nebulization were comparatively more effective, quicker onset, and safer than oral or intranasal routes for pediatric premedication [8,9,11,12].

Dexmedetomidine acts on α2 adrenergic receptors of the
**Fig. 1.** CONSORT flow diagram. CONSORT: consolidated standards of reporting trials, ASA PS: American Society of Anesthesiologists physical status, URTI: upper respiratory tract infection.

**Table 2.** Demographic Parameters and Other Clinical Parameters

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group D (n = 35)</th>
<th>Group K (n = 35)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>4.5 ± 1.7</td>
<td>4.5 ± 1.7</td>
<td>0.98</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>27/8</td>
<td>28/7</td>
<td>&gt; 0.99</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>96.2 ± 13.9</td>
<td>98.0 ± 12.6</td>
<td>0.56</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>14.4 ± 4.7</td>
<td>14.5 ± 4.0</td>
<td>0.98</td>
</tr>
<tr>
<td>ASA (I/II)</td>
<td>33/2</td>
<td>34/1</td>
<td>1</td>
</tr>
<tr>
<td>Anesthesia time (min)</td>
<td>37.1 ± 3.9</td>
<td>35.8 ± 2.3</td>
<td>0.09</td>
</tr>
<tr>
<td>Surgery time (min)</td>
<td>31.3 ± 4.1</td>
<td>30.1 ± 2.5</td>
<td>0.14</td>
</tr>
<tr>
<td>Recovery time (min)</td>
<td>9.5 ± 0.5</td>
<td>9.4 ± 0.4</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Values are represented as the mean±SD or number only. ASA: American Society of Anesthesiologists. Group D: dexmedetomidine group, Group K: ketamine group.

**Table 3.** Ramsay Sedation Scale between Groups

<table>
<thead>
<tr>
<th>Time</th>
<th>Group D (n = 35)</th>
<th>Group K (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td>2 (1–2)</td>
<td>2 (1–2)</td>
</tr>
<tr>
<td>5 min</td>
<td>2 (1–2)</td>
<td>2 (1–2)</td>
</tr>
<tr>
<td>10 min</td>
<td>2 (1–3)</td>
<td>2 (1–2)</td>
</tr>
<tr>
<td>15 min</td>
<td>2 (1–3)</td>
<td>2 (1–2)</td>
</tr>
<tr>
<td>20 min</td>
<td>2 (1–3)</td>
<td>2 (1–2)</td>
</tr>
<tr>
<td>25 min</td>
<td>3 (1–4)</td>
<td>2 (1–3)</td>
</tr>
<tr>
<td>30 min</td>
<td>3 (1–4)</td>
<td>3 (1–3)</td>
</tr>
</tbody>
</table>

Values are represented in median (range). Group D: dexmedetomidine group, Group K: ketamine group.

Locus coeruleus, resulting in quicker onset of sedation, mimicking natural sleep with less respiratory depression. Simultaneously, dexmedetomidine sedation is characterized by easy arousability without affecting the orientation and cooperation of the patient. The bioavailability of dexmedetomidine by non-intravenous routes, such as orogastric (16%), intranasal (65%), buccal (82%), and intramuscular (104%) [17–19]. Ketamine, a phencyclidine derivative, acts on the N-
yl-D-aspartate receptor and produces a state of dissociative anesthesia. Ketamine has been a popular drug for premedication in pediatric patients administered through various routes, but may result in excessive salivation, EA, or postoperative nausea and vomiting [20]. The pharmacokinetic properties of drugs administered through the nebulized route are still being investigated.

At 30 min, the majority of children (16/35, 45.7%) in the nebulized dexmedetomidine group had an acceptable sedation scale of 3, while only a few children (8/35, 22.8%) in the nebulized ketamine group had a sedation scale of 3. Similar results were found in a study by Sabry et al. [13], although they used higher doses compared to our study. They found comparatively calm, sedated children with better mask acceptance and fewer respiratory complications in the group receiving nebulized dexmedetomidine compared to the nebulized ketamine group and a mixture of nebulized ketamine and dexmedetomidine. This indicates that the dexmedetomidine group provided better sedation than the ketamine group.

Intranasal dexmedetomidine (2 µg/kg) was as effective as intranasal dexmedetomidine combined with ketamine (2 µg/kg + 1 mg/kg) for sedation during transthoracic echocardiography, with shorter recovery and discharge times, although the onset time was longer. The probable reason for delayed recovery and prolonged hospital stay in the combination group could be the excessive dose used for premedication [21].

However, both drugs have a different pharmacokinetic

---

### Table 4. Parental Separation Anxiety Scale and Mask Acceptance Scale

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group D (n = 35)</th>
<th>Group K (n = 35)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 – Excellent</td>
<td>9 (25.7)</td>
<td>1 (2.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>2 – Good</td>
<td>15 (42.9)</td>
<td>11 (31.4)</td>
<td></td>
</tr>
<tr>
<td>3 – Fair</td>
<td>5 (14.3)</td>
<td>19 (54.3)</td>
<td></td>
</tr>
<tr>
<td>4 – Poor</td>
<td>6 (17.1)</td>
<td>4 (11.4)</td>
<td></td>
</tr>
<tr>
<td>MAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 – Excellent</td>
<td>2 (5.7)</td>
<td>1 (2.9)</td>
<td>0.042</td>
</tr>
<tr>
<td>2 – Good</td>
<td>12 (34.3)</td>
<td>6 (17.1)</td>
<td></td>
</tr>
<tr>
<td>3 – Fair</td>
<td>7 (20.0)</td>
<td>17 (48.6)</td>
<td></td>
</tr>
<tr>
<td>4 – Poor</td>
<td>8 (22.9)</td>
<td>11 (31.4)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%). PSAS: parental separation anxiety scale, MAS: mask acceptance scale. Group D: dexmedetomidine group, Group K: ketamine group.
profile and their optimal dosage for combination to provide synergistic action while minimizing hemodynamic perturbation, and delayed recovery has not been established yet [22]. Due to delayed recovery with combination therapy, a single drug was used for nebulization in this study. A similar dosage of dexmedetomidine and ketamine via nebulization has been used in previous studies [11,12].

In this study, the PSAS was more satisfactory and MAS scores were higher in the dexmedetomidine group than in the ketamine group. These findings were in accordance with those of a previous study [11]. We also observed a decrease in HR and SBP from the baseline in the dexmedetomidine group due to the cardio-depressant effect, but slightly increased HR and SBP from the baseline in the ketamine group due to sympathetic stimulant properties of ketamine. A statistically significant difference was observed in HR and SBP at 30 min between the two groups. However, hemodynamic changes were clinically insignificant; hence, none of the patients required corrective interventions. Comparable hemodynamics in both groups reflect the usage of a smaller dosage and slower absorption of the drug from the nebulized route; hence, the plasma concentration for producing adverse effects was not built up in the body. Previous studies also demonstrated comparable hemodynamics with nebulized dexmedetomidine, ketamine, or a mixture of both as premedication in children [11–13].

The incidence of EA in pediatric patients ranges from 10 to 60%. In our study, EA was comparable between the groups. A recent systematic review and meta-analysis concluded that dexmedetomidine significantly decreased the incidence of post-anesthesia EA in pediatric patients compared with placebo, midazolam, and opioids [23]. Similarly, Ng et al. [24] also demonstrated the efficacy of ketamine in reducing EA in children undergoing surgery.

There are a few limitations to the present study. The serum concentrations of dexmedetomidine and ketamine after nebulization were not measured because of the lack of kits required for assays. The bioavailability of drugs varies according to the route of administration, and further studies are required to determine the pharmacokinetics and optimal dosage of these drugs administered through nebulization. Second, the time of onset of sedation was not compared in the present study.

**Fig. 3.** Hemodynamic parameters (mean heart rate and mean systolic blood pressure) between groups. SBP: systolic blood pressure, HR: heart rate. Group D: dexmedetomidine group, Group K: ketamine group.
study. Third, the scoring system used for the determination of parental separation and mask acceptance was not validated. Lastly, the results of our study cannot be extrapolated for children younger than 2 years of age.

Dexmedetomidine nebulization had better, acceptable sedation along with smooth separation from parents and had satisfactory acceptance of face mask for induction of general anesthesia compared to nebulized ketamine. Moreover, they had a similar profile for emergence agitation and the incidence of drug-related adverse reactions.

**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 not publicly available but are available from the corresponding author on reasonable request.

**AUTHOR CONTRIBUTIONS**


**ORCID**

Geeta Singariya, https://orcid.org/0000-0002-1887-0851

Namita Malhotra, https://orcid.org/0000-0003-2428-2244

Manoj Kamal, https://orcid.org/0000-0001-8314-0348

Rishabh Jaju, https://orcid.org/0000-0001-8555-0869

Shruti Aggarwal, https://orcid.org/0000-0002-2439-4118

Pooja Bihani, https://orcid.org/0000-0001-8790-1466

**REFERENCES**

13. Ahmad Sabry MI, El Gamal NA, Elhelw N, Ammar RA. Comparison of the use of nebulized dexmedetomidine, ketamine, and a mixture thereof as premedication in pediatric patients under-
going tonsillectomy: a double-blind randomized study. Res
14. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled
15. Davis PJ, Tome JA, McGowan FX Jr, Cohen IT; Latta K, Felder H.
Preanesthetic medication with intranasal midazolam for brief
pediatric surgical procedures. Effect on recovery and hospital
discharge times. Anesthesiology 1995; 82: 2-5.
16. Watcha MF, Ramirez-Ruiz M, White PF, Jones MB, Lagueruela
RG, Terkonda RP. Perioperative effects of oral ketorolac and ac-
etaminophen in children undergoing bilateral myringotomy.
17. Plambech MZ, Afshari A. Dexmedetomidine in the pediatric
18. Anttila M, Penttilä J, Helminen A, Vuorilehto L, Scheinin H. Bio-
availability of dexmedetomidine after extravascular doses in
al. Bioavailability of dexmedetomidine after intranasal admin-
Anaesthesia tutorial of the week tutorial 381 [Internet]. 2018 Jun
atotw/ketamine-recent-evidence-and-current-uses/.
intranasal dexmedetomidine and dexmedetomidine-ketamine
combination sedation for transthoracic echocardiography in
pediatric patients with congenital heart disease: a randomized
22. van den Berg JP, Vereecke HE, Proost JH, Eleveld DJ, Wietasch
JK, Absalom AR, et al. Pharmacokinetic and pharmacodynamic
interactions in anaesthesia. A review of current knowledge and
how it can be used to optimize anaesthetic drug administration.
dine on emergence agitation or delirium in children after anes-
thesia-a systematic review and meta-analysis of clinical studies.
Front Pediatr 2020; 8: 329.
24. Ng KT, Sarode D, Lai YS, Teoh WY, Wang CY. The effect of ket-
amine on emergence agitation in children: a systematic review
Effects of hydrocortisone-presensitized sugammadex on recovery from neuromuscular blockade induced by rocuronium: a rodent in vivo study

Hey-Ran Choi1, Hong-Seuk Yang2, Jae-Moon Choi3, Chungon Park4, Junyong In5, and Yong Beom Kim4

1Department of Anesthesiology and Pain Medicine, Seoul Paik Hospital, Inje University College of Medicine, Seoul, 2Department of Anesthesiology and Pain Medicine, Daejeon Eulji Medical Center, Eulji University College of Medicine, Daejeon, 3Department of Anesthesiology and Pain Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, 4Department of Anesthesiology and Pain Medicine, Gil Medical Center, Gachon University College of Medicine, Incheon, 5Department of Anesthesiology and Pain Medicine, Ilsan Hospital, Dongguk University College of Medicine, Goyang, Korea

Background: Sugammadex is a specific antagonist of aminosteroidal neuromuscular blocking agents with 1:1 binding to guest molecules. Sugammadex can also bind to other drugs having a steroid component in its chemical structure. In this in vivo experiment, we investigated the differences in the recovery of rocuronium-induced neuromuscular blockade using sugammadex pre-exposed with two different concentrations of hydrocortisone.

Methods: The sciatic nerves and tibialis anterior muscles of 30 adult Sprague–Dawley rats were prepared for the experiment. The sciatic nerves were stimulated using a train-of-four (TOF) pattern with indirect supramaximal stimulation at 20 s intervals. After 15 min of stabilization, a 250 µg loading dose and 125 µg booster doses of rocuronium were serially administered until > 95% depression of the first twitch tension of TOF stimulation (T1) was confirmed. The study drugs were prepared by mixing sugammadex with the same volume of three different stock solutions (0.9% normal saline, 10 mg/ml hydrocortisone, and 100 mg/ml hydrocortisone). The recovery of rats from neuromuscular blockade was monitored by assessing T1 and the TOF ratio (TOFR) simultaneously until T1 was recovered to > 95% and TOFR to > 0.9.

Results: In the group injected with sugammadex premixed with a high concentration of hydrocortisone, statistically significant intergroup differences were observed in the recovery progression of T1 and TOFR (P < 0.050).

Conclusions: When sugammadex was pre-exposed to a high dose of hydrocortisone only, recovery from neuromuscular blockade was delayed. Delayed recovery from neuromuscular blockade is not always plausible when sugammadex is pre-exposed to steroidal drugs.

Keywords: Hydrocortisone; Neuromuscular blockade; Neuromuscular blocking agent; Neuromuscular junction; Rocuronium; Sugammadex.
INTRODUCTION

Sugammadex is a prime antagonist of aminosteroidal neuromuscular blocking agents (NMBAs), especially rocuronium [1–3]. It directly encapsulates and inactivates rocuronium at the molecular level in a 1:1 manner [4]. Before the introduction of sugammadex, the main method of antagonizing neuromuscular blockade was by administering anticholinesterase, to increase acetylcholine levels in neuromuscular junctions, thereby competing with rocuronium in binding to postsynaptic nicotinic acetylcholine receptors [5,6]. However, this indirect manner of antagonizing neuromuscular blockade has a ceiling effect in reversing rocuronium-induced neuromuscular block, giving rise to limitations and considerations, such as the depth of neuromuscular block at the time of reversal [7]. In contrast, the mechanism of sugammadex-induced recovery from neuromuscular blockade is through the encapsulation of host molecules and their inactivation [4]. In sugammadex-induced antagonism, the depth of neuromuscular block at the time of reversal is irrelevant, which means that increasing the dose of sugammadex enables rapid recovery from a deep or intense neuromuscular block [1,3]. However, besides rocuronium, the host-guest binding property of sugammadex includes other molecules that have a steroid component [8]. Nevertheless, their affinity with sugammadex is not as strong as the affinity between rocuronium and sugammadex, and such molecules have minimal or no effects on sugammadex-induced recovery from rocuronium-induced neuromuscular blockade [9,10]. Zwiers et al. [8] reported that the affinity between sugammadex and steroidal NMBAs is strong, such that it is difficult for other molecules to displace their host-guest bonds. Choi et al. [9] reported that sugammadex-induced recovery from neuromuscular blockade was not affected by the clinical concentration of remifentanil, although the recovery may be delayed when an extremely high concentration of remifentanil is used. Choi et al. [10] reported that dexamethasone and hydrocortisone do not affect sugammadex-induced reversal of neuromuscular blockade. These observations were made when the drugs were in the form of free molecules. In other words, hydrocortisone and dexamethasone competed with rocuronium to simultaneously bind sugammadex. However, in clinical settings, sugammadex is usually administered through the intravenous (IV) line, which is a common route for the delivery of other drugs. If drugs with good affinity to sugammadex are present in the IV access line, sugammadex can bind to these drugs. Consequently, this might affect sugammadex-rocuronium binding in the bloodstream, which, in turn, might affect the sugammadex-induced recovery from the neuromuscular blockade. Therefore, we hypothesized that sugammadex-induced recovery from the neuromuscular blockade might be affected when sugammadex is premixed with molecules that have an affinity for it. In this in vivo experiment, we investigated the differences in the recovery of rocuronium-induced neuromuscular blockade between groups of anesthetized rats injected with sugammadex pre-exposed with two different concentrations of hydrocortisone or the same dose of sugammadex alone. We compared the T1 twitch tensions and train-of-four (TOF) ratios (TOFR) between the groups.

MATERIALS AND METHODS

The study protocol was approved by the Ethics Committee of the Laboratory of Animal Research, Asan Institute of Life Science (Seoul, Korea) on May 1, 2019 (no. 2019-13-083). All methods were performed in accordance with the Animal Research: Reporting of In Vivo Experiments (ARRIVE) guidelines and regulations. Thirty male Sprague-Dawley (SD) rats with an average age of 4–6 weeks were used in this study. The average body weight at the time of main experiment was 240.53 ± 6.01 g (range 225–250 g). All animals were bred at a constant temperature of 22°C under a regular diurnal cycle, with food and water supplied ad libitum. During the experiment, the temperature of the rats was monitored using a rectal thermistor and maintained at 35.5–37°C with a heat lamp.

Each rat was anesthetized with an intraperitoneal injection of 0.5 mg/kg urethane (Sigma-Aldrich Korea, Korea). Adequate anesthetic levels were confirmed by pinching the hind limbs with a clamp. After confirming that there were no responses to clamp pinching, preparations for the experiment were started. First, a tracheostomy was performed and a Y-tube was placed. Intrajugular venous cutdown was performed and an IV catheter was inserted. The tendons of both the tibialis anterior muscles were exposed and cut at their insertion sites. A black silk string was tied to each tendon and a lasso was made to hook the Grass FT03 force transducer (Grass Technologies, USA). The sciatic nerves in both glutal regions were exposed and fixed to platinum bipolar electrodes. The rat was then placed on a tray with both knees clamped and fixed to the frames of the tray. Platinum bipolar electrodes at both sciatic nerves were connected to a
Grass S88 stimulator (Grass Technologies), and the lassos at the tendons of both tibialis anterior muscles were hooked to the force transducer. Four 2 Hz indirect stimulations (TOF stimulations) were supplied to the sciatic nerves every 15 s. Supramaximal stimulation was set at 10% above the level of the current with which there was no further increase in the twitch tensions of both tibialis anterior muscles. A stabilization time of 15 min was allowed with mechanical ventilation with ambient air at 90–110 breaths/min and a tidal volume of 6–8 ml/kg, which was supplied with a rodent ventilator model 683 (Harvard Apparatus, USA). Experiments were conducted when T1 was consistent and maintained during resting time. The inclusion criteria were T1 twitch ≥ 200 mN, maintained for ≥ 15 min. However, the experiments were stopped and excluded if the monitored muscle twitch tensions were ≤ 200 mN or serially decreased to 0 mN. Data were excluded when the T1 twitch tension gradually decreased before the addition of the study drugs or when the maximum recovery of T1 twitch tension was ≤ 50 mN within 10 min.

In the initial set of experiments, the cumulative dose-response data of rocuronium (MSD Korea, Korea) were obtained with a loading dose of 250 μg and booster doses of 125 μg repeatedly injected until > 95% depression of T1 was observed. The total dose of rocuronium used at that point was defined as the effective dose (ED₉₅). The next booster dose injection was considered when the depression in muscle twitch tension depression was ≤ 3% or tended to increase compared with the previous twitch tension. The study drugs were prepared by mixing 1 mg/kg sugammadex (MSD Korea) with the same volume of 0.9% isotonic saline (control group), 10 mg/ml hydrocortisone (SGX + Low group), and 100 mg/ml hydrocortisone (SGX + High group). Hydrocortisone was purchased from Hanall Biopharma (Korea). After confirming that the responses to the TOF stimulations were 0, the ED₉₅ of rocuronium was injected. When the T1 responses reappeared, the allocated experimental drugs were injected, and the T1 twitch tensions and TOFR were serially monitored and recorded. The time interval from the injection of the study drugs to the point of 95% recovery of T1 twitch tension was recorded and compared between the groups. TOFRs were simultaneously obtained, while the recovery of T1 was monitored. The regression curves of these variables were compared between groups. Muscle twitches were sensed and changed through an electric signals using Grass FT03 force transducers, which were displayed and stored using the PowerLab 4/26 data acquisition system (AD Instruments, Australia) and LabChart 7 software (AD Instruments, USA). In addition, deeply anesthetized SD rats were placed in the CO₂ chamber or removed from mechanical ventilation after IV injection of rocuronium and intraperitoneal injection of urethane. The protocol of the main experiment is summarized in Fig. 1.

Data are expressed as mean ± standard deviation. Statistical analysis was performed using SPSS version 13.0 software (SPSS Inc., USA). Rats were allocated to each group (control, SGX + Low, and SGX + High) using random numbers generated with the following equation in Microsoft Excel 2010 program (Microsoft Office; Microsoft Corporation, USA); \( f_i = (INT(RAND(*3))) + 1 \). For group blinding, the principal investigator prepared premixed, non-labeled study drugs during the stabilization time and cumulative dose-response study of rocuronium, and provided them to the researcher when all TOF responses had disappeared. Recovery data were plotted by fitting nonlinear regression curves to group data. We used the equations \( y = 100 + \Omega (x - b)^3 \) and \( y = 1 + \lambda(x - c)^3 \) to describe T1 and TOFR recovery, respectively (\( R^2 > 0.8 \)). In these equations, \( y \) represents T1 or TOFR, \( x \) represents the time set from 5% T1 recovery (taken as the zero point) or injection of the study drug, \( b \) and \( c \) respectively represent the virtual time to > 95% T1 recovery, and > 0.9 TOFR, while the slope of each regression curve is denoted by \( \Omega \) and \( \lambda \). Differences in continuous variables among the groups were analyzed using analysis of variance, followed by the Bonferroni method for multiple pairwise comparisons. The mean group values of \( \Omega \) and \( \lambda \) were compared using the Kruskal–Wallis test. Statistical significance was set at \( P < 0.05 \). The primary objective of the present experiment was to determine the differences in recovery progression of rocuronium-induced neuromuscular blockade between groups by comparing slopes of the regression curves, which are represented as \( \Omega \) and \( \lambda \). The sample size of the present study was calculated following previous experiments [11,12] and a pilot study based on the slope of recovery time (\( \Omega \)) of T1 to reach > 95% of the initial T1. Although there are some issues with sample size estimation in in vivo neuromuscular studies, the calculation suggested that 10 samples per group would be sufficient at an \( \alpha = 0.05 \), a power of 0.80, and a dropout rate of 10%.

**RESULTS**

No statistically significant differences in body weight, weight of tibialis anterior muscles, and rocuronium dose
were observed among the groups (Table 1). Figs. 2 and 3 show the recovery data for T1 and TOFR, respectively. In Figs. 2A and 3A, the dot, triangle, and diamond symbols represent data obtained from the control, SGX + Low, and SGX + High groups, respectively. Solid, dashed, and dash-dot fitting lines represent the recovery progression and regression lines of the control, SGX + Low, and SGX + High groups, respectively. In Fig. 2, the regression line of each group is expressed as $y = 100 + \Omega(x - b)^3$, and the average values of $\Omega$ and $b$ were compared between the groups. The coefficients of determination ($R^2$) of all groups were well over 0.7 as listed in Table 2. $\Omega$ in the SGX + High group was statistically different from that in the control or SGX + Low groups (Fig. 2B, $P = 0.001$). The average $b$ represents the expected time to achieve 100% recovery of the T1 twitch tension. In SGX + High, the average $b$ was 374.8 s, which was significantly longer than that in the control (208.7 s) or SGX + Low (280.3 s) group ($P < 0.001$, and 0.037, respectively). Fig. 3 shows the

**Table 1.** Characteristics of Rats and Tissue Specimen

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 10)</th>
<th>SGX + Low (n = 10)</th>
<th>SGX + High (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BW (g)</td>
<td>240.48 ± 6.34</td>
<td>239.89 ± 6.23</td>
<td>241.24 ± 5.45</td>
</tr>
<tr>
<td>TA (mg)</td>
<td>374.29 ± 21.53</td>
<td>375.72 ± 23.72</td>
<td>368.51 ± 18.64</td>
</tr>
<tr>
<td>Roc (µg)</td>
<td>390.63 ± 104.32</td>
<td>375.06 ± 102.60</td>
<td>392.86 ± 112.47</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD. BW: body weight of the rat, TA: wet weight of the tibialis anterior muscle, Roc: average dose of rocuronium, SGX: sugammadex. No statistically significant differences were observed between the groups ($P > 0.05$).

**Table 2.** Coefficients of Determination

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 10)</th>
<th>SGX + Low (n = 10)</th>
<th>SGX + High (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R^2$ for T1 recovery</td>
<td>0.96 ± 0.01</td>
<td>0.97 ± 0.02</td>
<td>0.94 ± 0.05</td>
</tr>
<tr>
<td>$R^2$ for TOFR</td>
<td>0.86 ± 0.1</td>
<td>0.87 ± 0.08</td>
<td>0.89 ± 0.09</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD. The equation for the regression curves of T1 recovery was set as $y = 100 + \Omega(x - b)^3$. The equation for the regression curves of TOFR recovery was set as $y = 1 + \lambda(x - c)^3$. In these equations, $y$ represents T1 or TOFR, $x$ represents the time set from 5% T1 recovery (taken as the zero point) or injection of the study drug, $b$ and $c$ represent virtual time for reaching > 95% T1 and > 0.9 TOFR, respectively, and $\Omega$ and $\lambda$ represent the progression slope of each regression curve. SGX: sugammadex, TOFR: train-of-four ratio.
Fig. 2. Comparison of the progression of recovery of T1. We used the equation of $y = 100 + \Omega(x - b)^3$ where $y$ represents T1, $x$ represents the time set from 5% T1 recovery (taken as the zero point), $b$ represent the virtual time to > 95% T1 recovery, and $\Omega$ represent the slope of each regression curve. In (A), the T1 recovery progression in the SGX + High group (diamond, dash-dot line) was significantly delayed comparing with the control (dot, solid line), or SGX + Low (triangle, dashed line) group. In the box plot in (B), the mean value of $\Omega$ in the SGX + High (cross hatched box) was significantly lower than that of the control (hollow box), or SGX + Low (single hatched box) groups ($^{*}P = 0.001$). However, there were no significant differences in $\Omega$ between the control and SGX + Low groups ($P > 0.05$). T1: first twitch tension of train-of-four stimulation, SGX: sugammadex.

Fig. 3. Comparison of the progression of TOFR recovery. We used the equation of $y = 1 + \lambda(x - b)^3$ where $y$ represents TOFR, $x$ represents the time set from injection of the study drug (taken as the zero point), $c$ represent the virtual time to > 0.9 TOFR, and $\lambda$ represent the slope of each regression curve. In (A), the TOFR in the SGX + Low (triangle, dashed line) and SGX + High (diamond, dash-dot line) groups showed significantly slower recovery than that of the control (dot, solid line) group. In the box plot in (B), the mean value of $\lambda$ in control (hollow box) group was significantly higher than that in the SGX + Low (single hatched box, $P = 0.006$) and SGX + High (cross hatched box, $P = 0.004$) groups. T1: first twitch tension of train-of-four stimulation, SGX: sugammadex, TOFR: train-of-four ratio.

data for the recovery of TOFR, which appeared to be delayed in the SGX + High group. The mean value of $\lambda$ in SGX + High group was lower than that in the control or SGX + Low groups (Fig. 3B, $P = 0.006$, and 0.004, respectively). However, when comparing $\lambda$ between the control and SGX + Low groups, there were no statistically significant differences ($P$
Effects of sugammadex preexposed to steroids

This in vivo experiment demonstrated that T1 recovery might be delayed when sugammadex is pre-exposed with hydrocortisone before binding to rocuronium. In the present experiment, we premixed sugammadex with two different concentrations of hydrocortisone and injected the mixture into SD rat; thereafter, we simulated the environment in which sugammadex is bind to hydrocortisone before it binds to rocuronium. In clinical practice, IV extension lines and three-way connectors are often used because of the patient positioning and to allow easy access to additional fluids or drugs. The longer these lines are, the more time it takes for the drugs to remain inside them. Therefore, it is possible for the administered drugs to react with each other in the IV line before they reach the body to exert their own effects. Sugammadex binds to these molecules in a 1:1 manner and chelates them. However, this reaction often occurs when a steroid component is present in the structure of molecules. Zwiers et al. [8] reported that, although most drugs have a lower affinity to sugammadex than rocuronium and have minimal effects on sugammadex-induced recovery from neuromuscular blockade, some drugs have a fair affinity to sugammadex including drugs used during anesthesia induction and maintenance. Hydrocortisone is an adjuvant drug that has long been used during anesthesia and surgery.

Hydrocortisone and other glucocorticoids are used to treat reactive adverse events of the airway during intubation, acute nerve injury, nausea, and vomiting, as well as for immunosuppression during organ transplantation [13]. Recently, several recommendations have been published regarding the perioperative use of glucocorticoids [14,15]. Therefore, perioperative administration of glucocorticoids is increasingly being performed according to surgical and anesthetic conditions to improve prognosis, although more reliable evidence is still required [16]. Many researchers have investigated the potential for interactions between sugammadex and drugs other than rocuronium [17–19]. Generally, cyclodextrin interacts with benzene primarily through attractive van der Waals interactions, whose values change from approximately -10 to -13 kcal/mol during the binding of the molecules, which is opposed to the loss of configurational entropy [20]. As the backbone of sugammadex is a γ-cyclodextrin molecule, it may follow a mechanism similar to that of “guest” molecules. Stronger binding forces make the host-guest species more strongly immobilized. This leads to greater losses in configurational entropy [20,21]. Consequently, sugammadex molecules that react with guest molecules rather than rocuronium molecules do not react like free molecules. In this situation, the patterns of recovery from rocuronium-induced neuromuscular blockade will not be the same as those with “free” sugammadex. Our study followed this concept and obtained favorable results. In the present study, sugammadex was pre-exposed to two different concentrations of hydrocortisone, (10 mg/ml and 100 mg/ml), and the different mixtures showed different results. When 10 mg/ml hydrocortisone was used, the progression of the T1 recovery was not different from that of the control group. T1 and TOFR recovery was delayed in the group administered 100 mg/ml hydrocortisone. To find the differences between the groups, we compared Ω and λ (representing the slope of each regression curve). Most of the data obtained eventually reached full recovery. These were not only the results of the action of sugammadex but also the results of spontaneous recovery from rocuronium-induced neuromuscular blockade. We focused on the pattern of recovery progression from the neuromuscular blockade. The values of Ω and λ of SGX + High group were statistically different from those of the other groups (Figs. 2B, 3B). The association rate constant \( k_{\text{on}} \) of hydrocortisone is \( 5.48 \times 10^4 \) mol/L, which is much weaker than that of rocuronium \( (1.79 \times 10^7 \text{ mol/L}) \). This implies that the reaction between sugammadex and hydrocortisone might not be as rapid and strong as the reaction between sugammadex and rocuronium. Accordingly, more “free” sugammadex molecules might have remained in the group that was exposed to a low concentration of hydrocortisone. This explained that there were no significant differences between the control and SGX + Low groups. In the SGX + High group, there was a relatively large amount of hydrocortisone molecules, although the affinity of hydrocortisone to sugammadex was relatively weak, and the recovery of T1 and TOFR was delayed when a relatively low dose of sugammadex was used.

This study had several limitations. First, this was a rodent in vivo experiment. As we used SD rats for neuromuscular physiology experiments in our laboratory, the authors are familiar with its handling. In the clinical setting, the recovery time is approximately ≤ 5 min depending on the dose of

\[ = 0.978 \]. When comparing the expectation time to 1.0 of TOFR recovery, we did not find any statistically significant differences between groups \((P = 0.762, 1.000, \text{ and } 0.127 \text{ between the control vs. SGX + Low, SGX + Low vs. SGX + High, and control vs. SGX + High groups, respectively).}

DISCUSSION

This in vivo experiment demonstrated that T1 recovery might be delayed when sugammadex is pre-exposed with hydrocortisone before binding to rocuronium. In the present experiment, we premixed sugammadex with two different concentrations of hydrocortisone and injected the mixture into SD rat; thereafter, we simulated the environment in which sugammadex is bind to hydrocortisone before it binds to rocuronium. In clinical practice, IV extension lines and three-way connectors are often used because of the patient positioning and to allow easy access to additional fluids or drugs. The longer these lines are, the more time it takes for the drugs to remain inside them. Therefore, it is possible for the administered drugs to react with each other in the IV line before they reach the body to exert their own effects. Sugammadex binds to these molecules in a 1:1 manner and chelates them. However, this reaction often occurs when a steroid component is present in the structure of molecules. Zwiers et al. [8] reported that, although most drugs have a lower affinity to sugammadex than rocuronium and have minimal effects on sugammadex-induced recovery from neuromuscular blockade, some drugs have a fair affinity to sugammadex including drugs used during anesthesia induction and maintenance. Hydrocortisone is an adjuvant drug that has long been used during anesthesia and surgery.

Hydrocortisone and other glucocorticoids are used to treat reactive adverse events of the airway during intubation, acute nerve injury, nausea, and vomiting, as well as for immunosuppression during organ transplantation [13]. Recently, several recommendations have been published regarding the perioperative use of glucocorticoids [14,15]. Therefore, perioperative administration of glucocorticoids is increasingly being performed according to surgical and anesthetic conditions to improve prognosis, although more reliable evidence is still required [16]. Many researchers have investigated the potential for interactions between sugammadex and drugs other than rocuronium [17–19]. Generally, cyclodextrin interacts with benzene primarily through attractive van der Waals interactions, whose values change from approximately -10 to -13 kcal/mol during the binding of the molecules, which is opposed to the loss of configurational entropy [20]. As the backbone of sugammadex is a γ-cyclodextrin molecule, it may follow a mechanism similar to that of “guest” molecules. Stronger binding forces make the host-guest species more strongly immobilized. This leads to greater losses in configurational entropy [20,21]. Consequently, sugammadex molecules that react with guest molecules rather than rocuronium molecules do not react like free molecules. In this situation, the patterns of recovery from rocuronium-induced neuromuscular blockade will not be the same as those with “free” sugammadex. Our study followed this concept and obtained favorable results. In the present study, sugammadex was pre-exposed to two different concentrations of hydrocortisone, (10 mg/ml and 100 mg/ml), and the different mixtures showed different results. When 10 mg/ml hydrocortisone was used, the progression of the T1 recovery was not different from that of the control group. T1 and TOFR recovery was delayed in the group administered 100 mg/ml hydrocortisone. To find the differences between the groups, we compared Ω and λ (representing the slope of each regression curve). Most of the data obtained eventually reached full recovery. These were not only the results of the action of sugammadex but also the results of spontaneous recovery from rocuronium-induced neuromuscular blockade. We focused on the pattern of recovery progression from the neuromuscular blockade. The values of Ω and λ of SGX + High group were statistically different from those of the other groups (Figs. 2B, 3B). The association rate constant \( k_{\text{on}} \) of hydrocortisone is \( 5.48 \times 10^4 \) mol/L, which is much weaker than that of rocuronium \( (1.79 \times 10^7 \text{ mol/L}) \). This implies that the reaction between sugammadex and hydrocortisone might not be as rapid and strong as the reaction between sugammadex and rocuronium. Accordingly, more “free” sugammadex molecules might have remained in the group that was exposed to a low concentration of hydrocortisone. This explained that there were no significant differences between the control and SGX + Low groups. In the SGX + High group, there was a relatively large amount of hydrocortisone molecules, although the affinity of hydrocortisone to sugammadex was relatively weak, and the recovery of T1 and TOFR was delayed when a relatively low dose of sugammadex was used.

This study had several limitations. First, this was a rodent in vivo experiment. As we used SD rats for neuromuscular physiology experiments in our laboratory, the authors are familiar with its handling. In the clinical setting, the recovery time is approximately ≤ 5 min depending on the dose of...
sugammadex used. The use of 2 mg/kg sugammadex during a moderate neuromuscular block and 4 mg/kg sugammadex during a deep neuromuscular block resulted in ≤ 3 and 5 min of recovery time to TOFR > 0.9, respectively [3,22,23]. However, when we designed the present study and performed a pilot study, the TOFR recovery time was ≤ 1 min when 2 mg/kg of sugammadex was used. Moreover, T1 was fully recovered within 30 s. Within this time interval, sufficient cumulative data of T1 and TOFR per rat could not be obtained because only one or two data points were obtained. Therefore, we reduced dose of sugammadex to 1 mg/kg. This discrepancy between the in vivo experiment and the clinical setting means that the postoperative residual block remains an issue [24,25]. Second, this study focused on sugammadex premixed with hydrocortisone. In the pilot study, we needed to determine the adequate concentration of hydrocortisone because we found no data about the amount of hydrocortisone remaining in the IV lines after injection. Hydrocortisone stock solutions were prepared at 0.1, 1, 10, and 100 mg/ml in the pilot study. When the 0.1 and 1 mg/ml stock solutions were used, no statistical significance was observed. Meanwhile, stock solutions with concentrations of 10 and 100 mg/ml showed ambiguous results or statistical differences. Although the total volume of the IV extension line varies according to its length, we considered that it contained 8–10 ml of fluid. As such, we speculated that the minimum concentration of hydrocortisone might be obtained when 100 mg/ml hydrocortisone was mixed with 10 ml of fluid. Therefore, we selected 10 and 100 mg/ml stock solutions in the main experiment. We used a hydrocortisone product available at 100 mg/vial. It is commonly melted in 1 ml of solvent and injected via a bolus or mixed with IV fluid. Therefore, sugammadex is rarely pre-exposed with the same concentration of hydrocortisone that we used in the present experiment because it is diluted with the fluid in the IV line and sugammadex may not directly mix with the hydrocortisone fluid. We believe that there is a low possibility that sugammadex is completely pre-exposed by hydrocortisone. Although these drugs are administered simultaneously, the chemical and biophysiological environment in the clinical setting is different from that in our experiment. However, because there are products containing 500 mg hydrocortisone per vial and extremely high doses of steroids can be used as steroid pulse therapy or for other purposes of the positive effects of steroids [16]. The environment we set in the present study might still occur in clinical practice and sugammadex-induced recovery from neuromuscular block-ade might be delayed by pre-exposure with steroids. Finally, the regression equations we used were valid only for the present experiment data. In the present study, data collection was ended as soon as T1 recovery or TOFR reached 100% or 0.9, respectively. As we mentioned earlier, the present data fit well by these equations (R² > 0.8) within the range of time we monitored and collected the data. However, these results were confined to the present data because the data after recovery of T1 and TOFR were not included in this study. In the clinical setting, if initial calibration failed or acceleromyography was used for neuromuscular monitoring, T1 and TOFR might be over 100% and 1.0, respectively. However, under general conditions, T1 and TOFR remained stable after they reached full recovery.

In conclusion, our experiment showed that although sugammadex has a greater affinity for rocuronium than most other drugs, it is possible that the T1 and TOFR recovery times might be delayed when sugammadex is pre-exposed to drugs with a relatively high affinity to it. Fortunately, delays in the recovery from neuromuscular blockade induced by sugammadex which is pre-exposed to steroids are not mandatory. However, sugammadex-induced recovery from neuromuscular blockade might be delayed when there is sufficient time and quantity of steroids pre-exposed to sugammadex.

**FUNDING**

None.

**CONFLICTS OF INTEREST**

Junyong In 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.

Yong Beom Kim has been an editor of the Anesthesia and Pain Medicine since 2015; 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.

**DATA AVAILABILITY STATEMENT**

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

**AUTHOR CONTRIBUTIONS**

Conceptualization: Jae-Moon Choi, Hong-Seuk Yang, Yong Beom Kim. Data curation: Hey-Ran Choi, Jae-Moon Choi, Hong-Seuk Yang, Junyong In, Yong Beom Kim. Formal analysis: Hey-Ran Choi, Hong-Seuk Yang, Junyong In, Yong Beom Kim. Funding acquisition: Hong-Seuk Yang. Methodology: Hey-Ran Choi, Jae-Moon Choi, Hong-Seuk Yang, Junyong In. Project administration: Hong-Seuk Yang. Writing - original draft: Hey-Ran Choi, Chungon Park, Yong Beom Kim. Writing - review & editing: Hey-Ran Choi, Jae-Moon Choi, Hong-Seuk Yang, Junyong In, Chungon Park, Yong Beom Kim. Investigation: Jae-Moon Choi, Hong-Seuk Yang, Junyong In, Chungon Park, Yong Beom Kim. Resources: Jae-Moon Choi, Hong-Seuk Yang. Supervision: Hong-Seuk Yang.

**ORCID**

Hey-Ran Choi, https://orcid.org/0000-0002-9899-0158

Hong-Seuk Yang, https://orcid.org/0000-0003-2023-8705

Jae-Moon Cho, https://orcid.org/0000-0002-1161-6586

Chungon Park, https://orcid.org/0000-0002-8269-5058

Junyong In, https://orcid.org/0000-0001-7403-4287

Yong Beom Kim, https://orcid.org/0000-0003-2369-6525

**REFERENCES**


15. Woodcock T, Barker P, Daniel S, Fletcher S, Wiss JAH, Tomlinson JW, et al. Guidelines for the management of glucocorticoids during the peri-operative period for patients with adrenal insufficiency: guidelines from the Association of Anaesthetists, the Royal College of Physicians and the Society for Endo-


INTRODUCTION

Sugammadex is a selective muscle relaxant-binding agent with a modified γ-cyclodextrin structure. This can effectively antagonize aminosteroidal non-depolarizing neuromuscular blocking agents. While anticholinesterase reaches the synaptic cleft and must bind to acetylcholinesterase, sugammadex rapidly encapsulates a free neuromuscular blocking agent in the bloodstream without having to enter the synaptic cleft. After that, a concentration gradient is formed, and the neuromuscular blocking agent diffuses into the bloodstream at the receptor site, causing acetylcholine to recombine with the receptor. Due to the differences in these mechanisms, sugammadex exhibits a rapid onset of action [1]. In addition, sugammadex has no muscarinic effects, and neuromuscular blockade can be effectively reversed by adminis-
tration of an appropriate amount along with quantitative neuromuscular monitoring during a deep neuromuscular blockade.

In Korea, sugammadex was introduced in the market in 2013. Its clinical usage has gradually increased, with more than one million vials used by 2019. Although rare, several adverse events have been continuously reported.

Therefore, this study aimed to review all reported cases of adverse events associated with the use of sugammadex to date, that have been reported in Korean population, and to suggest a method to reduce adverse events based on the reported cases, as well as a literature review on this subject.

**MATERIALS AND METHODS**

**Study design**

This study was performed according to the recommendations of the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. The protocol was registered on PROSPERO (no. CRD42021286098, https://www.crd.york.ac.uk/PROSPERO).

**Information sources and search strategy**

Among the cases searched using the keywords “sugammadex”, “Bridion”, “Korea”, “anaphylaxis”, “allergic reaction”, “adverse event”, “adverse effect”, “side effect”, “complication” from January 2013 to December 2020 in *Korean Journal of Anesthesia, Anesthesia and Pain Medicine* (Seoul), KoreaMed, PubMed, EMBASE, Web of Science, and The Cochrane Library-CENTRAL those corresponding to the Korean population were selected. Medical Subject Heading (MeSH) terms were used.

**Data collection process and extracted items**

Two authors extracted data from the original articles, and another author independently confirmed all the extracted data. The collected information included the year of occurrence of adverse events, frequency of occurrence by type of adverse event, and the characteristics of patients, surgery, anesthesia, and adverse events. Patient characteristics included age, sex, height (cm), weight (kg), body mass index (kg/m²), American Society of Anesthesiologists physical status, and allergic history. The surgical characteristics included the type of surgery and surgical time (min). Anesthetic characteristics included the type of anesthesia and the use of a neuromuscular monitoring device. The characteristics of adverse events included the amount of rocuronium used (mg), amount of sugammadex used (mg), amount of sugammadex used per body weight (mg/kg), the time of sugammadex administration, onset time of an adverse event after sugammadex administration (min), and time duration from sugammadex administration to extubation (min).

**Statistical analysis**

We estimated the incidence of sugammadex-induced adverse events based on the frequency of use (corporate secret) and the number of reported cases. Categorical data are described as simple descriptions, numbers, median and percentages. As the incidence of side effects of sugammadex is less than 0.1%, there had been difficulties to secure the number of related cases. Since only 10 cases were reported during the period from January 2013 to December 2020, it was difficult to establish general statistical significance. But fortunately, the reporting efficiency of severe adverse drug reactions has been reported to be five times more than that of non-serious adverse events [2]. Most of the reported sugammadex-related adverse events were life threatening; therefore, we assumed that its reporting efficiency would have been higher than others.

**RESULTS**

**Study selection**

We initially retrieved 497 articles from *Korean Journal of Anesthesia, Anesthesia and Pain Medicine* (Seoul), KoreaMed, PubMed, EMBASE, Web of Science, and The Cochrane Library-CENTRAL. After adjusting for duplicates, 103 studies remained. Out of them, 91 studies were discarded after reviewing the title and abstracts for the following reasons: articles that reported irrelevant topics, were categorized as letter to editors and were not case reports. The full texts of the 12 remaining studies were reviewed in detail; 2 studies were excluded because side effects were not directly related with sugammadex: one was about the adverse event of remifentanil, not sugammadex, and the other one was a delayed onset of action upon re-administration of rocuronium after sugammadex. Thus, 10 cases were finally included in this article (Fig. 1).
Characteristics of the included studies

The 10 cases of adverse events reported in Korea included 5 cases of anaphylaxis, 1 case of cardiac arrest, 1 case of profound bradycardia, 1 case of negative pressure pulmonary edema, and 2 cases of incomplete recovery (Fig. 2). The year or date of occurrence of adverse events was determined based on the publication year of the case reports, as exact years were not reported. There was one case in 2015, two cases in 2016, two cases in 2017, three cases in 2019, and two cases in 2020 (Table 1) [3-12].

In terms of patient, surgical, and anesthetic characteristics, there were three cases with American Society of Anesthesiologists physical status ≥ 3, two cases with emergency surgery, two cases with allergic history (animal hair), and nine cases with neuromuscular monitoring (Tables 1 and 2). A skin prick test was performed in four of five anaphylaxis cases (patients 2 to 5) and a tryptase test was performed in one case (patient 3).

The average dose of sugammadex was 2.87 mg/kg, and there were six cases in which one full vial (200 mg) was used, regardless of the state of neuromuscular recovery. The administration time of sugammadex was immediately after the surgery in two cases, at train of four (TOF) 0 in four cases, at TOF 3 in one case, and after inspection of the clinical signs (handgrip, head lift, straight-leg raising, and tidal volume ≥ 8 ml/kg) without neuromuscular monitoring in one case (Tables 3 and 4).

The time between sugammadex administration and onset of adverse events was within 1 min in one case, 1–5 min in five cases, and 5–10 min in two cases (Tables 3 and 4).

After sugammadex administration, the extubation time was between 1–5 min in three cases, 5–10 min in one case, delayed more than 10 min due to incomplete recovery in two cases, 24 h after surgery in one case, and unknown in three cases (Tables 3 and 4). The case of incomplete recovery entailed underlying diseases, including amyotrophic lateral sclerosis and Duchenne muscular dystrophy.

**DISCUSSION**

The adverse events associated with sugammadex reported to date include hypersensitivity and anaphylaxis, cardiac arrest, profound bradycardia, incomplete reversal, negative pressure pulmonary edema, vomiting, dry mouth, tachycardia, hypotension, coagulopathy, interactions with steroids, and neuronal damage. These cases have also been reported in Korean populations; nevertheless, the incidence of or mortality due to adverse events has not been analyzed over...
the nine years of its clinical use in Korea. Based on the frequency of use and number of reported cases, the incidence of adverse events directly caused by sugammadex in Korea is approximately 0.0007%, and no cases of death caused by sugammadex have been reported to date. However, the actual number of cases are estimated to be higher than this. Potential explanations for this are that there may have been cases not analyzed for case reports. Additionally, cases may have been omitted because the causative drug is unclear. In addition, more than two vials may have been prescribed to one patient to reduce the incidence rate. However, even though the incidence rate is not yet high, certain adverse events can be fatal, and efforts are required to detect adverse events early and reduce the incidence rate.

The points of importance from the results include that there were three cases with American Society of Anesthesiologists physical status 3 and two cases with allergy history; sugammadex was administered immediately after surgery and at TOF 0 in several cases, even though neuromuscular

<table>
<thead>
<tr>
<th>Table 1. Summary of Patient, Operation, Anesthesia by Numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
<tr>
<td>9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2. Characteristics of Patients, Operation, Anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Patient characteristics</td>
</tr>
<tr>
<td>Sex (M/F)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>ASA physical status</td>
</tr>
<tr>
<td>≥ 3</td>
</tr>
<tr>
<td>Allergy history</td>
</tr>
<tr>
<td>Operative characteristics</td>
</tr>
<tr>
<td>Surgery time (min)</td>
</tr>
<tr>
<td>Emergency surgery</td>
</tr>
<tr>
<td>Type of surgery</td>
</tr>
<tr>
<td>Gastroenterology</td>
</tr>
<tr>
<td>Orthopedics</td>
</tr>
<tr>
<td>Neurosurgery</td>
</tr>
<tr>
<td>Urology</td>
</tr>
<tr>
<td>Gynecology</td>
</tr>
<tr>
<td>Otorhinolaryngology</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Anesthetic characteristics</td>
</tr>
<tr>
<td>Type of anesthesia</td>
</tr>
<tr>
<td>Volatile anesthesia</td>
</tr>
<tr>
<td>Neur muscular monitoring used</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number only. BMI: body mass index, ASA: American Society of Anesthesiologists, TIVA: total intravenous anesthesia.
Table 3. Summary of Adverse Events by Patient Numbers

<table>
<thead>
<tr>
<th>Patient</th>
<th>Rocuronium dose (mg)</th>
<th>Sugammadex dose (mg)</th>
<th>Sugammadex dose (mg)/Weight (kg)</th>
<th>Sugammadex administration time</th>
<th>Event onset time after sugammadex administration (min)</th>
<th>Extubation time after sugammadex administration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>100</td>
<td>2</td>
<td>TOF 2</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>200</td>
<td>3.28</td>
<td>End of surgery</td>
<td>2</td>
<td>UKN</td>
</tr>
<tr>
<td>3</td>
<td>40</td>
<td>200</td>
<td>3.13</td>
<td>End of surgery</td>
<td>3</td>
<td>UKN</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>200</td>
<td>2.56</td>
<td>TOF 0</td>
<td>&lt; 10</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>90</td>
<td>200</td>
<td>1.83</td>
<td>TOF 3</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>100</td>
<td>130</td>
<td>2</td>
<td>TOF 2</td>
<td>2</td>
<td>Postoperative day 1</td>
</tr>
<tr>
<td>7</td>
<td>55</td>
<td>400</td>
<td>5.33</td>
<td>TOF 0</td>
<td>2</td>
<td>&lt; 10</td>
</tr>
<tr>
<td>8</td>
<td>70</td>
<td>100</td>
<td>1.96</td>
<td>Confirming clinical signs*</td>
<td>Immediately</td>
<td>UKN</td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>250</td>
<td>4.63</td>
<td>TOF 0</td>
<td>Delayed recovery</td>
<td>15,6</td>
</tr>
<tr>
<td>10</td>
<td>42</td>
<td>100</td>
<td>1.89</td>
<td>TOF 0</td>
<td>Delayed recovery</td>
<td>15</td>
</tr>
</tbody>
</table>

UKN: unknown, TOF: train of four. *Hand grip, head lift, straight-leg raising, tidal volume above 8 ml/kg.

Table 4. Characteristics of Adverse Events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average sugammadex dosage (mg/kg)</td>
<td>2.87 ± 1.23</td>
</tr>
<tr>
<td>Use of entire vial (200 mg) of sugammadex</td>
<td>6</td>
</tr>
<tr>
<td>Sugammadex administration time (min)</td>
<td>2</td>
</tr>
<tr>
<td>End of surgery</td>
<td></td>
</tr>
<tr>
<td>TOF 0</td>
<td>4</td>
</tr>
<tr>
<td>TOF 2</td>
<td>2</td>
</tr>
<tr>
<td>TOF 3</td>
<td>1</td>
</tr>
<tr>
<td>Confirming clinical signs*</td>
<td>1</td>
</tr>
<tr>
<td>Adverse event onset time after sugammadex</td>
<td></td>
</tr>
<tr>
<td>administration (min)</td>
<td></td>
</tr>
<tr>
<td>Immediately (&lt; 1 min)</td>
<td>1</td>
</tr>
<tr>
<td>1 &lt; value ≤ 5</td>
<td>5</td>
</tr>
<tr>
<td>5 &lt; value ≤ 10</td>
<td>2</td>
</tr>
<tr>
<td>No adverse events</td>
<td>2</td>
</tr>
<tr>
<td>Extubation time after sugammadex administration (min)</td>
<td></td>
</tr>
<tr>
<td>1 &lt; value ≤ 5</td>
<td>3</td>
</tr>
<tr>
<td>5 &lt; value ≤ 10</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>2</td>
</tr>
<tr>
<td>Postoperative day 1</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number only. TOF: train of four. *Hand grip, head lift, straight-leg raising, tidal volume above 8 ml/kg.

Monitoring was performed in nine cases; an average of 2.87 mg/kg of sugammadex was administered even though 400 mg was administered in patient 7, and one full vial was used in 6 cases. Currently, 200 mg of sugammadex in one vial is used most commonly in clinical practice. Many practitioners tend to administer the entire 200 mg of sugammadex in one vial, as the remaining amount must be discarded. They also tend to use one full vial to prevent residual neuromuscular block by administering a larger amount than necessary [13]. Of the six cases in which one full vial was used, the use of one vial in a patient weighing 109 kg at TOF 3 was considered appropriate; in three cases, the use of one full vial of sugammadex at TOF 0 was not considered incorrect, but appropriate in consideration of the risk of adverse events. In two cases, the dose of 3.28 mg/kg and 3.13 mg/kg, respectively, without inspection of the TOF after surgery despite TOF monitoring was considered inappropriate. In these two cases, anaphylaxis occurred.

Neuromuscular monitoring provides an easy and effective method to reduce the excessive use of sugammadex. The minimal dose of sugammadex recommended by the manufacturer is 2 mg/kg at a TOF of 2. However, it is sufficient to use less than 2 mg/kg of sugammadex for a TOF of 2 or higher [14]. Therefore, the authors of this study predicted that administering sugammadex appropriately according to the degree of neuromuscular function recovery through quantitative neuromuscular monitoring and avoiding habitual administration of one full vial could effectively reduce the incidence and severity of adverse events. In addition, this can prevent interference in the neuromuscular-blocking effect when re-administering a neuromuscular blocking agent, as reintubation is required after extubation [15].

The most frequent adverse event in this study was anaphylaxis. The main structure of sugammadex, γ-cyclodextrin, is widely used in everyday life as a solubilizer or stabilizer for food and cosmetics. For the average person, the amount of γ-cyclodextrin consumed per day is 4–8.8 g [16]. This may have resulted in sensitization, which caused hypersensitivity to sugammadex. Therefore, even a patient ex-
posed to sugammadex for the first time may exhibit hypersensitivity due to cross-reactivity. Given that two out of five patients with cases of anaphylaxis had a history of allergies, a history of allergy itself may also help predict the occurrence of anaphylaxis. Anaphylaxis for sugammadex is thought to be mostly associated with IgE-mediated hypersensitivity (type 1 hypersensitivity). Therefore, as a diagnostic test, a skin test such as intradermal testing and skin prick test, and a tryptase test that can determine the activation of mast cells may be helpful [17]. Recently, it has been found that hypersensitivity not related to sugammadex-specific IgE or IgG exists. There are reports that anaphylaxis is caused by sugammadex-rocuronium complex and sugammadex molecules together, and not by the sugammadex molecule itself [18]. Unlike that of other drugs, the hypersensitivity reaction to sugammadex is dose-related. According to Min et al., no anaphylaxis occurred in 151 patients administered 4 mg/kg, but one case of anaphylaxis occurred in 148 patients administered 16 mg/kg [19]. Anesthesiologists should always be aware that anaphylaxis may occur within 10 min of sugammadex administration, even in patients with no allergic history in the past, and the relationship with the dose should also be considered.

Sugammadex is known to cause a third-degree atrioventricular block, QT prolongation, and coronary vasospasm, leading to profound bradycardia and cardiac arrest [20]. Such complications occurred in healthy patients with no underlying cardiac diseases. In Korea, cardiac arrests have occurred in a patient with no underlying cardiac disease or symptoms other than atypical chest pain [8]. Importantly, the severity may increase in proportion to the dose, as the cardiovascular effect of sugammadex is associated with free sugammadex molecules [21]. Therefore, in all patients administered sugammadex, cardiovascular monitoring must be performed for at least 10 min after administration, with appropriate dosing of sugammadex.

Negative pressure pulmonary edema is thought to have occurred due to rapid recovery of respiratory force due to administration of sugammadex in the presence of upper airway collapsibility, such as laryngospasm [22]. When a large inspiratory force is applied in the state of obstruction in the upper airway, a large intrathoracic negative pressure is created to increase the blood flow to the pulmonary vasculature. As a result, pulmonary edema may occur due to an excessive increase in hydrostatic pressure and distension of the pulmonary vessel [23]. Even in this case, excessive use of sugammadex could be problematic. The reason for this is that if laryngospasm is severe, it may be necessary to administer an additional neuromuscular blocker for reintubation [24]. At this time, free sugammadex molecules may interfere with neuromuscular blockade. Therefore, in this case, another type of neuromuscular blocking agent should be used. In addition, when excessive sugammadex is administered, T4 recovery is faster than expected, before T1 recovery, and the TOF ratio may increase, leading to errors in judgment [25]. From another point of view, negative pulmonary edema can also occur due to residual neuromuscular block. Inspiratory muscles, such as the diaphragm, are resistant to neuromuscular block agents and tend to be blocked less intensively or recover faster. Therefore, the onset and offset of neuromuscular blocking agents are more rapid [26]. Eikermann et al. reported that four patients displayed upper airway obstruction in the state of minimal residual neuromuscular block at a TOF ratio of 0.83 ± 0.06. This is because inspiratory muscles are less susceptible to curarization than expiratory muscles [27]. Negative pulmonary edema is also predicted to occur because of such an imbalance. Therefore, anesthesiologists should keep in mind that negative pressure pulmonary edema can occur due to residual neuromuscular block as well as rapid recovery by sugammadex and should focus on maintaining airway patency.

In two cases of incomplete recovery, there were underlying neuromuscular diseases (amyotrophic lateral sclerosis and Duchenne muscular dystrophy). In both cases, sugammadex was administered at TOF 0, and the time to extubation after sugammadex administration was 15.6 min and 15 min, respectively. However, the presence of neuromuscular diseases does not necessarily cause delayed recovery [28], and although rare, delayed recovery may occur in healthy patients [29]. Since these patients may also experience additional adverse events due to excessive sugammadex, determining the appropriate dose of sugammadex through quantitative neuromuscular monitoring will help prevent adverse events.

This study has several limitations. First, as the number of cases was small due to difficulties in obtaining the data; therefore, there may have been insufficient power to detect statistical significance. However, even based on the cases reported so far, increased attention to the monitoring of neuromuscular function and patients’ vital signs in conjunction with the use of sugammadex seems to be effective in reducing the incidence and severity of adverse events. Second, it was not known whether neuromuscular monitoring was performed after surgery. There was no mention of residual
paralysis in any of the ten cases. Since the authors of this study aimed to suggest the administration of sugammadex at an appropriate dose, such a suggestion may have been better supported if stability against residual paralysis was ensured by postoperative neuromuscular monitoring.

In conclusion, a review of the cases of adverse events directly caused by sugammadex in the Korean population shows that the incidence and severity of adverse events could be reduced through routine neuromuscular monitoring and careful administration of sugammadex [14]. In addition, sufficient recovery time as well as monitoring is required until extubation after administration [20]. Recently, sugammadex dose-ranging studies based on cost-saving strategies have been conducted. These studies commonly emphasize quantitative neuromuscular monitoring to prevent residual neuromuscular block [30]. A better guideline for sugammadex administration is required to contribute not only to cost-effectiveness but also to the reduction of adverse effects.

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: Woong Han, Dong Ho Park, Chang Yeong Jeong, Hong Seuk Yang. Data curation: Woong Han, Dong Ho Park, Hong Seok Yang. Formal analysis: Woong Han, Jong Min Lee, Hong Seok Yang. Methodology: Woong Han, Dong Ho Park, Chia An Lee, Chang Yeong Jeong, Hong Seuk Yang. Project administration: Woong Han, Chia An Lee, Chang Yeong Jeong, Hong Seuk Yang. Visualization: Woong Han, Chia An Lee, Chang Yeong Jeong, Hong Seok Yang. Writing - original draft: Woong Han, Jong Min Lee. Writing - review & editing: Dong Ho Park, Chia An Lee, Chang Yeong Jeong, Hong Seuk Yang.

ORCID

Woong Han, https://orcid.org/0000-0001-5589-6279
Jong Min Lee, https://orcid.org/0000-0003-2564-1624
Dong Ho Park, https://orcid.org/0000-0002-6587-3756
Chia An Lee, https://orcid.org/0000-0001-9143-7133
Chang Yeong Jeong, https://orcid.org/0000-0003-3951-1222
Hong Seuk Yang, https://orcid.org/0000-0003-2023-8705

REFERENCES

Comparison of two-lung and one-lung ventilation in bilateral video-assisted thoracoscopic extended thymectomy in myasthenia gravis: a retrospective study

Mijung Yun¹, Gunn Hee Kim¹, Sung-chul Ko¹, Yun Jae Han¹, and Wooshik Kim²

Departments of ¹Anesthesia and Pain Medicine, ²Cardiothoracic Surgery, National Medical Center, Seoul, Korea

Background: Myasthenia gravis (MG) is an autoimmune disease, and early thymectomy is recommended. Since the introduction of video-assisted thoracoscopic surgery, the safety and effectiveness of carbon dioxide insufflation in the thoracic cavity (capnothorax) has been controversial. This study aimed to compare the safety and effectiveness of ventilation methods in bilateral video-assisted thoracoscopic extended thymectomy (BVET) with capnothorax.

Methods: We retrospectively investigated the medical records of patients with MG who underwent BVET between August 2016 and January 2018. Patients were divided into two groups: group D (n = 26) for one-lung ventilation and group S (n = 28) for two-lung ventilation. We set nine anesthesia time points (T0–T8) and collected respiratory and hemodynamic variables, including arterial O₂ index (PaO₂/FiO₂).

Results: SpO₂ at T1–T3 and T8 was significantly lower in group D than in group S. The FiO₂ in group S was lower than that in group D at all time points. The number of PaO₂/FiO₂ ≤ 300 and PaO₂/FiO₂ ≤ 200 events was significantly higher in group D than in group S. Hemodynamic variables were not significantly different between the two groups at any time point. The duration of surgery and anesthesia was shorter in group S than in group D.

Conclusions: This retrospective study suggests that anesthesia using two-lung ventilation during BVET with capnothorax is a safe and effective method to improve lung oxygenation and reduce anesthesia time.

Keywords: Myasthenia gravis; One-lung ventilation; Thymectomy; VATS.

INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disease that affects nicotinic acetylcholine receptors in neuromuscular junctions. It mainly affects women in their 20s and 30s and can be treated with medical or surgical treatment. Generally, early thymectomy is recommended for early onset MG [1,2]. After Dr. Alfred Blalock succeeded in performing thymectomy in thymomatous MG patients using upper partial midline sternotomy in 1936, thymectomy in MG patients began to be widely performed [3]. However, sternotomy was accompanied by several side effects, such as bleeding, longer...
duration of hospitalization, and cosmetic problems. In the 1990s, video-assisted thoracic surgery (VATS) became popular and was introduced in various thoracic and mediastinal surgeries, such as sympathectomy, esophageal resection, and thymectomy. VATS has been reported to reduce postsurgical pain, hospitalization, and treatment costs, while showing similar therapeutic effects to open thymectomy [4]. Therefore, VATS and robotic-assisted thymectomy are used by an increasing number of centers and are usually preferred by patients [5].

After the introduction of VATS, the safety and effectiveness of carbon dioxide (CO₂) insufflation in the thoracic cavity (capnothorax) remains controversial. Although studies have shown that capnothorax helps to secure the vision of the surgeon and does not significantly affect the patient’s hemodynamic stability during anesthesia [6–8], other studies have also reported that capnothorax should be used only at low pressure, as it significantly affects the patient’s hemodynamic and pulmonary stability [9,10].

In our hospital, we have been performing capnothorax and one-lung ventilation (OLV) at the request of a thoracic surgeon since 2016, when bilateral VATS extended thymectomy (BVET) was introduced. However, we found that one-lung ventilation renders the maintenance of anesthesia very difficult; therefore, we decided to switch to two-lung ventilation using a single lumen tube after discussion with the surgeon.

We observed that there were differences in pulmonary function between the two anesthetic methods. Thus, this study aimed to compare the differences between the two anesthetic methods and to determine the appropriate anesthetic method.

The primary endpoint of our study was the arterial oxygen (O₂) index (partial pressure of arterial oxygen [PaO₂]/fraction of inspired oxygen [FiO₂]) during anesthesia time for the evaluation of pulmonary oxygen exchange deficit. The secondary endpoints were operation and anesthesia time for effectiveness of the surgery.

**MATERIALS AND METHODS**

This retrospective study was approved by the research board (Institutional Review Board) of our center (no. H-1806-091-003). We retrospectively investigated the medical records of patients with MG who underwent BVET between August 2016 and January 2018.

The inclusion criteria were as follows: age 18–65 years, American Society of Anesthesiologists physical status I–III, preoperative vital capacity (VC) > 2 L, no history of sternotomy, and no cardiovascular or pulmonary disease. Patients who underwent conversion from one-lung ventilation to two-lung ventilation or switched from VATS to sternotomy were excluded. We divided the patients into two groups: group D (the double-lumen tube group), with patients who underwent ventilation for one lung, and group S (the single-lumen tube group), with those who underwent ventilation for two lungs during surgery. Ultimately, 83 patients were enrolled in the present study.

We set nine anesthesia time points (T0–T8) and collected the data. The time points were set as follows: T0 was immediately after tracheal intubation, T1 was the time of incision on the right side, T2 was set as 10 min after the CO₂ insufflation of the right lung. T3 was set as 30 min from the right lung CO₂ insufflation, T4 refers to the transition period from the right to the left side (in group D, two-lung ventilation), T5 the time of incision on the left side, T6 was set as 10 min after the CO₂ insufflation of the left lung, T7 was set as 30 min after the left lung CO₂ insufflation, and T8 referred to the end of the left side operation (in group D, two-lung ventilation). Two-lung ventilation was used at all time points in group S, and one-lung ventilation was used at T1–T3/T5–T7 in group D.

The basic characteristics of the patients, such as age, sex, body mass index (BMI), American Society of Anesthesiologists physical status, Myasthenia Gravis Foundation of America (MGFA) class, operation, and anesthesia time were recorded. The end-tidal CO₂ (EtCO₂), peak inspiratory pressure (PIP), respiratory rate (RR), peripheral capillary oxygen saturation (SpO₂), FiO₂, mean blood pressure (MBP), heart rate (HR), and cardiac index (CI) were recorded at T0–T8, and all variables were compared at each time point. Because arterial blood gas analysis was mainly measured after one-lung ventilation, PaO₂ and arterial oxygen index (PaO₂/FiO₂) were recorded at T1 and T5. Postoperative complications, intensive care unit (ICU) stay time, and hospitalization days (HD) were also recorded.

None of the patients received premedication. Intraoperative monitoring included noninvasive blood pressure measurement, invasive arterial blood pressure monitoring, electrocardiography, pulse oximetry, capnography, bispectral index (BIS) monitoring, and neuromuscular function assessment (TOF Watch SX monitor®, Organon Ltd., Ireland). General anesthesia was induced using total intravenous anesthesia. Propofol and remifentanil were administered to end organ concentrations of 4–5 and 3–4 ng/ml, respectively, using a target-controlled infusion pump (Orchestra®, Fresenius
Ventilation methods for thymectomy of MG

Vial, France). Rocuronium (0.6 mg/kg) was administered to facilitate intubation. In group D, a 35-F or 37-F left-sided double-lumen tube was inserted using videolaryngoscopy, and its correct position was confirmed by auscultation and eventually by bronchoscopy. In group S, a 7.0-mm or 8.0-mm internal diameter single-lumen tube was inserted using videolaryngoscopy. Mechanical ventilation with O2 and air (FiO2 0.5) was started with tidal volumes (TVs) of 8–10 ml/kg and an initial RR of 9–10 breaths/ min. In group D, passive lung collapse and contralateral OLV were started immediately before the first trocar insertion. During OLV, the FiO2 was adjusted to 0.5–1.0, the TV was reduced to 6–8 ml/kg to maintain a PIP of < 35 cm H2O, and the RR was increased to avoid respiratory acidosis. In group S, the TV was reduced to 6–8 ml/kg. Propofol and remifentanil infusions were titrated to maintain an MBP within 20% of the baseline during anesthesia and to maintain a BIS < 50. Rocuronium was continuously injected to maintain a train of four (TOF) count of 1 or 2. A radial arterial pressure line was placed, and a central venous catheter was inserted via the right internal jugular vein. CI was monitored using a minimally invasive hemodynamic monitor (FloTrac System®, Edwards Lifesciences, USA).

BVET was performed with patients in the supine position with a 15° reverse Trendelenburg position. Both arms were placed at 90° forearm abduction external rotation position without any pressure on the brachial plexus nerve. The right-side approach was performed first. First, a 5-mm trocar was placed along the upper edge of the fifth intercostal space in the midaxillary line. After inspection of the right thoracic cavity to evaluate the adhesions and pathology, CO2 insufflation was performed using a pressure limit of 8–14 mmHg and a flow rate of 4 L/min. Under thoracoscopic guidance, a second 5-mm trocar was inserted near the anterior axillary line of the sixth intercostal space, and a third 5-mm trocar was placed in the sixth or seventh intercostal space near the sternum without injury to the internal mammary vessel. The procedure on the left side was performed in the same manner.

At the end of the surgery, fentanyl (25 µg) was injected intravenously, and intravascular patient-controlled analgesia was used for postoperative pain control. Additionally, neuromuscular relaxation was reversed with sugammadex (2 mg/kg). After a TOF ratio > 0.9, the tracheal tube was removed, and all patients were transferred to the ICU.

Statistical analyses

The Statistical Package for the Social Sciences program version 26.0 (IBM, USA) was used for statistical analysis. Variables with a normal distribution are indicated by the mean value (standard deviation), and variables with a non-normal distribution are indicated by the median (1Q, 3Q). Normality was tested using the Shapiro–Wilk test. The Student’s unpaired t-test and Mann–Whitney U test were used for continuous variables (operation time and anesthesia time), and the chi-squared test was used for categorical variables (arterial oxygen index). Statistical significance was set at P < 0.05.

RESULTS

A total of 29 of the 83 patients were excluded from the analysis due to incomplete data. Therefore, the data of 54 patients were analyzed with 26 and 28 patients in groups D and S, respectively.

Age, sex, weight, height, BMI, MGFA class, and American Society of Anesthesiologists physical status were not significantly different between the two groups (Table 1). However, the duration of surgery and anesthesia was longer in group D than in group S. The durations of ICU and HD were not significantly different between the two groups.

The respiratory variables are presented in Table 2. The EtCO2 values at T0 were not significantly different between the two groups but were maintained at a higher level during surgery in group D, although statistical significance was only observed in T1–T3 and T7. The SpO2 at T1–T3 and T8 was significantly lower in group D than in group S. The FiO2 was lower in group S than in group D at all time points. PIP and RR were not significantly different between the two groups at any time point. The number of PaO2/FiO2 ≤ 300 and PaO2/FiO2 ≤ 200 was significantly higher in group D than in group S (Table 3).

The hemodynamic variables are shown in Table 4. MBP, HR, and CI were not significantly different between the two groups at any time point.

No complications were presumed to be related to myasthenic crisis in either group.

DISCUSSION

As a result of the study, the duration of the operation and anesthesia in group S was short, and SpO2 > 90% was maintained even when the FiO2 level was lower in group S than that in group D. The number of PaO2/FiO2, which was 300 or less, was also significantly lower in group S than in group D.
Table 1. Characteristics of Patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group D (n = 26)</th>
<th>Group S (n = 28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>34.0 (23, 38)</td>
<td>36.0 (25.7, 43.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>6/20</td>
<td>9/19</td>
<td>NS</td>
</tr>
<tr>
<td>ASA class</td>
<td>2.0 (1, 2)</td>
<td>2.0 (2, 2)</td>
<td>NS</td>
</tr>
<tr>
<td>MGFA (l/lila/lIlb/lIlia)</td>
<td>12/12/2/0</td>
<td>15/8/4/1</td>
<td>NS</td>
</tr>
<tr>
<td>Pyridostigmine (mg/d)</td>
<td>360 (225, 480)</td>
<td>360 (195, 465)</td>
<td>NS</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163.5 (159.0, 168.4)</td>
<td>164.7 (159.6, 170)</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>57.5 (50.4, 72.1)</td>
<td>62.4 (53.4, 71.1)</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.2 (20.2, 23.5)</td>
<td>22.3 (19.7, 25.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>243.0 (200, 300)</td>
<td>210.0 (176.2, 308.8)</td>
<td>0.012</td>
</tr>
<tr>
<td>Anesthesia time (min)</td>
<td>308.5 (268.5, 359.7)</td>
<td>272.0 (234, 303.8)</td>
<td>0.030</td>
</tr>
<tr>
<td>ICU stay (d)</td>
<td>2.0 (1, 2)</td>
<td>2.0 (2, 2)</td>
<td>NS</td>
</tr>
<tr>
<td>Hospital stay (d)</td>
<td>8.0 (6.7, 11)</td>
<td>8.5 (6, 14.5)</td>
<td>NS</td>
</tr>
<tr>
<td>Bleeding (ml)</td>
<td>100.0 (37.5, 100)</td>
<td>0.00 (0, 175)</td>
<td>NS</td>
</tr>
<tr>
<td>Input (L)</td>
<td>1.8 (1.4, 2.3)</td>
<td>1.8 (1.4, 2.2)</td>
<td>NS</td>
</tr>
<tr>
<td>Urine (ml)</td>
<td>302.5 (200, 393.7)</td>
<td>317.5 (172.5, 47.5)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are presented as median (1Q, 3Q) or number only. ASA: American Society of Anesthesiologists, MGFA: Myasthenia gravis foundation of America, BMI: body mass index, NS: not significant.

Table 2. Respiratory Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>T5</th>
<th>T6</th>
<th>T7</th>
<th>T8</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ET CO₂</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group D</td>
<td>33.0 (32, 35)</td>
<td>34.0* (31, 34)</td>
<td>38.0* (35, 40)</td>
<td>39.0* (37, 43)</td>
<td>38.0* (33, 46)</td>
<td>40.0 (36, 45)</td>
<td>42.0 (35, 44)</td>
<td>42.0* (40, 47)</td>
<td>35.0 (32, 41)</td>
</tr>
<tr>
<td>Group S</td>
<td>33.5 (31, 37)</td>
<td>31.0 (30, 34)</td>
<td>35.0 (33, 37)</td>
<td>36.0 (34, 38)</td>
<td>37.0 (34, 40)</td>
<td>39.5 (36, 45)</td>
<td>38.0 (36, 42)</td>
<td>36.5 (34, 41)</td>
<td>37.0 (33, 38)</td>
</tr>
<tr>
<td><strong>Sp O₂</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group D</td>
<td>100 (99)</td>
<td>100* (96)</td>
<td>100* (91)</td>
<td>100* (96)</td>
<td>100 (96)</td>
<td>100 (94)</td>
<td>100 (95)</td>
<td>100 (96)</td>
<td>100 (97)*</td>
</tr>
<tr>
<td>Group S</td>
<td>100 (99)</td>
<td>100 (99)</td>
<td>100 (98)</td>
<td>100 (99)</td>
<td>100 (99)</td>
<td>100 (99)</td>
<td>100 (98)</td>
<td>100 (99)</td>
<td>100 (100)</td>
</tr>
<tr>
<td><strong>Fi O₂</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group D</td>
<td>0.5 (0.5, 0.6)</td>
<td>0.6* (0.5, 1.0)</td>
<td>0.6* (0.5, 1.0)</td>
<td>0.7* (0.5, 1.0)</td>
<td>0.7* (0.5, 1.0)</td>
<td>0.8* (0.6, 1.0)</td>
<td>0.8* (0.6, 1.0)</td>
<td>0.6* (0.5, 1.0)</td>
<td></td>
</tr>
<tr>
<td>Group S</td>
<td>0.5 (0.6, 0.6)</td>
<td>0.5 (0.5, 0.6)</td>
<td>0.5 (0.5, 0.7)</td>
<td>0.5 (0.5, 0.7)</td>
<td>0.5 (0.5, 0.7)</td>
<td>0.5 (0.5, 0.6)</td>
<td>0.5 (0.5, 0.6)</td>
<td>0.5 (0.5, 0.6)</td>
<td>0.5 (0.5, 0.5)</td>
</tr>
<tr>
<td><strong>PIP</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group D</td>
<td>18.5 (14, 22)</td>
<td>20.5 (17, 26)</td>
<td>21.0 (18, 28)</td>
<td>26.0 (21, 30)</td>
<td>27.0 (21, 30)</td>
<td>26.0 (22, 30)</td>
<td>26.0 (25, 30)</td>
<td>30.0 (25, 31)</td>
<td>23.0 (19, 26)</td>
</tr>
<tr>
<td>Group S</td>
<td>16.5 (14, 18)</td>
<td>20.0 (17, 25)</td>
<td>25.0 (21, 27)</td>
<td>28.0 (25, 29)</td>
<td>28.0 (25, 29)</td>
<td>28.0 (26, 30)</td>
<td>29.5 (26, 30)</td>
<td>29.0 (25, 31)</td>
<td>26.0 (19, 30)</td>
</tr>
<tr>
<td><strong>RR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group D</td>
<td>12.0 (10, 12)</td>
<td>12.0 (10, 12)</td>
<td>13.0 (10, 14)</td>
<td>14.0 (13, 15)</td>
<td>14.0 (13, 15)</td>
<td>15.0 (14, 16)</td>
<td>15.0 (14, 16)</td>
<td>15.0 (14, 16)</td>
<td>12.0 (12, 15)</td>
</tr>
<tr>
<td>Group S</td>
<td>11.5 (10, 12)</td>
<td>12.0 (10, 13)</td>
<td>13.0 (11, 13)</td>
<td>14.0 (13, 16)</td>
<td>14.0 (13, 16)</td>
<td>15.0 (13, 16)</td>
<td>15.0 (13, 16)</td>
<td>15.0 (13, 16)</td>
<td>15.0 (13, 16)</td>
</tr>
</tbody>
</table>

Values are presented as median (1Q, 3Q) or median (minimum). T0: immediately after tracheal intubation, T1: right-side incision time, T2: 10 min after right lung CO₂ insufflation, T3: 30 min from right lung CO₂ insufflation, T4: the transition period from the right to the left side (in group D, two-lung ventilation), T5–T8: T1–T4 on the left side, ETCO₂: end tidal carbon dioxide, SpO₂: saturation of percutaneous oxygen, FiO₂: fraction of inspired oxygen, PIP: peak inspiratory pressure, RR: respiratory rate. *P < 0.05 compared to group S.

Hemodynamic variables were not significantly different between the two groups. The present study showed that two-lung ventilation was a safer and more effective method during BVET with capnothorax than one-lung ventilation.

The reason for the longer anesthesia time in group D is presumed to be because it takes more time to insert the double-lumen tube and check the proper position. The operation time was measured continuously from the start of the operation on the right side to completion of the left, so the time of the process of expanding the right lung and depleting the left lung again when moving from right to left was included in the operation time. Therefore, it is difficult to interpret this period as operation time. In addition, since surgery using a single lumen tube was performed after surgery using a double-lumen tube, the possibility that it affected the skill level of the surgeon cannot be excluded. Thus, it is
Nevertheless, ventilation during CO\textsubscript{2} reported that low- 

Group D (n = 20) 

P value

<table>
<thead>
<tr>
<th>P/F ratio</th>
<th>Group D (n = 41)</th>
<th>Group S (n = 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO\textsubscript{2}/FiO\textsubscript{2} ≤ 300</td>
<td>24 (58,5)</td>
<td>6 (13,0)</td>
</tr>
<tr>
<td>PaO\textsubscript{2}/FiO\textsubscript{2} ≤ 200</td>
<td>18 (43,9)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Values are presented as number (%). The arterial oxygen index is known as the P/F ratio, which is a powerful objective tool to identify acute hypoxemic respiratory failure. PaO\textsubscript{2}/FiO\textsubscript{2} ≤ 300 indicates mild, and PaO2/FiO\textsubscript{2} ≤ 200 indicates moderate acute respiratory failure. n: arterial blood gas analysis, PaO\textsubscript{2}: partial pressure of arterial oxygen, FiO\textsubscript{2}: fraction of inspired oxygen, P/F: PaO\textsubscript{2}/FiO\textsubscript{2}.

### Table 4. Hemodynamic Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>T0</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>T5</th>
<th>T6</th>
<th>T7</th>
<th>T8</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI (L/min/m\textsuperscript{2})</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group D</td>
<td>NS</td>
<td>2.8 (2.4, 3.3)</td>
<td>2.8 (2.4, 3.3)</td>
<td>2.5 (2.1, 3.1)</td>
<td>2.7 (2.3, 3.2)</td>
<td>3.1 (2.4, 3.9)</td>
<td>3.4 (2.5, 3.9)</td>
<td>3.2 (2.4, 3.8)</td>
<td>3.3 (2.9, 4.2)</td>
</tr>
<tr>
<td>Group S</td>
<td>NS</td>
<td>2.6 (1.9, 3.6)</td>
<td>2.6 (2.1, 3.5)</td>
<td>2.6 (2.1, 3.0)</td>
<td>2.6 (2.1, 3.1)</td>
<td>2.8 (1.9, 3.3)</td>
<td>2.7 (2.3, 3.1)</td>
<td>3.0 (2.3, 3.4)</td>
<td>3.1 (2.8, 3.9)</td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>(82, 111)</td>
<td>(81, 94)</td>
<td>(91, 95)</td>
<td>(75, 23)</td>
<td>(80, 24, 97)</td>
<td>(76, 7, 82)</td>
<td>(74, 0, 94)</td>
<td>(70, 3, 96)</td>
<td>(77, 9)</td>
</tr>
<tr>
<td>Group D</td>
<td>90.5 (74, 104.5)</td>
<td>82.0 (50, 78.3)</td>
<td>80.0 (62, 94.5)</td>
<td>83.0 (77, 90)</td>
<td>85.0 (77, 90)</td>
<td>86.0 (77, 90)</td>
<td>85.0 (78, 90)</td>
<td>82.5 (78, 90)</td>
<td>88.0 (75, 95.8)</td>
</tr>
<tr>
<td>Group S</td>
<td>(74, 82)</td>
<td>(65, 73)</td>
<td>(66, 85)</td>
<td>(65, 87)</td>
<td>(67, 89)</td>
<td>(67, 89)</td>
<td>(72, 0, 95)</td>
<td>(74, 0, 93)</td>
<td>(65, 85)</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>(63, 85.0)</td>
<td>(63, 72.3)</td>
<td>(66, 85)</td>
<td>(65, 87)</td>
<td>(67, 89)</td>
<td>(67, 89)</td>
<td>(72, 0, 95)</td>
<td>(74, 0, 93)</td>
<td>(65, 85)</td>
</tr>
<tr>
<td>Group D</td>
<td>76.0 (64, 85)</td>
<td>66.5 (59, 76)</td>
<td>73.0 (65, 79)</td>
<td>73.0 (64, 76)</td>
<td>70.5 (64, 79)</td>
<td>70.5 (66, 87)</td>
<td>75.0 (65, 87)</td>
<td>75.0 (63, 84)</td>
<td>(57.2, 75.0)</td>
</tr>
<tr>
<td>Group S</td>
<td>75.0 (64, 85)</td>
<td>66.5 (59, 76)</td>
<td>73.0 (65, 79)</td>
<td>73.0 (64, 76)</td>
<td>70.5 (64, 79)</td>
<td>70.5 (66, 87)</td>
<td>75.0 (65, 87)</td>
<td>75.0 (63, 84)</td>
<td>(57.2, 75.0)</td>
</tr>
</tbody>
</table>

Values are presented as the median (1Q, 3Q). T0: immediately after tracheal intubation, T1: right-side incision time, T2: 10 min after right lung CO\textsubscript{2} insufflation, T3: 30 min after right lung CO\textsubscript{2} insufflation, T4: the transition period from the right to the left side (in group D, two-lung ventilation), T5–T8: the same as T1–T4 of the left side, CI: cardiac index, MBP: mean blood pressure, HR: heart rate, NS: not significant.

debatable whether the use of a single lumen tube during BVET reduces the operation time.

EtCO\textsubscript{2} was higher in group D than in group S, from T1 to T3. The difference between the two groups was no longer observed after T4, which can be estimated as the residual CO\textsubscript{2} effect after operation on the right side. In the case of SpO\textsubscript{2}, the median value between the two groups was not different; however, due to the difference in the minimum values, the SpO\textsubscript{2} from T1 to T3 in group D was lower than that in group S. After T4, the difference between the two groups was no longer observed, which can be interpreted to be a result of the increase in the FiO\textsubscript{2} value of group D over time. This is interpreted to mean that FiO\textsubscript{2} had to be increased in group D to maintain adequate SpO\textsubscript{2} for the patient.

The effectiveness and side effects of CO\textsubscript{2} insufflation in VATS are controversial. Ohtsuka et al. [6] reported that low-flow CO\textsubscript{2} insufflation does not compromise the human heart with normal to moderately depressed function and can be an efficacious adjunct in specific thoracoscopic procedures. In contrast, Brock et al. [10] investigated the hemodynamic and respiratory effects of one-lung ventilation and CO\textsubscript{2} insufflation in 13 adult patients undergoing VATS. They suggested that the combined use of one-lung ventilation and CO\textsubscript{2} insufflation increases the hazards, as both hypoxia and low CI are expected. In our study, although the O\textsubscript{2} index < 300 was higher in group D than in group S, hypoxia (SpO\textsubscript{2} < 90%) and hemodynamic exacerbation were not observed. Hence, the results were different from those reported by Brock et al. [10].

After Brock et al. [10]’s study, researchers attempted to avoid one-lung ventilation in the presence of capnothorax. No active clinical studies have been conducted since the publication of this study. However, it was difficult to prevent the introduction of capnothorax with one-lung ventilation in a field where minimally invasive surgery was developed and actively introduced into the clinic. It is notable that one-lung ventilation was safely used with capnothorax in VATS in hospitals that actively utilized BVET before our hospital did [11]. Nevertheless, ventilation during CO\textsubscript{2} insufflation should be titrated to maintain adequate oxygenation and a normal PCO\textsubscript{2} and pH. Anesthesiologists must be aware that damage to the contralateral pleura may occur, resulting in CO\textsubscript{2} flow to the contralateral chest, making ventilation difficult and resulting in tension pneumothorax or severe subcutaneous emphysema, which subsequently produces a hemodynamic compromise [2].

Recently, single lumen tube and CO\textsubscript{2} insufflation have
been considered safe alternative treatments for one-lung ventilation because they reduce the side effects caused by the double-lumen tube, shorten the duration of surgery and anesthesia, and allow anesthesia to be performed by inex- pert anesthesiologists [12–16]. However, in their studies, two-lung ventilation in the presence of capnothorax and one-lung ventilation in the absence of capnothorax were compared. In the present study, one-lung ventilation and two-lung ventilation were compared with various variables in the presence of capnothorax, which is different from the results of other studies. Although the results of our study showed that two-lung ventilation in the presence of capnothorax is a better anesthetic method, it should be noted that there are various risks of CO₂ insufflation, such as venous gas embolism, compromised venous return, severe bradycardia, and progressive arterial desaturation [17].

Upon clarification with the surgeon, the only thoracic surgeon in our hospital, it was noted that he was satisfied with both anesthetic methods. However, most anesthesiologists and anesthesiology residents prefer two-lung ventilation. Failure to investigate the satisfaction score is one of the limitations of this study.

Thymectomy for MG is the most frequently performed surgery in our hospital in South Korea. This is possibly because the diagnoses and treatment consultations of MG patients are active between the MG specialty center and our hospital. If a neurologist at the MG specialty center refers patients to our hospital, a neurologist, thoracic surgeon, and anesthesiologist at our hospital discuss patient surgery. After the operation, the patient is referred to the MG specialty center again. The indications for surgical treatment of patients with MG have not yet been clearly established. The American Academy of Neurology published the international consensus guidelines for the management of MG [18]. In non-thymomatous MG, thymectomy is performed as an option to avoid or minimize the dose or duration of immunotherapy, or if patients fail to respond to an initial trial of immunotherapy or have intolerable side effects from that therapy. In our center, the occurrence of clinical symptoms with an ACh receptor antibody positivity within 5 years of symptom onset and age 18–65 years are considered indications for surgery.

MG patients may experience two crises: cholinergic crisis and myasthenic crisis. A cholinergic crisis is usually caused by an excess of cholinesterase inhibitors. Hypersalivation, sweating, abdominal cramps, bradycardia, and muscle weakness may occur. A myasthenic crisis, which refers to a life-threatening condition that is defined as the worsening of myasthenic weakness requiring intubation or noninvasive ventilation, can be triggered by emotional and physical stress, such as infections, certain medications, and surgery [19]. Postoperative myasthenic crisis with respiratory muscle paralysis can be a severe complication and reportedly occurs in 12–18% of patients. Kanai et al. [20] reported that the significant preoperative clinical predictive factors for postoperative myasthenic crises were percentage VC < 80% (3 points), duration of MG before thymectomy < 3 months (2 points), and bulbar symptoms immediately before thymectomy (1 point), with scores ranging from 0 to 6. Myasthenic crises were observed in 0.9% of patients with scores < 3 vs. 25.9% of patients with scores ≥ 3. There were no cases of post-thymectomy myasthenic crisis in our study. Limitations were observed in the present study as the investigations were conducted only up to 24 h postoperatively; however, the patients included in this study were able to determine that no postoperative myasthenic crisis occurred because the VC was normal and patients with low MGFA grades accounted for the majority.

In conclusion, this retrospective study suggests that anesthesia using two-lung ventilation during BVET with capnothorax is a safe and effective method to improve lung oxygenation and reduce anesthesia time.

FUNDING
None.

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

DATA AVAILABILITY STATEMENT
Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.
AUTHOR CONTRIBUTIONS


ORCID

Mijung Yun, https://orcid.org/0000-0001-5838-4893
Gunn Hee Kim, https://orcid.org/0000-0002-0014-8297
Sung-chul Ko, https://orcid.org/0000-0001-8460-2962
Yun Jae Han, https://orcid.org/0000-0002-4027-786X
Wooshik Kim, https://orcid.org/0000-0003-2787-2186

REFERENCES

INTRODUCTION

End-stage renal disease (ESRD) is chronic kidney disease (CKD) stage 5 and these patients need lifelong dialysis or transplantation for survival [1,2]. CKD patients tend to be older (> 65 years) and have diabetes mellitus (DM), hypertension, coronary vessel disease, and obesity [3-5]. The prevalence of ESRD in the USA has almost doubled in the last 20 years due to an increasing number of incident cases and the prolonged survival of ESRD patients, supposedly due to improved hemodialysis (HD) care [2,6]. In Korea, there were more than 100,000 ESRD patients in 2019, and the number is increasing by 7-10% annually [7]. The number of patients with ESRD who need surgery has increased with the number of HD-dependent patients with ESRD [2,8]. Moreover, patients with ESRD have a significantly higher risk of postoperative death than those with normal kidney function [2,9-12].

Background: The number of patients with end-stage renal disease (ESRD) who are dependent on hemodialysis is increasing rapidly. As a result, more patients with ESRD need surgery. These patients have a significantly higher risk of postoperative death than those with normal kidney function. Therefore, this study analyzed the causes of postoperative mortality in ESRD patients undergoing surgery under general anesthesia and the risk factors for postoperative mortality.

Methods: This retrospective analysis examined the mortality of ESRD patients, 20 to 80 years old, undergoing surgery under general anesthesia. We excluded patients who underwent cardiac, cancer, or emergency surgery or organ transplantation from the analysis. The primary outcome was the cause of postoperative 30-day mortality in ESRD patients. We also assessed the mortality rate and risk factors.

Results: There were 2,459 eligible ESRD patients. When patients underwent multiple surgeries during the study period, only the last surgery was considered. In total, 167 patients died during the study period, including 65 within 30 days postoperatively. The cause of death was sepsis in 22 cases (33.8%) and a major cardiac event in 16 (24.6%). Atrial fibrillation, current angina, previous myocardial infarction, asthma, lower hemoglobin and albumin levels, and a larger intraoperative colloid volume were likely to increase mortality.

Conclusions: Our study suggests that immunological issues have a significant role in the death of ESRD patients after general anesthesia.

Keywords: Cause of death; End-stage renal disease; General anesthesia; Infection.
In non-cardiac surgery, patients with CKD had a two- to five-fold higher risk of cardiovascular events than those with normal kidney function [13]. Patients with ESRD undergoing HD were nearly three times as likely to return to the operating room, and their postoperative 30-day mortality was ten times higher than those without ESRD [11,12]. Therefore, anesthesiologists and surgeons have to pay particular attention to these high-risk patients. We conducted this study to analyze the primary cause of postoperative 30-day mortality in patients with ESRD undergoing surgery under general anesthesia. We also evaluated potential risk factors for postoperative 30-day mortality in these patients.

**MATERIALS AND METHODS**

This retrospective single-center study ran from January 2018 to January 2020. This retrospective single-center study ran from January 2018 to January 2020. The Institutional Review Board of Soonchunhyang University Hospital, Seoul, Republic of Korea, approved this study (no. SCHUH 2021-07-015). Patient demographics, comorbidities, and laboratory results were obtained from the hospital's electronic medical records. An initial search identified all patients 20 to 80 years old with ESRD who underwent general anesthesia. The patients who underwent cardiac, cancer, or emergency surgery or organ transplantation were excluded. General anesthesia combined with any type of regional block was included. When patients underwent multiple surgeries during the study period, only the last surgery was eligible. The requirement for informed consent was waived because of the study design.

The primary outcome was the primary cause of postoperative 30-day mortality in ESRD patients. The cause of death was defined as that recorded in the electronic medical records or registered in national data. The secondary outcomes were the all-cause postoperative 30-day mortality rate in ESRD patients and the identified risk factors for postoperative 30-day mortality. Mortality data, including date and primary cause of death, were obtained from the electronic medical records and by submitting data requests to the Korean National Statistical Office (Microdata Integrated Service, on-demand, https://mdis.kostat.go.kr). If the cause of death was recorded as ‘ESRD’, it was classified as ‘Unknown’. Risk factors were identified statistically among demographic, comorbidity, and preoperative laboratory parameters. In our institution, when a patient diagnosed with ESRD or requiring dialysis is scheduled for surgery, we check the blood urea nitrate, creatinine, and electrolytes (sodium, potassium, and chloride) after preoperative dialysis and early the morning of surgery.

**Statistical analysis**

Multivariable logistic regression analysis was performed to identify risk factors for postoperative 30-day mortality under general anesthesia. The factors included as potential confounding variables were age, sex, body mass index (BMI), relevant pre-admission comorbidities subsequent atrial fibrillation, current angina pectoris, congestive heart failure, valvular heart disease, dilated cardiomyopathy, asthma, chronic obstructive pulmonary disease, interstitial lung disease, liver cirrhosis, diabetes mellitus, cerebrovascular disease, dementia, hypertension, previous myocardial infarction, preoperative post HD sodium, potassium, chloride, hemoglobin, albumin, and calcium, type and duration of anesthesia, and total amounts of crystalloid and colloid administered. The relations between mortality and potential confounding variables were evaluated separately in a univariable logistic model and those with P < 0.1 were subsequently subject to multivariable logistic regression. All variables included in the multivariable model required complete patient data; cases with missing co-variates were excluded from the analysis. We used a two-sided 5% α-level to evaluate differences in the model. We report the cause and mortality rate as a number and percentage and the odds ratios (OR) of confounding variables for postoperative 30-day mortality along with the 95% confidence intervals. Values of P < 0.05 were considered statistically significant. All statistical analyses were performed using Rex Excel-based statistical analysis software, ver. 3.6.0 (RexSoft, Korea, http://rexsoft.org/) based on R ver. 4.0.0 (R Foundation for Statistical Computing, Austria).

**RESULTS**

Initially, 3,367 surgical procedures in ESRD patients were extracted from our hospital database. After excluding 31 organ transplantations, 13 cardiac surgeries, 50 cancer surgeries, 180 emergency surgeries, and 634 additional procedures performed in the same patients, 2,469 patients were included in the study. Table 1 summarizes the baseline characteristics of the study population. Of the 2,459 patients, 2,029 (82.5%) were diagnosed with hypertension preoperatively, and 1,223 (49.7%), 361 (14.7%), and 306 (12.4%) were diagnosed with diabetes mellitus, cerebrovascular disease, and
Table 1. Baseline Characteristics of the Patients with ESRD Undergoing General Anesthesia

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n = 2,459)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient factor</strong></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>64.9 ± 41.3</td>
</tr>
<tr>
<td>Sex, male</td>
<td>551 (53.0)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.3 ± 20.4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.8 ± 9.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.5 ± 5.0</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>155 (6.3)</td>
</tr>
<tr>
<td>Current angina pectoris</td>
<td>144 (5.9)</td>
</tr>
<tr>
<td>Previous MI</td>
<td>101 (4.1)</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>65 (2.6)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>306 (12.4)</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>TIA/CVA</td>
<td>361 (14.7)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2,029 (82.5)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1,223 (49.7)</td>
</tr>
<tr>
<td>Asthma</td>
<td>49 (2.0)</td>
</tr>
<tr>
<td>COPD</td>
<td>25 (1.0)</td>
</tr>
<tr>
<td>ILD</td>
<td>1 (0.04)</td>
</tr>
<tr>
<td>Post HD plasma Na (mmol/L)</td>
<td>140.3 ± 7.2</td>
</tr>
<tr>
<td>Post HD plasma K (mmol/L)</td>
<td>4.4 ± 0.7</td>
</tr>
<tr>
<td>Post HD plasma Cl (mmol/L)</td>
<td>100.5 ± 5.2</td>
</tr>
<tr>
<td>Post HD plasma BUN (mg/dl)</td>
<td>34.9 ± 22.4</td>
</tr>
<tr>
<td>Post HD plasma Cr (mg/dl)</td>
<td>5.4 ± 3.3</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>11.2 ± 1.7</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>34.4 ± 5.2</td>
</tr>
<tr>
<td>Platelet (10⁹/µl)</td>
<td>192.0 ± 74.1</td>
</tr>
<tr>
<td>Plasma albumin (g/dl)</td>
<td>4.2 ± 1.0</td>
</tr>
<tr>
<td>Plasma Ca (mg/dl)</td>
<td>9.2 ± 2.3</td>
</tr>
<tr>
<td>Ejection Fraction (%)</td>
<td>63 (58.69)</td>
</tr>
</tbody>
</table>

Table 2. Primary Causes of Postoperative 30-day Mortality in Patients with End-stage Renal Disease

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Total (n = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>22 (33.8)</td>
</tr>
<tr>
<td>Major cardiac event</td>
<td>16 (24.6)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4 (6.2)</td>
</tr>
<tr>
<td>Thromboembolic event</td>
<td>4 (6.2)</td>
</tr>
<tr>
<td>Cancer</td>
<td>3 (4.6)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (3.1)</td>
</tr>
<tr>
<td>Hypovolemia</td>
<td>2 (3.1)</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>2 (3.1)</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (12.3)</td>
</tr>
</tbody>
</table>

Values are presented as number of patients (%). Data were obtained from electronic medical records and by submitting a data request to the Korean National Statistical Office (Microdata Integrated Service, on-demand, https://mdis.kostat.go.kr). ‘Major cardiac event’ comprised ST-elevation, non-ST-elevation, and acute myocardial infarctions, ischemic heart disease, aortic stenosis, congestive heart failure, secondary pulmonary hypertension, and cardiac arrest. The category ‘Unknown’ contained eight patients (12.4%) with out-of-hospital deaths of unknown cause or ‘ESRD’. Other causes of death were pneumonia (four patients, 6.2%), thromboembolic event (four patients, 6.2%), and cancer (three patients, 4.6%). For the patients whose cause of death was categorized as ‘sepsis’, along with a statement in the medical records, we found evidence for the diagnosis based on ‘The Third International Consensus Definitions for Sepsis and Septic Shock, JAMA, 2016’ [14]. Regarding the origin of sepsis, no case was directly related to surgical site infection in our study. If ‘pneumonia’ was the primary cause of sepsis, the case was categorized as ‘pneumonia’.

The multivariable analysis including 15 factors with P < 0.1 in the univariable analyses identified atrial fibrillation, previous myocardial infarction, asthma, hemoglobin, plasma albumin, volatile anesthesia, and intraoperative colloid volume as statistically significant (Table 3). All patients were included in the analysis because there were no missing data.

DISCUSSION

In our study, the most common cause of death was sepsis (33.8%), followed by major cardiac events (24.6%), suggest-
Table 3. Expected Risk Factors as Odds Ratio for Postoperative 30-day Mortality in Patients with End-stage Renal Disease according to the Baseline Characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Crude OR (95% CI)</th>
<th>P value</th>
<th>Univariable analysis</th>
<th>Crude OR (95% CI)</th>
<th>P value</th>
<th>Multivariable analysis</th>
<th>Crude OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient factor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>1.00 (1.00–1.00)</td>
<td>0.243</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex, male</td>
<td>0.94 (0.66–1.34)</td>
<td>0.726</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.92 (0.86–0.99)</td>
<td>0.020</td>
<td></td>
<td>0.94 (0.88–1.02)</td>
<td>0.128</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>2.00 (1.15–3.49)</td>
<td>0.015</td>
<td></td>
<td>2.14 (1.21–3.78)</td>
<td>0.009</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current angina pectoris</td>
<td>2.05 (0.96–4.40)</td>
<td>0.065</td>
<td></td>
<td>1.13 (0.47–2.70)</td>
<td>0.790</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous MI</td>
<td>4.46 (2.04–7.94)</td>
<td>&lt; 0.001</td>
<td></td>
<td>2.90 (1.12–7.59)</td>
<td>0.029</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1.24 (0.50–3.50)</td>
<td>0.645</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>3.67 (2.13–6.34)</td>
<td>&lt; 0.001</td>
<td></td>
<td>1.80 (0.90–3.60)</td>
<td>0.096</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>1.844 × 10⁻⁴ (–0–inf)</td>
<td>0.978</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIA/CVA</td>
<td>1.48 (0.79–2.77)</td>
<td>0.224</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.71 (0.47–1.08)</td>
<td>0.109</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.04 (0.73–1.48)</td>
<td>0.848</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>5.87 (2.39–14.39)</td>
<td>&lt; 0.001</td>
<td></td>
<td>7.72 (2.79–21.38)</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COPD</td>
<td>1.29 (0.31–5.39)</td>
<td>0.728</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ILD</td>
<td>39.54 (0.45–637.61)</td>
<td>0.985</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dementia</td>
<td>4.998 (2.18–11.47)</td>
<td>&lt; 0.001</td>
<td></td>
<td>2.62 (0.99–6.92)</td>
<td>0.052</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>0.60 (0.51–0.70)</td>
<td>&lt; 0.001</td>
<td></td>
<td>0.57 (0.43–0.76)</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post HD plasma Na (mmol/L)</td>
<td>0.99 (0.97–1.01)</td>
<td>0.502</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post HD plasma K (mmol/L)</td>
<td>0.66 (0.47–0.84)</td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperkalemia (&gt; 5.1 mmol/L)</td>
<td>1.44 (0.59–3.52)</td>
<td>0.430</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia (&lt; 3.5 mmol/L)</td>
<td>3.73 (1.89–7.36)</td>
<td>&lt; 0.001</td>
<td></td>
<td>1.78 (0.81–3.93)</td>
<td>0.152</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post HD plasma Cl (mmol/L)</td>
<td>1.00 (0.96–1.04)</td>
<td>0.950</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma albumin (g/dl)</td>
<td>0.22 (0.15–0.31)</td>
<td>&lt; 0.001</td>
<td></td>
<td>0.35 (0.22–0.56)</td>
<td>&lt; 0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma Ca (md/dl)</td>
<td>0.67 (0.50–0.90)</td>
<td>0.009</td>
<td></td>
<td>1.09 (0.75–1.60)</td>
<td>0.647</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perioperative factor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volatile anesthesia</td>
<td>3.08 (1.07–8.82)</td>
<td>0.036</td>
<td></td>
<td>3.21 (1.10–9.34)</td>
<td>0.032</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anesthesia duration (min)</td>
<td>1.01 (1.00–1.01)</td>
<td>&lt; 0.001</td>
<td></td>
<td>1.00 (1.00–1.01)</td>
<td>0.281</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraoperative crystalloids (ml)</td>
<td>1.00 (1.00–1.00)</td>
<td>&lt; 0.001</td>
<td></td>
<td>1.00 (1.00–1.00)</td>
<td>0.950</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraoperative colloids (ml)</td>
<td>1.00 (1.00–1.00)</td>
<td>&lt; 0.001</td>
<td></td>
<td>1.00 (1.00–1.00)</td>
<td>0.011</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


As has been well established, the primary cause of morbidity and mortality in patients after non-cardiac surgery is that of adverse cardiovascular events [15]. CKD is a significant risk factor for perioperative adverse cardiovascular events because the presence of CKD may predispose patients to changes in the sodium and fluid balance, vascular calcification, and inflammatory changes, leading to atherosclerotic plaque destabilization [16]. Across various types of non-cardiac surgery, patients with ESRD had a significantly higher risk of postoperative death and cardiovascular events than those with normal kidney function [2,9–12]. Moreover, the primary cause of mortality in ESRD patients is also cardiovascular events [7]. Therefore, we expected that the most common cause of postoperative mortality would be adverse cardiovascular events. However, sepsis was responsible for more than 30% of the postoperative 30-day mortality in our ESRD patients, making it the most common cause.

Several studies have reported higher infection rates in ESRD patients. After hip arthroplasty, the deep infection rate exceeded 10% in dialysis patients [17,18]. De la Garza Ramos et al. [19] found that the infection rate was significantly in-
creased in patients with late-stage renal disease, who had almost 2.4 times greater odds of experiencing a surgical site infection than matched controls within 90 days after posterolateral lumbar fusion. Many orthopedic surgery studies have found that the patients with CKD or ESRD had higher surgical site infection and wound complication rates than patients with normal renal function [19,20]. In our study, the origin of sepsis in the mortality cases was not directly related to surgical site infection. However, surgery causes significant physiological stress and suppresses immune system activity [21–24]. Therefore, we presumed that the sepsis causing death resulted from exacerbating the immunologic vulnerability of ESRD by surgical stress. ESRD patients have immune changes due to protein-energy wasting, which means losing protein mass and energy stores due to oxidative stress, acidemia, and nutrient loss [22,23]. Furthermore, neutrophils tend to undergo apoptosis in uremic plasma conditions, especially in ESRD patients, which leads to lymphocytopenia and T lymphocyte function impairment [25,26]. CKD and ESRD patients also have more pro-inflammatory cytokine interleukin-6 receptors due to decreased excretion than healthy controls [27]. Moreover, their fluid overload and edematous state and comorbidities like atherosclerosis and diabetes mellitus can exacerbate the pro-inflammatory condition [28]. Gupta et al. [29] found that the plasma pro-inflammatory cytokine levels and positive acute-phase proteins were higher in participants with lower kidney function and greater albuminuria. HD has also long been thought to contribute to the inflammatory response [30]. Regardless of the cause of sepsis, it is clear that ESRD patients undergoing general anesthesia are more susceptible to inflammation and infection by various routes.

Erkocak et al. [20] found that DM and a higher BMI were significantly associated with increased infection risk. Although almost 50% of our ESRD cohort had DM, the association between DM and mortality was not significant. Nevertheless, the relation between DM and infection is worthy of further research regarding ESRD patients’ postoperative mortality due to inflammation [6]. Inconsistent with Erkocak et al. [20], ESRD patients with a higher BMI had low mortality (OR = 0.92, P = 0.020) in our univariable analysis and BMI was not significant in the multivariable analysis. The mean BMI in our patients was lower than in Erkocak et al. [20] (23.48 vs. 30.25 kg/m²). This is likely to reflect malnutrition and might increase mortality. This is consistent with the relationship between lower plasma albumin and higher mortality in our study (OR = 0.35, P < 0.001). Further studies are required to verify the association between the postoperative mortality of ESRD patients and low BMI or malnutrition, rather than obesity.

When we used the serum potassium as a confounding variable, the finding that the higher the serum potassium, the lower the risk was found to be misleading because there was little hyperkalemia in the data, because adequate serum potassium levels were achieved through preoperative dialysis. Therefore, we included hyperkalemia and hypokalemia in the analysis to address this issue, instead of serum potassium levels. Since there was almost no hyperkalemia, it was difficult to find statistical significance in hyperkalemia, while hypokalemia was significant in the univariable analysis, but not in the multivariable analysis. Further studies are needed to compare volatile anesthesia in ESRD patients, which was significant in our multivariable analysis (OR = 3.21, P = 0.032), with total intravenous anesthesia.

This study has several limitations. First, it was a single-center retrospective study and there was no control group of patients with normal renal function or not under dialysis. We cannot assure that our data represent all ESRD patients. Second, we did not consider patients with a broad range of disease severity during the period when they required dialysis, including patients with preoperative sepsis or who were immunocompromised. There might be a relationship between disease severity and postoperative mortality; further study considering a broader range of disease severity in ESRD patients is needed to verify this. Third, we did not analyze the types of surgery; certain types might have affected the patient mortality. In addition, patients who had multiple surgeries during the period might have had a much higher mortality risk, but this was not included in the analysis. Finally, we lacked laboratory data that reflect the level and severity of inflammation and infection, such as C-reactive protein.

In the general population, adverse cardiovascular events are a major cause of morbidity and mortality after non-cardiac surgery. In our study, however, more than 30% of the postoperative mortality was caused by sepsis. This suggests that immunological issues have a significant role in the death of ESRD patients after general anesthesia. However, considering the above-mentioned limitations and numerous factors affecting mortality that could not be investigated, our study has low explanatory power. Nevertheless, it could inform surgeons and anesthesiologists that it is essential to understand ESRD patients’ immune-suppressed state, emphasizing the importance of preventing inflammation and infection.
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


ORCID

Sanghoon Song, https://orcid.org/0000-0002-9327-2472
Chaeyeon Cho, https://orcid.org/0000-0003-1992-8215
Sun Young Park, https://orcid.org/0000-0003-3186-7371
Ho Bum Cho, https://orcid.org/0000-0003-4573-9100
Sang Ho Kim, https://orcid.org/0000-0003-3781-5353

REFERENCES


Clinical Research

Intraoperative lactic acid concentration during liver transplantation and cutoff values to predict early mortality: a retrospective analysis of 3,338 cases

Kyoung-Sun Kim¹, Sang-Ho Lee¹, Bo-Hyun Sang², and Gyu-Sam Hwang¹

¹Department of Anesthesiology and Pain Medicine, Laboratory for Cardiovascular Dynamics, Asan Medical Center, University of Ulsan College of Medicine, Seoul, ²Department of Anesthesiology and Pain Medicine, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Korea

Background: We aimed to explore the distribution of intraoperative lactic acid (LA) level during liver transplantation (LT) and determine the optimal cutoff values to predict post-LT 30-day and 90-day mortality.

Methods: Intraoperative LA data from 3,338 patients were collected between 2008 to 2019 and all-cause mortalities within 30 and 90 days were retrospectively reviewed. Of the three LA levels measured during preanhepatic, anhepatic, and neohepatic phase of LT, the peak LA level was selected to explore the distribution and predict early post-LT mortality. To determine the best cutoff values of LA, we used a classification and regression tree algorithm and maximally selected rank statistics with the smallest P value.

Results: The median intraoperative LA level was 4.4 mmol/L (range: 0.5–34.7, interquartile range: 3.0–6.2 mmol/L). Of the 3,338 patients, 1,884 (56.4%) had LA levels > 4.0 mmol/L and 188 (5.6%) had LA levels > 10 mmol/L. Patients with LA levels > 16.7 mmol/L and 13.5–16.7 mmol/L showed significantly higher 30-day mortality rates of 58.3% and 21.2%, respectively. For the prediction of the 90-day mortality, 8.4 mmol/L of intraoperative LA was the best cutoff value.

Conclusions: Approximately 6% of the LT recipients showed intraoperative hyperlactatemia of > 10 mmol/L during LT, and those with LA > 8.4 mmol/L were associated with significantly higher early post-LT mortality.

Keywords: Intraoperative hyperlactatemia; Lactic acid; Liver transplantation; Mortality.

INTRODUCTION

The liver plays a key role in lactate metabolism. Hyperlactatemia is generally considered as an increase in lactate production due to anaerobic metabolism in a state of reduced organ perfusion. However, measured lactic acid (LA) concentrations are the sum of metabolic and catabolic process, therefore hyperlactatemia may be due to an increase in production or a reduction in clearance in liver disease [1,2].

Additionally, the liver can be transformed into a lactate-producing organ in cases of hypoxia, sepsis, or liver surgery [1–4]. Therefore, given the enhanced lactate produc-
tion, reduction in clearance, and lactate-producing liver itself after reperfusion of the allograft, extremely high intraoperative LA levels are expected in patients undergoing liver transplantation (LT). However, compared to those of critically ill patients, characteristics of intraoperative LA concentrations during LT have been poorly studied in a large cohort of LTs. In addition, although there are studies that found that lactate clearance shortly after reperfusion of an allograft is associated with short-term prognosis [5–7], research on cut-off levels of intraoperative LA to predict early mortality remains poorly investigated [8,9].

To better understand the changes in LA concentration during LT, we thoroughly explored both preoperative and intraoperative LA and, furthermore, determined optimal cutoff values of intraoperative LA to predict post-LT 30-day and 90-day mortality.

MATERIALS AND METHODS

Study population

The Institutional Review Board approved the study design and a waiver of informed consent for participants (no. 2021-0664). Data from the institution’s LT Registry, which prospectively registered patients who underwent LT, was extracted via the software, a fully computerized and automatic data extraction program. From January 2008 to December 2019, there were 4,604 potentially eligible LT recipients. Among them, 3,338 patients with measured intraoperative LA levels were chosen. We included the majority of heterogeneous LT recipients because we aimed to characterize intraoperative LA and determine optimal cutoff values of hyperlactatemia to predict early post-LT mortality.

Data collection

Patient demographics, medical history, Model for End-stage Liver Disease score (MELDs), and preoperative laboratory variables were obtained automatically using the hospital software. All-cause mortality data were obtained from patients’ electronic medical records and the updated record of the institution’s LT Registry, which regularly follows all the registered LT recipients.

Measurement of intraoperative LA during LT

Intraoperative LA levels were measured three times during the preanhepatic, anhepatic, and neohepatic periods as per the institution’s routine intraoperative protocol. Of these, the peak level of intraoperative LA was used to analyze its distribution and predict early post-LT mortality. Preoperative LA concentration was also measured before LT as a routine work-up.

Study end-point

Primary and secondary end-points were 30-day and 90-day mortality, respectively.

Statistical analysis

Data are expressed as the mean ± standard deviation or median (1st quartile, 3rd quartile) for continuous variables, and numbers and percentages for categorical variables. Analyses between groups were performed using the Student’s t-test, the Mann–Whiney U test, analysis of variance, or the Kruskal–Wallis test for continuous variables and the χ² test or Fisher’s exact test for categorical variables, as appropriate. The Kolmogorov–Smirnov test was used to test the normality assumption. To determine the best cutoff values of LA, we used a classification and regression tree (CART) algorithm of recursive partitioning and maximally selected rank statistics with the smallest P value (‘caret’ and ‘maxstat’ R package).

Briefly, in maximally selected rank statistics. The prognostic cutoff point was determined by evaluating every possible cutoff point classifying all patients into two groups according to their level and selecting the most discriminant threshold for death, corresponding to the minimum P value according to the log-rank test [10–12]. The Kaplan–Meier (KM) survival curve was used to depict the risk of 30-day and 90-day mortality.

RESULTS

The mean age of the 3,338 LT recipients included was 53.3 ± 9.0 years. Of the patients, 2,443 (73.2%) were men. The mean MELDs was 18.2 ± 10.9 (Table 1). The primary causes of liver disease were virus-related liver cirrhosis (63.1%) and alcoholic liver disease (20.3%), followed by others (18%).

Distribution of preoperative and intraoperative LA

The preoperative median LA level was 1.9 mmol/L (range:
### Table 1. Patients’ Demographics according to the Intraoperative Lactic Acid Levels

<table>
<thead>
<tr>
<th>Variable</th>
<th>LA ≤ 8.4 mmol/L (n = 2,997)</th>
<th>LA &gt; 8.4 mmol/L (n = 341)</th>
<th>Total (n = 3,338)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>53.2 ± 9.1</td>
<td>54.0 ± 8.8</td>
<td>53.3 ± 9.0</td>
<td>0.123</td>
</tr>
<tr>
<td>Sex, male</td>
<td>2,171 (72.4)</td>
<td>272 (79.8)</td>
<td>2,443 (73.2)</td>
<td>0.005</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.2 ± 3.7</td>
<td>24.8 ± 3.7</td>
<td>24.3 ± 3.7</td>
<td>0.003</td>
</tr>
<tr>
<td>Diabetes</td>
<td>731 (24.4)</td>
<td>69 (20.2)</td>
<td>800 (24.0)</td>
<td>0.102</td>
</tr>
<tr>
<td>Hypertension</td>
<td>559 (18.7)</td>
<td>60 (17.6)</td>
<td>619 (18.5)</td>
<td>0.688</td>
</tr>
<tr>
<td>MELD score</td>
<td>18.1 ± 10.8</td>
<td>18.9 ± 12.0</td>
<td>18.2 ± 10.9</td>
<td>0.262</td>
</tr>
<tr>
<td>MELDs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MELD &lt; 15</td>
<td>1,619 (54.0)</td>
<td>188 (55.1)</td>
<td>1,807 (54.1)</td>
<td>0.138</td>
</tr>
<tr>
<td>MELD 15–35</td>
<td>1,062 (35.4)</td>
<td>107 (31.4)</td>
<td>1,169 (35.0)</td>
<td></td>
</tr>
<tr>
<td>MELD &gt; 35</td>
<td>316 (10.5)</td>
<td>46 (13.5)</td>
<td>362 (10.8)</td>
<td></td>
</tr>
<tr>
<td><strong>Causes for liver disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral</td>
<td>1,874 (62.5)</td>
<td>231 (67.7)</td>
<td>2,105 (63.1)</td>
<td>0.067</td>
</tr>
<tr>
<td>Alcoholic</td>
<td>620 (20.7)</td>
<td>56 (16.4)</td>
<td>676 (20.3)</td>
<td>0.074</td>
</tr>
<tr>
<td>Biliary</td>
<td>99 (3.3)</td>
<td>4 (1.2)</td>
<td>103 (3.1)</td>
<td>0.047</td>
</tr>
<tr>
<td>Others</td>
<td>543 (18.1)</td>
<td>57 (16.7)</td>
<td>600 (18.0)</td>
<td>0.572</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1,363 (45.5)</td>
<td>185 (54.3)</td>
<td>1,548 (46.4)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fulminant hepatic failure</td>
<td>136 (4.5)</td>
<td>25 (7.3)</td>
<td>161 (4.8)</td>
<td>0.032</td>
</tr>
<tr>
<td>Intractable ascites</td>
<td>951 (31.7)</td>
<td>96 (28.2)</td>
<td>1,047 (31.4)</td>
<td>0.198</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>473 (15.8)</td>
<td>64 (18.8)</td>
<td>537 (16.1)</td>
<td>0.179</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>401 (13.4)</td>
<td>41 (12.0)</td>
<td>442 (13.2)</td>
<td>0.538</td>
</tr>
<tr>
<td>Spontaneous bacterial peritonitis</td>
<td>123 (4.1)</td>
<td>15 (4.4)</td>
<td>138 (4.1)</td>
<td>0.908</td>
</tr>
<tr>
<td><strong>Laboratory variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraoperative</td>
<td>4.1 (2.9, 5.6)</td>
<td>10.4 (9.2, 12.2)</td>
<td>4.4 (3.0, 6.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lactic acid (mmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>10.4 (8.9, 12.2)</td>
<td>10.7 (9.0, 12.7)</td>
<td>10.4 (8.9, 12.3)</td>
<td>0.052</td>
</tr>
<tr>
<td>Leukocytes (× 10^3/µl)</td>
<td>3.6 (2.5, 5.3)</td>
<td>3.5 (2.5, 5.6)</td>
<td>3.6 (2.5, 5.3)</td>
<td>0.739</td>
</tr>
<tr>
<td>Platelet count (× 10³/µl)</td>
<td>61 (42, 94)</td>
<td>60 (41, 91)</td>
<td>61 (42, 94)</td>
<td>0.786</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>2.1 (1.0, 9.6)</td>
<td>2.0 (1.8, 4.8)</td>
<td>2.1 (1.0, 9.8)</td>
<td>0.844</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.1 (2.7, 3.5)</td>
<td>3.1 (2.7, 3.6)</td>
<td>3.1 (2.7, 3.5)</td>
<td>0.158</td>
</tr>
<tr>
<td>Prothrombin time (INR)</td>
<td>1.4 (1.2, 1.8)</td>
<td>1.4 (1.2, 1.9)</td>
<td>1.4 (1.2, 1.9)</td>
<td>0.507</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.80 (0.7, 1.0)</td>
<td>0.84 (0.7, 1.1)</td>
<td>0.80 (0.7, 1.1)</td>
<td>0.012</td>
</tr>
<tr>
<td><strong>Preoperative therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasopressor support</td>
<td>145 (4.8)</td>
<td>36 (10.6)</td>
<td>181 (5.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>245 (8.2)</td>
<td>54 (15.8)</td>
<td>299 (9.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>297 (9.9)</td>
<td>52 (15.2)</td>
<td>349 (10.5)</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Operative variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deceased-donor</td>
<td>475 (15.8)</td>
<td>51 (15.0)</td>
<td>526 (15.8)</td>
<td>0.726</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>740.8 ± 142.4</td>
<td>754.4 ± 140.6</td>
<td>742.2 ± 142.3</td>
<td>0.096</td>
</tr>
<tr>
<td>Total ischemic time (min)</td>
<td>147.5 ± 71.7</td>
<td>130.5 ± 53.4</td>
<td>140.8 ± 65.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Transfusion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pRBC (unit)</td>
<td>11.3 ± 14.1</td>
<td>13.1 ± 16.4</td>
<td>11.5 ± 14.3</td>
<td>0.052</td>
</tr>
<tr>
<td>FFP (unit)</td>
<td>11.7 ± 14.0</td>
<td>12.7 ± 14.9</td>
<td>11.8 ± 14.1</td>
<td>0.193</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± SD, number (%), or median (IQR, 3Q). LA: lactic acid, MELD score: Model for End-stage Liver Disease score, pRBC: packed red blood cells, FFP: fresh frozen plasma, INR: international normalized ratio.
0.4–24.6, interquartile range [IQR]: 1.5–2.6 mmol/L, n = 1,741), but it was markedly increased intraoperatively to a median LA level of 4.4 mmol/L (range: 0.5–34.7, IQR: 3.0–6.2 mmol/L, n = 3,338) (Fig. 1).

A total of 1,884 (56.4%) patients had intraoperative LA levels > 4.0 mmol/L, and while 188 (5.6%) had intraoperative LA levels > 10 mmol/L.

**Distribution of intraoperative LA according to MELDs**

When the patients were grouped according to MELDs of < 15 (n = 1,807, 54.1%), 15–35 (n = 1,169, 35%), and > 35 (n = 362, n = 10.8%), preoperative LA levels increased and separated clearly along with the increase of MELDs (1.8, IQR: 1.4–2.3 vs. 2.0, IQR: 1.5–2.6 vs. 2.6, IQR: 1.9–4.2 mmol/L, respectively; P < 0.001), whereas, despite the marked increase of intraoperative LA levels, the separation of LA levels were modest and somewhat inversed (4.5, IQR: 3.2–6.3 vs. 4.3, IQR: 2.9–6.2 vs. 4.1, IQR: 2.7–6.0, respectively; P = 0.002) compared to preoperative LA (Fig. 2).

**Prognostic cutoff values of intraoperative LA**

To predict 30-day all-cause mortality, tree-structured survival analysis using CART of a recursive partitioning algorithm demonstrated that intraoperative LA cutoffs of 13.5% and 16.7% were found to be optimal. In addition, maximally selected log-rank statistics of the “maxstat” R package revealed that LA cutoffs of 8.4% were the best cutoff for predicting for 90-day all-cause mortality (Fig. 3).

**Application of thresholds of LA to predict early mortality**

The 30-day and 90-day mortality rates were 2.5% (n = 83) and 4.7% (n = 157), respectively.

When the patients were grouped according to the best cutoff values of 8.4 mmol/L, those with LA > 8.4 mmol/L yielded a 30-day mortality rate of 6.7% and a 90-day mortality rate of 9.4% (P < 0.001) (Fig. 4). In particular, derived LA cutoffs of 16.7% and 13.5% by CART to predict 30-day mortality showed a wide separation of the KM curve. Patients with LA levels > 16.7 mmol/L and 13.5–16.7 had significantly higher 30-day mortality rates of 58.3% and 21.2%, respectively, compared to those with LA < 13.5 mmol/L, who had a 2.1% 30-day mortality rate (log-rank P < 0.001) (Fig. 4).
DISCUSSION

It has long been known that LA levels might reflect critically ill hepatic patients and are independently associated with the short-term mortality affiliated with end-stage liver disease (ESLD) [6,13,14]. In fact, the LA levels and its clearance are known predictors of the outcome of critically ill patients in the intensive care unit [15]. There has been widespread research, especially in septic patients, that evaluate the use of LA as a potential resuscitation marker or prognosticator. Therefore, the Surviving Sepsis Campaign Bundle suggested that if the initial LA is > 2 mmol/L, it should be remeasured within 2–4 h. Moreover, if the LA is > 4 mmol/L in those with sepsis, the initiation of rapid administration of > 30 ml/kg crystalloid is strongly recommended in sepsis [16].

However, lactate metabolism in cirrhosis differs substantially from that in patients without hepatic impairment. In the current study, we found that approximately 50% patients are associated with preoperative LA > 2 mmol/L, confirming that the LA level in patients with ESLD is quite different from those without ESLD. Therefore, management guidelines proposed “repeated measurement of blood lactate levels, even though the interpretation may be complicated by impaired clearance in cirrhosis” [17].

Furthermore, we found that 1,884 (56.4%) patients showed intraoperative LA > 4.0 mmol/L, and 188 (5.6%) exceeded intraoperative LA of 10 mmol/L. These rates are surprisingly high, given that LA levels > 10 mmol/L are associated with high mortality rates of 80% or more in critically ill patients [15,18]. In the current study on intraoperative LA exploration, patients with LA > 16.7 mmol/L and 13.5–16.7 mmol/L demonstrated significantly higher 30-day mortality rates of 58.3% and 21.2%, respectively.

LT is often an extremely difficult event for ESLD patients because LT recipients frequently suffer from severe hypotension, acute blood loss with extreme anemia, massive transfusion, inferior vena cava clamping, prolonged refractory hypotension with high-dose vasopressors, perturbed hemodynamics shortly after graft reperfusion, and/or pr-existing multiple organ failures, such as circulatory, respiratory, and kidney failures [12,19]. Additionally since initial grafts can poorly handle lactate load and may serve as a lactate-producing organ, intraoperative LA concentration is not only extremely high compared with preoperative LA, but also remains high regardless of increasing MELDs during LT surgery. It is thought that high intraoperative LA levels regardless of MELDs are likely to be due to the initial poor graft function and lactate-producing liver itself.

On the other hand, given that acidosis and hyperlactatemia can occur independently, hyperlactatemia might only be moderately predictive for acidosis. Both acidosis and lactate independently predicted mortality in critically ill patients suffering from sepsis [20]. Additionally, it has been reported that lactate clearance calculated at 6 h after reperfusion of an allograft was associated with the development of

![Decision tree diagram for 30-day mortality, showing intraoperative lactic acid cutoffs of 13.5 mmol/L and 16.7 mmol/L as optimal cutoffs in predicting 30-day all-cause mortality. LA: lactic acid, LA_op_MAX: lactic acid_intraoperative_maximal value.](image-url)
Fig. 4. Kaplan-Meier survival plot shows 30-day mortality according to intraoperative lactic acid > 16.7 mmol/L, 13.5-16.7 mmol/L and < 13.5 mmol/L (A) 90-day mortality according to intraoperative lactic acid > 8.4 mmol/L and 8.4 ≤ mmol/L (B). LA: lactic acid.

Early allograft dysfunction and in-hospital and 6 m mortalities after deceased donor liver transplantation [5]. In the current study, we did not evaluate the combining acidosis and hyperlactatemia and lactate clearance; therefore, further study including both of the aforementioned in a model will yield higher predictiveness of the short-term outcome in patients undergoing LT.

This study has several limitations. The enrolled patients
are from the observational cohort study in a single center and retrospective observational design. Therefore, further prospective randomized control studies are warranted to validate our results. Additionally, higher LA resulted in higher mortality rates, but did not completely exclude factors other than LA. Therefore, future study is needed to consider non-LA factors in patients with LT.

In conclusion, in this large cohort LT study determining cutoff levels of intraoperative LA, patients with LA > 13.5 mmol/L showed significantly higher 30-day mortality rates, and > 8.4 mmol/L was the optimal cutoff value for the 90-day mortality. Therefore, identifying intraoperative cutoffs of LA and correction of hyperlactatemia may play a potential role in lowering early mortality rates after LT.

**FUNDING**

This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI18C2383).

**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**


**ORCID**

Kyoung-Sun Kim, https://orcid.org/0000-0002-6643-9177
Sang-Ho Lee, https://orcid.org/0000-0001-5943-7715
Bo-Hyun Sang, https://orcid.org/0000-0001-6890-4629
Gyu-Sam Hwang, https://orcid.org/0000-0002-3627-1107

**REFERENCES**


Intradural disc herniations (IDH) are very rarely reported in the literature with an estimated incidence ranging between 0.04–1.5%, affecting males more than females with an onset between 50–60 years of age [1,2]. IDH is defined as fragmented disc material that breaks through the annulus, posterior longitudinal ligament (PLL), and dura migrating into the thecal sac. The exact etiology is unknown, but a few theories have been proposed, including fibrosis or adhesions of the dura to the annulus, prior history of spinal surgery, congenital narrowing, advanced degenerative disc disease with resulting chronic inflammation leading to erosion and dural thinning, congenital dura thinness or fusion between the dura and posterior ligaments [3–7].

The majority of cases reported in the literature suggest a clinical picture of acute-on-chronic lower back pain (LBP) with bilateral lower extremity pain, motor and/or sensory findings, often accompanied by symptoms of cauda equina syndrome (CES). Magnetic resonance imaging (MRI) is required to define the location of the disc pre-operatively, but the absolute diagnostic confirmation is made intraopera-
tively [3–7]. Treatment of IDH is often surgical, and there is a paucity of literature regarding interventional pain management outcomes, prognosis, and follow-up due to the rarity of this condition. We report a unique case presentation of IDH at the L3-4 level, initially managed with lumbar epidural steroid injection (LESI) due to patient preference to avoid surgery, but ultimately requiring surgical intervention due to progressive neurologic deficits. The patient provided written consent for the publication of this report.

**CASE REPORT**

A 54-year-old male with body mass index of 32 presented with a one-month history of acute-on-chronic LBP following heavy lifting during a recent move. The pain was experienced constantly, characterized as sharp, stabbing, and shooting, and radiated into the right buttock, lateral hip, and anterior thigh. He had associated right lower extremity numbness and tingling, in addition to weakness affecting the gluteal and quadriceps muscles. Pain was worse with lying supine and improved with sitting. He reported new onset difficulties with ambulation, including navigating stairs, transfers, and activities of daily living. Visual analog pain score was reported at 10/10. He denied symptoms of saddle anesthesia, bowel or bladder dysfunction and other CES-like symptoms. He tried over-the-counter analgesics, opioids, muscle relaxants, gabapentinoids and therapeutic exercises without improvement. Of note, he reported that these symptoms were significantly different from his intermittent axial, non-radicular LBP symptoms, which typically resolved spontaneously in 2–3 weeks with over-the-counter analgesics and adherence to his home-exercise program.

The patient was evaluated by a neurosurgeon and an interventional pain medicine physician. Physical exam revealed 5/5 strength on manual muscle testing of the bilateral lower extremities, except for 4/5 strength in the right quadriceps and hamstrings muscles. Sensation was intact to light touch in all dermatomes throughout the bilateral lower extremities. Perineal sensation was intact. Right-sided straight-leg raise was positive eliciting increased low back pain with aggravation of pain and tingling down the right leg, including the gluteal region and anterior thigh. Right lower extremity deep tendon reflexes (DTRs) were hypoactive compared to the contralateral side. Babinski’s sign was negative. MRI of the lumbar spine revealed high-grade central canal stenosis due to intradural disc herniation completely effacing the subarachnoid space and causing bilateral nerve root compression at the L3–4 level (Figs. 1, 2). The case was discussed among the neurosurgeon, pain physician and patient/family, and the decision was made to pursue a LESI as the patient

![Fig. 1. Sagittal and axial T2 weighted images demonstrate a large disc herniation extending through the dura into the thecal sac, with filling of the thecal sac and non visualization of the nerve roots.](http://www.anesth-pain-med.org)
declined surgery at this time, since he was leaving the city for an out-of-state job. The first LESI was performed roughly 6-weeks post injury. Due to nerve root redundancy above the level of the herniation (L3-4) and intolerance to injection at the L3-4 level due to pain, the epidural space at the L2-3 level was targeted via interlaminar approach under fluoroscopic guidance with notable cranial and caudal contrast spread (Fig. 3). A standardized solution of 1% lidocaine anesthetic and 80 mg of methylprednisolone acetate was injected. There were no procedural complications. At one-week follow-up post injection, the patient reported minimal pain relief, and the decision was made to proceed with a second LESI. Two weeks later, the patient underwent the second LESI by right-sided interlaminar approach at the same L2-3 level without complication. He reported approximately 40% overall improvement with reduction in pain, improved mobility, and increased ability to participate in daily activities and work duties. However, there was no recovery in motor weakness or DTRs at either post-injection follow-up visit.

At three-month follow-up post injury, the patient reported worsening and debilitating LBP characterized as sharp, electrical shock-like sensations involving the back and legs.
at work, particularly, he noted having ambulated 14,000 steps the day prior to pain exacerbation. He endorsed associated lumbar muscle spasms with impaired ability to stand or walk for more than five minutes. He reported significant fear-avoidance behavior and inability to find comfortable positions. He tried meloxicam, gabapentinoids and opioid analgesics, as well as physical therapy without improvement. The patient reconsulted with the neurosurgeon and the pain physician four months after initial injury. His physical examination was unchanged from prior visits and an updated lumbar spine MRI (Fig. 4) was obtained reconfirming the intradural location of the disc herniation without significantly increased mass effect on the nerve roots within the thecal sac. Based upon the progressive nature of the patient’s symptoms, the decision was made to proceed with surgical intervention.

In this case, the patient underwent an L3-L4 laminectomy and intradural resection of the disc herniation (Fig. 5). The ventral dural rent was identified and noted to be adherent to the annulus of the L3 disc space. Following complete resection of the intradural disc herniation, the dural was closed primarily. The dural repair was tested with intraoperative Valsalva to 30 mm water with no evidence of cerebrospinal fluid (CSF) leak. The dural repair was reinforced with Tissel® and the remainder of the incision was closed in anatomical layers. Intraoperative motor evoked potential monitoring was performed throughout the course of the case, and there was no change between the preoperative and intraoperative recordings. The patient tolerated the procedure well, was monitored for cerebral spinal fluid leak post-operatively, and ultimately discharged on post-operative day 4 to acute inpatient rehabilitation. At the 6-week postoperative visit, the patient’s symptoms had resolved, his neurologic exam had normalized, and he was able to return to full employment without restriction. At five month follow-up, his Oswestry Disability Score was 8/50 (16%), a 79% decreased from the pre-surgical score of 39/50 points (78%) of complete disability.

DISCUSSION

The first reported case of IDH was in 1942, and since other cases have been reported [1–4,6,8,9], yet it remains a very rare cause of lower extremity radiculopathy and CES [1–4,
Most IDH are found in the lumbar spine (95%) with the L4-5 level being the most commonly affected (55%) followed by the L3-4 level (16%) and then the L5-S1 level (10%) [2,6]. IDH has a 4:1 male to female ratio with an average age of onset of 50–60 years [1–4,5–7].

The pathogenesis for IDH remains uncertain. Several factors are thought to be responsible for this atypical herniation, including narrowing of the spinal canal due to congenital or iatrogenic causes, adhesions between the annulus fibrosus, PLL, and dura, and dura fragility [1–4]. Adhesion formation is thought to be the most important factor [2,6,7]. In normal conditions, the PLL and the dura are loosely attached. However, in the setting of prior spinal surgery, chronic disc herniation and/or traumatic forces dense adhesions may form, predisposing the area to IDH [1–4,6–8]. These adhesions, attaching the dural sac to the anterior wall of the central canal, may pull extruded disc material into the dural space [1,7]. An anatomical investigation by Yildizhan et al. [7] demonstrated that the firmest attachment of the ventral dura to the PLL was at the L4-5 level, which coincides with prior prevalence reports [1–4,6,8].

There is no difference in clinical signs between IDH and extradural disc herniations [5,8,9]. However, most IDH cases, as reported in the literature, suggest a similar clinical presentation of acute-on-chronic LBP with associated bilateral lower extremity symptoms and higher incidence of CES. In fact, CES has been reported in up to 30% of IDH cases in comparison to 0.5–1% in other disc herniations [5,8]. In contrast to most cases currently reported in the literature, our case reports a rare unique clinical presentation without CES, without previous surgical history and with initial unilateral lumbosacral radiculopathy that over several months progressed to bilateral radicular symptoms, with IDH at the L3-4 level, only present in 16% of cases.

IDH remains a challenge to diagnose. Mut et al. [10] proposed a classification system for IDH: Type A: herniation of disc into the dural sac and Type B: herniation of disc into dural sheath in the preganglionic region of the nerve root (also named intraradicular disc herniation). Historically, IDH has been diagnosed intraoperatively. This is in large...
part due to its rarity and the propensity to confuse the pathology with other space occupying lesions in the spinal canal, such as meningiomas, metastases, cysts, etc [2,5–7].

Neuroradiology perspective

In the present case, the imaging appearance was adequate to confirm the diagnosis. In the literature, several MRI signs that are reported to suggest IDH include a “Y-sign” in the ventral dura in which the disc material splits the ventral dura and arachnoid mater on T2-weighted sagittal images, a “crumble disc sign” in which there is discontinuity of the PLL and anterior thecal sac on T2-weighted sagittal images, and a “hawk-beak sign” in which a beak shaped lesion compresses the dural sac on T2-weighted axial images [6,11–15]. If MRI cannot be performed, myelography can show the presence of soft tissue compressing the thecal sac or filling the thecal sac, as in the case of IDH [5,6,13]. In addition to being used for pre-operative planning, it can be used to characterize the degree of CSF block at the suspected level [5,6,11–13]. On the axial and sagittal MRI pictures (Fig. 4), the herniated disc was seen to penetrate the posterior longitudinal ligament and dura, with disc material and blood filling the thecal sac, as there are no intrathecal boundaries to expansion. The disc had marginal enhancement, typical of chronic herniation with surface granulation. The obvious extension from the disc space and marginal enhancement excluded entities such as tumor or infection [14]. There was no mass effect on the dura/ thecal sac, as is seen in typical herniations, as the bulk of the disc entered and filled the thecal sac.

The present case fits the typical demographic profile for IDH in the setting of previous disc herniation but is rare in that the IDH occurred at L3–4 level, reported in 16% of cases, and resulted in unilateral radiculopathy without CES [2,6]. Unilateral radiculopathy, the absence of CES, functional ambulatory status and no prior lumbar spine surgical history, such as in our case, have rarely been reported in cases of IDH [1–4,6–8,14,15]. Unilateral radiculopathy without CES are considered good prognostic indicators for pain and motor recovery, in contrast to the presence of previous disc herniations, history of spinal surgery, chronic symptoms and CES [5–8].

Neurosurgery perspective

Early surgical intervention has generally been considered the treatment of choice for IDH to prevent further neurologic decline [2,7–9]. To our knowledge, no case report exists on successful conservative treatment of IDH. The current case is rare not only in presentation, but also in management as this patient was initially treated conservatively with satisfactory pain relief and improved function for at least 4 months, prior to re-injury and progression of the IDH. It is unclear whether early surgical management of IDH in individuals with minimal neurologic deficits is superior to initial conservative management with delayed surgery. Nevertheless, conservative management with spinal injections may improve pain control and function temporarily pre-operatively. Definitive treatment of IDH is surgical, which should preferably be performed with a microsurgical approach with a paramedian or median dural incision for better visualization of the hernia and to avoid damage to spinal roots [2,7,12].

IDH is a rare and challenging diagnosis, as demonstrated by a limited number of case reports and imaging similarities to other spinal cord pathologies. While the pathogenesis of IDH remains uncertain, it appears likely that adhesion formation between the annulus fibrosus, PLL, and dura from prior spinal surgery, disc herniation, or trauma predispose patients to developing this atypical herniation. Diagnostic evaluation should include an MRI pre-operatively and evidence of a large central disc herniation. Some studies report that findings such as the “Y-sign,” “crumble disc sign,” and/or “hawk-beak sign” should raise suspicion for IDH. Confirmatory diagnosis is made intraoperatively, and definitive management remains surgical; however, patients with minimal neurologic deficits may initially be managed non-surgical with spinal injections to improve pain control, restore function and increase early mobilization during the preoperative phase.

FUNDING

None.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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


ORCID

Vinicius Tieppo Francio, https://orcid.org/0000-0001-6513-0058
Christopher S. Wie, https://orcid.org/0000-0002-7784-7301
Micheal T. Murphy, https://orcid.org/0000-0003-2173-4882
Matthew T. Neal, https://orcid.org/0000-0002-5337-4407
Mark K. Lyons, https://orcid.org/0000-0001-8133-0295
Wende N. Gibbs, https://orcid.org/0000-0002-6493-1942
Natalie H. Strand, https://orcid.org/0000-0002-9489-2550

REFERENCES

Two cases of late-onset cardiovascular toxicities after a single injection of local anesthetics during supraclavicular brachial plexus block - A report of two cases -

Ji Yeon Kim, Beom Il Park, Min Hee Heo, Kyoung Woo Kim, Sang-Ill Lee, Kyung-Tae Kim, Won Joo Choe, Jang Su Park, and Jun Hyun Kim

Department of Anesthesiology and Pain Medicine, Inje University Ilsan Paik Hospital, Goyang, Korea

Background: Local anesthetics systemic toxicity (LAST) is a grave complication of regional anesthesia that usually occurs immediately after local anesthetics injection. Here, we report on rare late-onset toxicity cases after supraclavicular brachial plexus blocks.

Case: Two patients underwent surgery for radius fractures. We used lidocaine 100 mg and ropivacaine 150 mg for blocking and infused dexmedetomidine for intraoperative sedation. The 63-year-old male patient’s blood pressure dropped to 87/60 mmHg after 3 h 15 min after blocking. Ventricular fibrillation occurred 10 min later. After five defibrillations, electrocardiography showed ventricular tachycardia that was normalized through one cardioversion. The 54-year-old female patient’s heart rate decreased to 35 beats/min 2 h 30 min after blocking. Her vital signs returned to normal after administering atropine, ephedrine, epinephrine, and lipid emulsion.

Conclusions: Physicians should remember that LAST may occur long after local anesthetic injection and be aware of factors that may adversely affect the course of LAST.

Keywords: Adverse effects; Brachial plexus block; Lidocaine; Local anesthetic; Ropivacaine; Toxicity.

CASE REPORT

Case 1

A 64-year-old male (170 cm, 88 kg) with a history of hypertension and hyperlipidemia (American Society of Anesthesiologists physical status 2) visited our hospital with a radius fracture. The patient’s blood pressure was well controlled and there were no abnormalities in his preoperative electro-
cardiogram (EKG), blood tests, or chest radiograph images. The patient was scheduled to undergo open reduction and internal fixation surgery using supraclavicular BPB. The patient was moved to the block room to monitor his non-invasive blood pressure (NIBP), pulse oximetry, and EKG status.

The location of the brachial plexus was identified with an EPIQ 7 3.0–12.0 MHz 38 mm linear transducer ultrasound device (Philips, Netherlands) and a 22 gauge 50 mm Stimuplex Ultra 360 needle (B. Braun, Germany) was introduced into the target area using an in-plane technique (Fig. 1). The target nerve was identified by stimulating it with a current of 0.4 mA and observing the corresponding muscle twitching. To prevent intravascular injection, we ensured that blood was not aspirated through several regurgitations during the procedure. We used a mixed solution of 1% lidocaine 10 ml (100 mg) (Daihan Pharm, Korea) and 0.75% ropivacaine 20 ml (150 mg) (Mitsubishi Tanabe Pharma Korea, Korea) as local anesthetics. We checked whether there was a change in mental status through verbal communication during and immediately after the procedure. The patient’s vital signs immediately after anesthesia were stable (NIBP: 147/97 mmHg, heart rate: 88 beats/min). We confirmed sensory blockage by asking the patient to compare the sensation in the arm that received the anesthetic with that of the contralateral arm and confirmed the motor blockage by checking that the patient could not lift his anesthetized arm over his head. Dexmedetomidine (Pfizer Pharmaceuticals Korea, Korea) infusion was started 5 min after local anesthetic injection for intraoperative sedation in the operating room. It was infused at 480 µg/h for 10 min for loading then at 48 µg/hr. We infused dexmedetomidine for 1 h 50 min (total dose: 160 µg, 40 ml) and the operation took 2 h 30 min. After the cessation of dexmedetomidine infusion 1 h 55 min after local anesthetic administration, the EKG monitor showed premature ventricular contraction bigeminy, but it quickly disappeared and the patient’s vital signs did not show any abnormalities (NIBP: 115/77 mmHg, heart rate: 62 beats/min). We checked that there was no change in the patient’s mental status by communicating with him.

The patient was moved to the post-anesthesia care unit (PACU) and monitored by standard monitoring procedures after 3 h 5 min after local anesthetic administration. Ten min after being moved to the PACU, which was 1 h 10 min after dexmedetomidine cessation, the patient’s NIBP suddenly decreased to 87/60 mmHg and his heart rate was 61 beats/min. We administered ephedrine 5 mg intravenously and his NIBP slightly increased to 90/62 mmHg and his heart rate was 56 beats/min. However, after eight min, the patient seemed drowsy and did not respond to his name. As his peripheral oxygen saturation decreased to 87%, we assisted the patient’s breathing with a Jackson-Rees circuit (King Systems, USA). Two min after his mental state changed, the EKG monitor showed ventricular fibrillation (Fig. 2A) and we started chest compressions. We defibrillated the patient immediately and the EKG returned to a normal rhythm and maintained this pattern for a while. However, ventricular fibrillation occurred again. The patient’s EKG changed to ventricular tachycardia (Fig. 2B) after five defibrillations (200 J) and returned to a normal sinus rhythm through one synchronized cardioversion (50 J). We intubated the patient during cardio-pulmonary resuscitation and administered epinephrine 1 mg intravenously six times. We confirmed that the patient’s mental status had recovered after spontaneous circulation resumed 30 min after the cardiac arrest occurred (Fig. 3). Afterward, the patient was transferred to the intensive care unit and norepinephrine was infused at 0.2 µg/kg/min to maintain BP. Immediately after the patient was moved to the intensive care unit, we took 12 leads EKG that showed QT prolongation (Fig. 2C). Pulmonary edema was found on the chest radiograph and chest computed tomography (CT). We decided to maintain mechanical ventilation and started sedation with dexmedetomidine. No abnormal findings were found in the blood tests, EKG, and chest CT but Holter’s test showed multiple premature ventricular contractions (3,192 times/24 h). One day after sur-

![Fig. 1. Ultrasonography image of supraclavicular brachial plexus with color doppler. BP: brachial plexus, SA: subclavian artery.](www.anesth-pain-med.org)
gery, chest X-ray images did not show pulmonary edema and we performed extubation. Five days after surgery, the patient was moved to the general ward and was discharged eight days after surgery without any sequelae.

Case 2

A 54-year-old female (150 cm, 70 kg) without any underlying diseases (American Society of Anesthesiologists physical status 1) visited the hospital with a radius fracture. The patient was scheduled to undergo open reduction and internal fixation surgery using supraclavicular BPB. There were no abnormalities in her preoperative exams.

Anesthesia was performed in the same manner as in the previous case using the same local anesthetic drug and dose. There were no abnormalities in the patient’s condition during the procedure. Dexmedetomidine was administrated for intraoperative sedation. After 1 h 50 min of surgery, the

Fig. 2. Electrocardiography of the patient. (A) Ventricular fibrillation. (B) Ventricular tachycardia. (C) QT prolongation: heart rate-corrected QT interval = 484 milliseconds.
Patient was transferred to the PACU. Two hours 20 min after local anesthetic administration, the patient was moved to the PACU and monitored by standard monitoring. After 10 min, the patient showed a drowsy mental state. Seven min later, her NIBP was maintained at 98/57 mmHg but her heart rate decreased to 35 beats/min. To resolve bradycardia, we administered atropine 0.5 mg intravenously. Her heart rate increased slightly to 41 beats/min, but her NIBP could not be measured. Hypotension and bradycardia were treated with two intravenous administrations of ephedrine 10 mg. The patient seemed confused, so we assisted her breathing with a Jackson-Rees circuit (King Systems, USA). Then, suspecting LAST, we injected 20% lipid emulsion (LE) (Fresinius Kabi Korea, Korea) 100 ml as a bolus over three min followed by infusion at a rate of 17.5 ml/min and injected epinephrine 20 μg. After injection of epinephrine and LE, the patient’s NIBP and heart rates increased and her mental state returned to normal (NIBP: 193/97 mmHg, heart rate: 121 beats/min) (Fig. 4). The LE infusion was terminated 10 min after the patient’s vital signs were confirmed to be stable. The patient stayed in the PACU for about 1 h and was then transferred to the general ward after she was confirmed to have made a full recovery. Unlike in the previous case, a blood sample was taken from her radial artery to measure the concentration of ropivacaine, which was determined to be 1.1 μg/ml.

Written informed consent to publish these cases was obtained from both patients.
DISCUSSION

This case report was about a 64-year-old male and a 54-year-old female who underwent supraclavicular BPB for surgery to treat radius fractures and developed cardiovascular symptoms 2–3 h after local anesthetic administration.

For these cases, symptoms occurred long after the injection of local anesthetics, so we did not initially suspect LAST. It usually occurs shortly after the injection of local anesthetics and is usually caused by unintended direct intravascular injection. When toxicity is delayed, it is caused by infiltrated anesthetics being absorbed through the surrounding tissues [3]. More than 70% of LAST cases occurred within 1 h of local anesthetic administration and those that occurred after 1 h mainly occurred during continuous infusion of local anesthetics [4].

Rarely, cases of late-onset LAST that occurred after a single local anesthetic injection during BPB have been reported. Oh et al. [5] reported LAST that occurred 1 h after interscalene-axillary BPB single injection. They injected 0.75% ropivacaine 12 ml (90 mg) into the interscalene brachial plexus and then injected a mixed solution of 0.75% ropivacaine 8 ml (60 mg), 2% mepivacaine 20 ml (400 mg), and normal saline 20 ml to the axillary brachial plexus. They additionally injected 1% lidocaine 5 ml (50 mg) to block the intercostobrachial nerve. The patient experienced seizures 1 h after injection of local anesthetics but no cardiovascular system symptoms. Incérib et al. [6] reported LAST that occurred 7 h after infraclavicular BPB single injection. However, they used bupivacaine and prilocaine, which have longer half-lives than the local anesthetics used in our cases and the total amount of drugs used was also large (0.5% bupivacaine 11.25 ml, 56.25 mg + 2% prilocaine 11.25 ml, 225 mg). In addition, unlike our first case, cardiac arrest did not occur in their case.

There are no well-established diagnostic criteria for LAST. LAST is diagnosed through clinical symptoms. Differential diagnoses of LAST include anaphylaxis, anxiety, methemoglobinemia, and reaction to the vasoconstrictor. These complications have similar presentations to LAST’s clinical features, making differential diagnosis difficult. If possible, a blood test should be used to measure the concentration of local anesthetics [7]. In the first case, we could not measure the concentration of the local anesthetic, but in the second case, we took a blood sample to measure the concentration of the local anesthetics while administering an LE. We collected blood samples from the radial artery and confirmed the plasma concentration of free-form ropivacaine to be 1.1 μg/ml. The concentration was measured 2 h 50 min after injection of local anesthetics and 3 min after LE injection. The toxic threshold for ropivacaine has not been clearly established, so it may be challenging to ascertain whether the concentration of 1.1 μg/ml caused LAST or not. Knudsen et al. [8] found that ropivacaine toxicity occurred at concentrations of 0.34–0.85 μg/ml (arterial blood, free form) and Scott et al. [9] found ropivacaine toxicity at concentrations of 1–2 μg/ml (venous blood). Therefore, it is possible ropivacaine induced LAST in our cases. It is worth mentioning that concentrations differ vastly according to whether the blood sample was taken from an artery or vein and whether it was free-form or bound-form, so toxicity concentrations should be interpreted carefully.

We also used lidocaine but we could not measure its concentration due to technical issues. Lidocaine may aggravate LAST, but it has a shorter half-life than ropivacaine. A mixture of local anesthetics is used to achieve anesthesia sooner and reduce toxicity. However, there is some controversy about accelerating anesthesia onset [10] and whether the anesthetics’ toxicities are additive [11]. Therefore, it would be safer to assume that anesthetics’ toxicities are additive.

Although LAST likely occurred in these two cases, other factors might have worsened its clinical course. The first factor is that dexmedetomidine can cause bradycardia, hypotension, and even cardiac arrest as side effects [12]. Severe bradycardia and even cardiac arrest have been reported when dexmedetomidine is combined with other agents, such as lidocaine [13]. These symptoms were observed in both our cases. The second factor is that arm slings could have caused carotid sinus hypersensitivity. When the carotid sinus baroreceptor is compressed, it induces parasympathetic activation, which leads to hypotension and bradycardia. In severe cases, it can progress to syncope or cardiac arrest. Canbora et al. [14] reported carotid sinus hypersensitivity due to arm sling use in a 56-year-old female PACU patient who had undergone shoulder surgery. Both patients in our cases were wearing arm slings while sedated, so the weight of the anesthetized arm may have directly compressed the carotid sinus.

The use of ultrasound reduces most of the rapid-onset LAST caused by the direct intravascular injection of local anesthetics. However, it still occurs, so physicians must be vigilant about it and determine whether any of the following risk factors are present: Previous local anesthesia experience; being young or old because newborns, young chil-
dren, and elderly patients have less lean muscle mass than other patients; having a low total body mass; having a systemic, cardiac, renal, hepatic, or metabolic disease or protein binding abnormality; being pregnant; and having low plasma binding protein or albumin levels, which is particularly common in infants. Anesthetic characteristics and dosages should be carefully analyzed and the injection site should be carefully planned. Ultrasound-guided nerve blockades, incremental injections with frequent aspiration, and using pharmacological markers, such as epinephrine can help prevent LAST [1,3,15].

If LAST occurs despite all these measures, certain measures need to be carefully taken to improve patient outcomes. According to the American Society of Regional Anesthesia and Pain Medicine, airway maintenance and oxygenation are prioritized in treatment. If seizures occur, benzodiazepine should be administered. Treatment of arrhythmia and hypotension that occurs as the result of LAST is different from their treatment as part of standard advanced cardiac life support. Epinephrine doses should start at less than 1 μg/kg. The American Society of Regional Anesthesia and Pain Medicine also recommends the early administration of LE. Patients weighing more than 70 kg should be administered a maximum of 100 ml bolus over 2–3 min then receive an infusion of up to 250 ml for 15–20 min. Patients weighing less than 70 kg should receive an injection of a maximum of 1.5 ml/kg bolus over 2–3 min followed by an infusion of up to 0.25 ml/kg/min [15].

In conclusion, physicians should be aware that LAST may occur long after a single injection of local anesthetics and should consider factors that may adversely affect its course, such as the use of dexmedetomidine and arm slings.

FUNDING

None.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

None.

REFERENCES


Hereditary angioedema (HAE) is an autosomal dominant genetic disease with a prevalence of 1:50,000. The etiology of HAE includes low level of C1-esterase inhibitor (C1-INH) antigen and/or low activity of C1-INH. The disease is characterized by recurrent, nonpitting edema typically on the upper or lower extremities, genital area, trunk, and face, as well as submucosal edema involving the digestive tract or upper airway tract [1]. The greatest concern of patients with HAE is upper airway edema induced by direct mechanical irritation due to the endotracheal tube during general anesthesia [2]. Laryngeal edema warrants urgent treatment and immediate hospitalization in 37% of all angioedema episodes [3].

We present a clinical case of a 59-year-old female patient who underwent total laparoscopic hysterectomy under general endotracheal anesthesia, managed successfully.

CASE REPORT

Institutional Review Board (IRB) waived the requirement of written consent for the publication of this case (no. 2021-03-060-002 CHA Bundang Medical Center IRB). The patient has also provided prior consent to the publication of procedures and anonymous case details in this report.
A 59-year-old female patient (height, 162 cm; weight, 59 kg) with type I HAE was scheduled for total laparoscopic hysterectomy. The patient’s medical history revealed a diagnosis of type I HAE at the age of 49 years, based on genetic testing. She experienced recurrent episodes of angioedema involving legs or hands once every 2–3 months. However, she had not experienced an edema attack for the past one year, so she had been using 100 mg of danazol once a week for long-term symptom control. Preoperative blood tests revealed normal range of biochemical parameters except for total cholesterol (216 mg/dl, normal range: 0–200 mg/dl). Protein immunoassay revealed a C4 level of 14 mg/dl (normal range: 10–40 mg/dl). The patient’s C1-INH antigen level was 9.70 mg/dl (normal range: 21.0–39.0 mg/dl) and the C1-INH activity was 33% (normal range: 70–130%). Chest X-ray and electrocardiography findings were normal.

The patient was treated with danazol 200 mg the day before surgery. Before induction, the blood pressure was 135/78 mmHg, and the pulse rate was 82 beats/min. General anesthesia was induced with intravenous (IV) glycopyrrolate 0.2 mg, propofol 100 mg, sufentanil 5 μg and rocuronium 40 mg. The endotracheal intubation was performed smoothly using a video laryngoscope, and no abnormalities such as edema of the epiglottis or vocal cords were detected. Anesthesia was maintained with an end-tidal concentration of sevoflurane 2–3 volume%, and intermittent sufentanil with 40% oxygen. Left radial artery was cannulated. We transfused 3 pints of fresh frozen plasma (FFP) as recommended by the allergy department. At the end of the surgery, video laryngoscopy confirmed the absence of edema in the patient’s epiglottis and vocal cord. Further, no edema was detected in the trachea and carina with a fiberoptic bronchoscope. The patient was reversed with glycopyrrolate 0.2 mg mixed with pyridostigmine 10 mg IV, and then extubated after responding to the verbal command. At the end of the operation, an adequate amount of opioid was administered. Spontaneous breathing was restored, followed by extubation with minimal stimulation via the endotracheal tube. The patient did not have any particular complaints and the vital signs were stable. The total fluid intake during the surgery was 1,310 ml including 3 pints of FFP, and the output was 680 ml including blood loss. She stayed at the sub-intensive care unit for 1 day to monitor possible late-onset airway edema after surgery. No special events were detected until discharge, and the patient took danazol as usual and was discharged 4 days after the operation.

The patient visited the outpatient clinic a week after discharge and reported no significant event. However, four weeks later, during her second visit, she complained that edema alternated between her left and right feet every 10 days. The patient no longer experienced edema by week 8 of outpatient follow-up.

**DISCUSSION**

HAE is divided into three types. Type I HAE appears in about 85% of HAE patients and is characterized by a low level of C1-INH antigen (less than 35%) and low inhibitory activity. The functional C1-INH activity in type I HAE is typically 20–35%. Type II HAE is less common and occurs in ≤15% of HAE patients; it is associated with a functional defect involving C1-INH. In type II HAE, the C1-INH antigen level is normal or sometimes elevated. In addition, type N HAE is detected in a few cases [1]. Our patient is type I HAE and also had a low C1-INH antigen level of 9.7 mg/dl (32%) and 33% of low C1-INH activity. The C4 level is simple and inexpensive to test and is used as a screening tool; however, in our patient, the preoperative C4 level was in the normal range. Rarely, the C4 levels are normal between angioedema episodes [4]. Low or dysfunctional activity of C1-INH interferes with kallikrein, preventing normal bradykinin synthesis. As a result, bradykinin-mediated vascular permeability is altered [5].

Bork and Barnstedt [6] reported four deaths due to laryngeal edema after tooth extraction. Patients with HAE who require tooth extraction also carry a risk of developing facial or laryngeal edema and prophylactics can be used to reduce the risk of symptoms [7]. Angioedema associated with surgery usually appears in surgical areas, but may occasionally involve unrelated areas. Among 19 reports of angioedema-associated surgery, a case of laryngeal angioedema was detected after laparoscopic surgery and two cases after adenoidec- tomy. Reintubation was performed to manage a case of laparoscopy-induced laryngeal edema [8]. Despite the absence of a direct correlation between intubation and laryngeal angioedema in HAE patients, laryngeal angioedema has been reported after oral surgery in patients who did not receive prophylactic treatment [6,7]. Upper airway stimulation should be avoided as much as possible to ensure safety. In our case, no laryngeal mask airway (LMA) was used because it was a laparoscopic surgery. LMA does not stimulate the vocal cord or trachea, but its large contact area in the oral cavity may lead to oral mucosa stimulation. Fatal airway edema was reported after tooth extraction rather than air-
way intubation [6,7]. Therefore, irritation of the oral mucosa can also cause asphyxia, and in the case of edema, it is considered safe to perform endotracheal intubation.

In general, to prevent postoperative laryngeal edema, an endotracheal tube of adequate size should be selected first. Second, the duration of intubation should be minimized. Third, the cuff pressures should be measured regularly to prevent tracheal stimulation due to high cuff pressure.

Regional anesthesia, such as brachial plexus block or neuraxial block, is considered to be a good alternative for general anesthesia to reduce the possible incidence of airway edema induced by mechanical stimulation due to endotracheal tube.

The two ways to approach HAE patient include preventing attacks with prophylaxis and on-demand treatment of edema episodes. Both are very important in perioperative patients. Patients who have frequent, above-moderate degree of angioedema episodes need prophylactic and on-demand treatment during medical or surgical procedures [9]. Before 2009, antifibrinolytics (e.g., tranexamic acid and ε-amino-caproic acid) and 17beta-hydroxy steroid (danazol) were used as prophylactics to increase the synthesis of C1-INH in liver. A number of agents that have been approved over the past few decades are available for prophylactic use. Between 2008 and 2017, the US Food and Drug Administration approved three plasma-derived C1-INH agents: Cinryze® (2008, Shire ViroPharma, USA), Berinert® (2009, CSL Behring, USA), and Haegarda® (2017, CSL Behring, USA) [10]. Consensus guidelines recommend giving 500–1,500 U of Berinert® as a prophylaxis one hour before the procedure to prevent severe angioedema [11]. In 2018, Takzyry® (Shire Dyax Corp., USA), a plasma kallikrein inhibitor, was approved [10]. When plasma-derived C1-INH is not available, solvent-treated FFP is recommended 1–2 h prior to procedure, or administration of danazol is recommended days prior to increased liver synthesis of C1-INH. FFP is more effective in preventing or minimizing angioedema than danazol [11]. In our case, the dose of danazol was raised to only 200 mg a day and FFP was given after induction, because there was no edema in the last one year.

On-demand treatment is needed to reduce the degree of angioedema and pain during HAE attack and induce rapid recovery. Until plasma-derived C1-INH became popular, FFP was the first choice of on-demand treatment and is still the only treatment when C1-INH is not available. A few units of FFP (1–4 U) are effective (96%) in all types of acute attack including severe subcutaneous and submucosal laryngeal edema. FFP is considered effective in preventing and treating acute angioedema attacks before surgery [12]. However, the time to resolution is slower than in targeted therapies [13]. In addition to Berinert®, Ruconest® (Pharming, Bridgewater, USA), which is a recombinant C1-INH, can also be used as a prophylactic. Firazyr® (bradykinin antagonist, Shire, USA) and Kalbitor® (Shire Dyax Corp.) are also used as treatments [10]. In HAE patients over 12 years of age, 20 IU/kg of Berinert® is used for treatment [14].

We transfused 3 pints of FFP immediately before surgery in this patient and extubated safely. In Korea, Berinert® was approved by the Korean Ministry of Drugs and Food Safety in 2011, and on April 1, 2021, CSL Korea signed a contract to import Berinert®, although it has yet to be imported. Therefore, the best option was to use danazol as a prophylactic treatment and FFP as a prophylactic and on-demand treatment under the circumstances prevailing in South Korea.

In HAE, an edema follows a predictable course. In many cases, it involves prodromal signs such as a tingling sensation or a non-itching serpiginous rash. Swelling classically progresses slowly but continues for the first 24 hours, followed by a gradual decline over the subsequent 48 to 72 h. According to one report, laryngeal angioedema is symptom-free for 4 to 30 h [6]. Therefore, active monitoring of the patient should be performed at least one day after the surgery. Fortunately, there was no airway edema in our patient following extubation after the surgery. However, the patient was monitored in the sub-intensive care unit due to the risk of angioedema up to 12–24 h after surgery.

Several weeks after discharge, the patient present at the outpatient clinic with complaints of recurring foot edema, despite the continued use of danazol.

Successful management of HAE requires close and appropriate teamwork between the departments of allergy and immunology, surgery, anesthesiology and critical care medicine for accurate diagnosis, prevention, and treatment.

Histamine-mediated angioedema (HMA) must be distinguished from HAE, which exhibits a similar clinical pattern. HMA is often accompanied by urticaria and pruritus, lasts for 24–48 h, and responds to administration of antihistamines and corticosteroids [15]. HAE does not show histamine-mediated wheals or bronchoconstriction; therefore, steroids or antihistamines are not very effective in treating HAE.

The standard treatment for HAE is prophylactic C1-INH before surgery and on-demand treatment of recombinant C1-INH for symptom management, and close observation.
for at least 24 h after surgery for delayed angioedema. However, if C1-INH is not available, prophylactic danazol and FFP should be administered before surgery, as in our case, followed by close observation for 24 h. It is also recommended to use FFP for therapeutic purposes even if symptoms appear.

In conclusion, edema prophylaxis and on-demand treatment are important since airway edema can be induced by surgical stress. In addition, careful observation after surgery is necessary to rapidly detect delayed manifestations of edema.

**FUNDING**

None.

**CONFLICTS OF INTEREST**

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

**DATA AVAILABILITY STATEMENT**

None.

**AUTHOR CONTRIBUTIONS**


**ORCID**

Yun-Sic Bang, https://orcid.org/0000-0002-0930-4313
Jaeho Cho, https://orcid.org/0000-0002-5181-6937
Chunghyun Park, https://orcid.org/0000-0003-1916-6644

**REFERENCES**

Intraoperative pulmonary aspirations are rare events that occur in approximately one in 2,000 to 3,000 operations, but are potentially fatal complications associated with significant morbidity. Numerous risk factors can cause anesthesiarelated aspiration events, including delayed gastric emptying, an incompetent lower esophageal sphincter (LES), need for emergency surgery, and obesity [1]. Among them, achalasia, which is characterized by impaired transit of swallowed food due to LES relaxation disorder and loss of esophageal peristalsis, is a rare disease [2]. The authors experienced the occurrence of unpredictable intraoperative aspiration events during anesthesia induction in the patient with no special underlying disease, and the patient was subsequently diagnosed with achalasia after obtaining a detailed medical history and using diagnostic tools. Therefore, we report the management of pulmonary aspiration during induction of anesthesia in one patient and discuss possible measures to prevent intraoperative aspiration.
CASE REPORT

The Institutional Review Board of our hospital waived the need to obtain the patient’s informed consent for publication of this case report (no. 4-2021-1071). A 70-year-old female patient (height, 144 cm; weight, 65 kg) was admitted to the hospital to undergo bilateral total knee arthroplasty (TKA) for the treatment of degenerative knee joint osteoarthritis. The patient had been previously diagnosed with hypertension, and her preoperative test results were within normal range.

The patient underwent an overnight fast starting at midnight one night before surgery, and entered the operating room at 3 pm. The initial vital signs in the operating room were stable: blood pressure, 147/81 mmHg; heart rate, 89 beats/min; and oxygen saturation, 100%. A spinal needle was inserted for spinal anesthesia in the lateral position, but the patient complained of pain and anxiety during the procedure. Therefore, the plan was changed to perform general anesthesia.

Propofol 110 mg was administered intravenously to induce consciousness loss, and 50 mg of rocuronium was injected to relax the muscles. When manual ventilation using a bag and mask began with a peak airway pressure < 10 cmH₂O, the patient regurgitated food material from the mouth. Therefore, we put the patient in the Trendelenburg position and performed oral suctioning. However, the patient’s oxygen saturation decreased to 82%. Additional administration of 30 mg of rocuronium and rapid-sequence intubation were performed with a 6.5-mm tube using a video-guided laryngoscope. After intubation, oxygen saturation was maintained at 95–98% and arterial line cannulation was performed for continuous vital sign monitoring and arterial blood gas analysis (ABGA), while a substantial amount of food material in the bronchi was suctioned using a bronchoscope. Nasogastric tube placement was performed with a video-guided laryngoscope to identify persistent reflux patterns, and suctioning was also performed (Supplementary Video 1). Additionally, the gastric content and volume were assessed using ultrasonography, but the total gastric volume was lower than 1.5 × the body weight (kg), which is the threshold for an elevated high risk of aspiration. Moreover, the gastric content did not include any solid material (Fig. 1) [3]. The patient was referred for a pulmonology consultation for the treatment of aspiration pneumonia, and a pulmonologist performed fiberoptic bronchoscopy (FOB) in the operating room. Small amounts of foamy secretions were observed in the right lower lobe, and very small amounts of remnant material were aspirated in the bronchi of both lungs through FOB. Lung recruitment maneuvers were performed, and the patient was mechanically ventilated at a tidal volume of 350 ml and a positive end-expiratory pressure of 5 cmH₂O. However, ABGA tests conducted after FOB showed that the PaO₂ was 84 mmHg at a FiO₂ of 0.6 and peak airway pressure of 15 cmH₂O. Therefore, we decided to cancel the surgery and focus on management of the aspiration pneumonia before rescheduling the surgery. Sugammadex (200 mg) was used to reverse the neuromuscular blockade, and extubation was performed after recovery of spontaneous respiration and consciousness. On interviewing the patient to determine the exact fasting time and obtain a detailed medical history, we found that the patient had experienced severe reflux symptoms, including episodes of waking up after vomiting during sleep, but these were not treated. Low-dose chest computed tomography (CT) examination to determine the cause of vomiting suggested esophageal motility disorder, as well as esophagogastroduodenoscopy (EGD), esophagography, and esophageal manometry were performed to confirm these findings. EGD and esophagography findings showed a dilated esophageal lumen and narrowing of the esophagogastric (EG) junction, and the presence of achalasia were confirmed on manometry, so the patient was diagnosed with achalasia (Fig. 2A, B). Moreover, we suspected aspiration pneumonia in both lungs, especially in the left lower lobe, on the basis of the chest posteroanterior radiographs obtained after anesthesia and treated her with antibiotics for approximately 2 weeks (Fig. 3). She showed no other symptoms other than fever of 37.8°C in the general ward, and her oxygen satu-
tion was maintained over 95% by administering oxygen through a nasal cannula at a rate of 3 L/min and tapering off the next day. The patient was discharged after a 6-day hospital stay and prescribed oral antibiotics for 1 week.

She was hospitalized 2 months later for the rescheduled TKA. The patient was put on a soft-food diet from 2 days before the surgery, and EGD was performed at 5 pm on the day before the surgery to remove a large amount of water and food material from the esophagus. No food material remained in the stomach. Ultrasound-guided spinal anesthesia was successfully performed in a sitting position. The patient underwent bilateral TKA without any complications and was discharged on postoperative day 2.

**DISCUSSION**

Intraoperative pulmonary aspiration is a rare complication, but it may cause serious sequelae. The predisposing risk factors for anesthesia-related aspiration include a full stomach, delayed gastric emptying, an incompetent LES, esophageal cancer, previous esophageal surgery, gastrointestinal obstruction, need for emergency surgery, lack of coordination of swallowing or respiration, and obesity [1]. Among these, achalasia is a rare disease caused by the in-

---

**Fig. 2.** The diagnostic images. (A) Diffuse and extensive dilatation of the esophagus with narrowing at the esophagogastric junction in chest CT. (B) Marked tortuous dilatation of mid to distal esophagus with abrupt narrowing at the gastroesophageal junction in esophagography (bird-beak sign). CT: computed tomography.

**Fig. 3.** Posteroanterior chest radiographs. (A) Preoperative image; (B) diffuse consolidation on both lungs on postoperative day 3; (C) improved consolidation at 4 weeks postoperatively.
complete relaxation of the LES and the loss of esophageal peristalsis. Its incidence and prevalence in Korea have been reported to be 0.4 and 6.3 per 100,000 individuals, respectively [4]. The clinical presentations of this condition may include dysphagia, regurgitation, chest pain, weight loss, and odynophagia.

In the present case, the patient was diagnosed with achalasia because of regurgitation of food materials during induction of general anesthesia, although she showed no specific underlying disease other than hypertension. A detailed evaluation of her medical history revealed occasional episodes of severe reflux symptoms, including vomiting during sleep. Using the Eckardt Symptom score [5], the patient’s symptoms were assigned to the subsets of no dysphagia and occasional regurgitation, no retrosternal pain, and weight loss of < 5 kg, each of which was rated at 2 points, with scores ≥ 3 considered suggestive of active achalasia [6]. According to the 2019 Seoul consensus on esophageal achalasia guidelines [5], endoscopy and CT/endoscopic ultrasound (EUS) can be performed to diagnose patients with suspected achalasia. In this patient, low-dose chest CT indicated esophageal motility disorder, while EGD showed a dilated esophageal lumen and a tightly closed EG junction, which indicated achalasia. Furthermore, esophagography and high-resolution manometry were recommended to confirm achalasia. The esophagographic findings were dilation of the esophagus, narrowing at the EG junction with a bird-beak appearance, and incomplete LES relaxation. After esophageal manometry, this patient was diagnosed with Chicago classification achalasia subtype 2 [5]. This subtype is the most common type, and is characterized by the absence of peristalsis along with an abnormal pan-esophageal pressurization and a good response to pneumatic dilation. Considering the patient’s advanced age and the severity of the disease, pneumatic balloon dilation was recommended as an initial treatment before the knee surgery. However, the patient wished to undergo orthopedic surgery first. Therefore, follow-up treatment of achalasia was planned after the surgery.

Prevention is the ideal approach for the management of intraoperative pulmonary aspiration. Thus, identification of predisposing factors and risk assessment through a thorough preoperative physical examination and a review of the current symptoms are important [1]. The predisposing risk factors can be classified as patient-related, operative, and anesthetic factors. Patient-related factors include a full stomach, delayed gastric emptying, an incompetent LES, and esophageal diseases; operative factors include upper gastrointestinal surgery and laparoscopy; and anesthetic factors include light anesthesia, supraglottic airways, positive-pressure ventilation, and a difficult airway. Preoperative fasting for a few days before the procedure is recommended in cases where the patient is expected to show poor gastric emptying and retention of solid food matter in the stomach [1]. For patients at a high risk of achalasia undergoing peroral endoscopic myotomy (POEM) procedures, preoperative EGD may reduce the aspiration risk, while preemptive nasogastric tube placement may also be an alternative approach [7].

If aspirations occur despite proper application of preventive measures, rapid-sequence induction and management of the cricoid pressure for prompt placement of an endotracheal tube to secure the airway are critical [8]. The cricoid pressure should be reduced if this practice interferes with airway management [9]. After securing the airway, FOB should be considered for endotracheal suctioning. Subsequently, a decision regarding continuation of the surgery can be taken on the basis of the patient’s oxygen saturation, pulmonary compliance, and response to bronchodilator and positive end-expiratory pressure. Although antibiotics and steroids are not used routinely, they can be used if necessary.

Anesthesia management in patients diagnosed with achalasia has been covered in some previous case reports. Creagh-Barry et al. [10] reported performing intubation with cricoid pressure along with fasting for solids and fluid for 12 h before the operation, 45° reverse Trendelenburg positioning during induction of anesthesia, and extubation with clear consciousness without any complications. Their findings showed that reducing the contents of the esophagus through nasogastric tube insertion can lower the risk of pulmonary aspiration. However, Choi et al. [11] reported a case of regurgitation and aspiration pneumonitis even after preoperative fasting for 12 h in a patient who had undergone a POEM procedure 6 months before surgery. In our case, despite 16 h of fasting, the aspiration events occurred, and immediate treatments such as Trendelenburg positioning, oral suction, rapid-sequence intubation, endotracheal suctioning through a bronchoscope, nasogastric tube insertion, and FOB in the operating room were performed. Takenaka et al. [12] reported that a 10° Trendelenburg position with the Sellick position or more than 35° Trendelenburg positioning in simple neck extension had the potential to completely prevent aspiration. However, this position cannot be used in patients with cervical spine instability and may make trache-
al intubation difficult. When general anesthesia is provided to patients at high risk of pulmonary aspiration, it is important to prevent pulmonary aspiration and adopt an optimal posture for rapid-sequence intubation [13]. When the patients were hospitalized for reoperation, EGD was performed on the day before the surgery to remove a large amount of water and food materials from the esophagus. Subsequently, ultrasound-guided spinal anesthesia was performed successfully, and the patient underwent bilateral TKA without facing any complications.

Another notable point in the present case is related to the usefulness of imaging techniques. Recently, gastric ultrasound was reported to be useful to identify or rule out a full stomach and assess the risk of pulmonary aspiration [14,15]. However, gastric ultrasound cannot predict a high risk of pulmonary aspiration in patients with esophageal mobility disorder, similar to our patient. In the EGD performed following anesthesia, a substantial amount of food material was found only in the esophagus, not in the stomach. In patients with undiagnosed esophageal diseases, the risk of pulmonary aspiration can only be predicted by detailed interviews. The patient in this case was not diagnosed with achalasia, but experienced severe reflux symptoms such as vomiting during sleep, indicating that a detailed evaluation of the patient’s medical history before anesthesia is important.

Symptoms related to a high risk of pulmonary aspiration include gastrointestinal reflux disease, esophageal dysmotility, difficulty in swallowing, gas bloating, and other signs of delayed gastric emptying [1]. Further, patients that are considered to be at a high risk of pulmonary aspiration should receive an adequately detailed explanation of aspiration and undergo appropriately long preoperative fasting. The current guidelines recommend consumption of a light meal and clear liquid up to 6 and 2 h, respectively, prior to the surgery [16]. However, there is limited knowledge concerning the appropriate fasting time in surgical patients at a high risk of anesthesia-related regurgitation and aspiration. Although it is safe to maintain consciousness through regional anesthesia, in cases requiring general anesthesia, preoperative EGD or nasogastric tube insertion is necessary, and rapid-sequence intubation should be considered to allow safe induction of anesthesia.

If the patient is judged to be at high risk, adequate preoperative fasting and regional anesthesia or rapid-sequence intubation should be considered for the safe induction of general anesthesia.

SUPPLEMENTARY MATERIALS

Supplementary video is available at https://doi.org/10.17085/apm.21102.

FUNDING

None.

CONFLICTS OF INTEREST

Yong Seon Choi has been an editor of the Anesthesia and Pain Medicine since 2018; however, she 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.

DATA AVAILABILITY STATEMENT

None.

AUTHOR CONTRIBUTIONS


ORCID

Hee Jung Kim, https://orcid.org/0000-0002-2143-3943
Yong Seon Choi, https://orcid.org/0000-0002-5348-864X
Jeong Hyun Jin, https://orcid.org/0000-0002-5348-864X
Bora Lee, https://orcid.org/0000-0002-7699-967X

REFERENCES

4. Kim E, Lee H, Jung HK, Lee KJ. Achalasia in Korea: an epidemi-


High-flow nasal cannula oxygenation for awake craniotomy in patients with obesity: looking beyond oxygenation

TO THE EDITOR: We read with interest the use of high-flow nasal cannula (HFNC) oxygenation to prevent sedation-induced hypoxia in patients undergoing awake craniotomy. The authors report interesting observations, particularly the case of obstructive sleep apnea (OSA) [1]. While the findings could be applied in future clinical practice, some methodological aspects are worth a discussion.

The authors used the oxygen reserve index (ORI) to predict desaturation early and found it better compared to peripheral oxygen saturation. While monitoring for oxygenation is vital in procedural sedation, the ventilation status is equally critical in patients with neurosurgical disorders as it can impact carbon dioxide removal and, subsequently, intracranial blood flow and pressure. Although end-tidal carbon dioxide monitoring can provide information regarding ventilation, it has disadvantages of technical difficulty and a high error rate in patients receiving HFNC oxygenation [2]; the recent technology of transcutaneous carbon dioxide monitoring might be an alternative in the future [3]. Sedation with propofol and remifentanil can lead to severe hypoventilation and even airway compromise, particularly in patients with OSA. The authors managed to perform intraoperative sedation well with targeted bi-spectral index values. Nonetheless, airway collapse is common with the drugs used, i.e., propofol and remifentanil infusion after midazolam premedication. Patients with obesity and OSA often require high pressure to prevent upper airway collapse as their pharyngeal critical closing pressure (Pcrit) is higher [4]. While HFNC oxygenation exerts a continuous airway pressure-like effect, it is flow-dependent. In such a scenario, the flow of 15–30 L/min applied by the authors might not be sufficient to overcome the Pcrit. Therefore, the methods used for the assessment of ventilation and prevention of hypoventilation should be outlined.

Airway management is crucial during awake craniotomy, as is sedation. HFNC oxygenation plays a role in preventing hypoxemia [1,5]. We congratulate the authors for their compelling case and highlighting the role of ORI in early detection of impending desaturation during HFNC oxygenation. However, we feel that dexmedetomidine, known to produce effects, it is flow-dependent. In such a scenario, the flow of 15–30 L/min applied by the authors might not be sufficient to overcome the Pcrit. Therefore, the methods used for the assessment of ventilation and prevention of hypoventilation should be outlined.

Habib Md Reazaul Karim, Pradipta Bhakta, Antonio M Esquinas, and Parmod Kumar Bithal

1 Department of Anaesthesiology and Critical Care, All India Institute of Medical Sciences, Raipur, India. 2 Department of Anaesthesiology and Intensive Care, University Hospital of Waterford, Waterford, Ireland. 3 Intensive Care Unit, Hospital Morales Meseguer, Murcia, Spain. 4 Editor in Chief, Journal of Neuroanaesthesiology and Critical Care, Noida, India

FUNDING
None.

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

AUTHOR CONTRIBUTIONS

ORCID
Habib Md Reazaul Karim, https://orcid.org/0000-0002-6632-0491
Pradipta Bhakta, https://orcid.org/0000-0002-6101-396X
Antonio M Esquinas, https://orcid.org/0000-0003-0571-2050
Parmod Kumar Bithal, https://orcid.org/0000-0001-5348-2814

REFERENCES
AUTHORS’ REPLY: We thank Reazaul Karim and colleagues for their comments. In this case report, we addressed the usefulness of high-flow nasal cannula (HFNC) and oxygen reserve index for adequate oxygen reserves in patients undergoing awake craniotomy.

We absolutely agree with Reazaul Karim’s comment that dexmedetomidine is a better agent in patients of obstructive sleep apnea (OSA) because of less occurrence of respiratory depression. However, we experienced several cases that patients could not wake up during deep sedation with dexmedetomidine when awake is requested. Thus, a careful approach is needed when using dexmedetomidine, in case of awake craniotomy that requires frequent transition of sedation and awake for neurocognitive testing. In our institution, propofol and remifentanil are standard anesthetics for monitored anesthesia care in awake craniotomy. Dexmedetomidine is prepared for adjuvant anesthetics in all cases and used together if necessary. In the first case, dexmedetomidine was prepared but not used, however, in the second case, it was infused during wound closure.

In terms of HFNC, according to comment that, in patients with obesity and OSA, high pressure is often required to overcome the pharyngeal critical closing pressure, preoperative patient training for high pressure and application of higher flow up to 60 mmHg depending on the patient’s condition should be considered in this population undergoing awake craniotomy.
Liver transplant and the sweet-bitter truth

TO THE EDITOR: Kim et al. [1] recently published a research report in Anesthesia & Pain Medicine highlighting the early mortality predictive value of intraoperative hyperlactatemia during liver transplantation (LT). While the results of this considerably large patient cohort retrospective analysis, highlighting the prognostic implications of metabolic alterations in LT, are undeniably commendable [1], the index findings need to be carefully interpreted in light of several observations.

Given that Kim et al. [1] focused on the intraoperative factors affecting outcomes following LT, the lack of the consideration of intraoperative glycemic fluctuations in their analysis deserves attention. This is extremely important, considering that hyperglycemia can be caused intraoperatively during LT from intrinsic diabetogenic patient characteristics, and extrinsic factors such as perioperative stress, corticosteroids, and catecholamine infusions [2-4]. Apart from the problems surrounding intraoperative hyperglycemia, the larger problem lies in the proposition of von Platen et al. [4] of evaluating the lactate levels during LT in close conjunction with the glucose values. They elaborate on the unique activity of hepatocytes in response to ischemia by glycogenolysis, which contributes to hyperglycemia and is further compounded by the likelihood of stress-induced insulin resistance [4]. Thus, ischemia is intricately linked to both intraoperative lactate and glucose dynamics during LT. Indeed, the total ischemia time in the hyperlactatemia group was higher in the analysis by Kim et al. [1].

Apart from ischemia, prior studies have also associated hyperglycemia with concomitant lactate elevations in diverse clinical settings, indicating glycometabolic interactions [5].

Even from a practical standpoint, the institutional glucose management protocol in the study by Kim et al. [1] was not adhered to, as in a major surgical procedure should be followed. The prognostic importance of intraoperative hyperglycemia in LT has been described by Ammori et al. [2] and Park et al. [3]. Interestingly, of the 184 patients included in the study by Ammori et al. [2], as many as 124 recipients had poor glycemic control (defined as mean blood glucose [BG] level ≥ 150 mg/dl), eventually demonstrating a mean intraoperative BG level of 184 mg/dl. Park et al. [3] reported an incidence rate of severe intraoperative hyperglycemia (BG level ≥ 200 mg/dl) of 37.8% in 76 LT patients with surgical site infections (SSIs), as opposed to a 21.9% incidence in 604 LT patients not with SSIs (P = 0.002). Focusing specifically on mortality, which was the primary outcome in Kim et al.’s study [1], being evaluated at 30 and 90 days, Ammori et al. [2] notably outlined an elevated 1-year mortality rate in patients with poor glycemic control compared to those with well-controlled glucose levels (21.9% vs. 8.8%, P = 0.05).

Irrespective of whether it is viewed as an independent prognostic factor or as glycometabolic interactions [5], hyperglycemia in LT cannot be neglected.

REFERENCES

FUNDING
None.

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

AUTHOR CONTRIBUTIONS

ORCID
Varun Suresh, https://orcid.org/0000-0003-2521-1149
Rohan Magoon, https://orcid.org/0000-0003-4633-8851
Shalvi Mahajan, https://orcid.org/0000-0002-8657-0586

Letter to the Editor
Varun Suresh1, Rohan Magoon2, and Shalvi Mahajan3
1 Department of Anesthesiology, Government Medical College, Thiruvananthapuram, 2 Department of Cardiac Anesthesia, Atal Bihari Vajpayee Institute of Medical Sciences (ABVIMS) and Dr. Ram Manohar Lohia Hospital, New Delhi, 3 Department of Anesthesia and Intensive Care, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Corresponding author: Varun Suresh, M.D., DNB, DM
Department of Anesthesiology, Government Medical College, Medical College P.O., Thiruvananthapuram, Kerala 695011, India
Tel: 91-9041426743, Fax: 91-471-2528412
E-mail: varunsuresh@pgi.ac.in

Revised: February 8, 2022; Revised: March 29, 2022; Accepted: March 30, 2022
Corrigendum: Effect-site concentration of remifentanil for preventing propofol injection pain during induction of balanced anesthesia

Joungmin Kim¹,², Daehoon Kim², and Hyung Gon Lee¹,²

Department of Anesthesiology and Pain Medicine, ¹Chonnam National University Medical School, ²Chonnam National University Hospital, Gwangju, Korea

https://doi.org/10.17085/apm.2020.15.2.152

In the article by Kim et al. in the April 2020 issue of Anesthesia & Pain Medicine (Effect-site concentration of remifentanil for preventing propofol injection pain during induction of balanced anesthesia [pages 152-156]), the name of one of the authors was incorrectly spelled. The name of the third author on first and last pages of this article is incorrectly stated as Hyung Gong Lee.

The correct author name follows:

Before
Hyung Gong Lee

After
Hyung Gon Lee

The authors apologize for any inconvenience that it may have caused.

Corresponding author
Hyung Gon Lee, M.D.
Department of Anesthesiology and Pain Medicine, Chonnam National University Hospital, Chonnam National University Medical School, 42 Jebongro, Dong-gu, Gwangju 61469, Korea
Tel: 82-62-220-6893
Fax: 82-62-232-6294
E-mail: leehg@chonnam.ac.kr

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/4.0) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

Copyright © the Korean Society of Anesthesiologists, 2022
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.

4) Before submitting the reviewed manuscripts, please ensure that the title page contains the author names, affiliations, and corresponding author information.

5) Failure to submit responses to comments by reviewers and editors, along with the revised manuscript, within 60 days will be considered as “no intention to publish,” and the review process will be terminated.

2. Mandatory English editing for Korean authors

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).
Anesthesia and Pain Medicine (APM) is the official scientific journal of 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), Korean Neuromuscular Research Society (KNRS), Korean Society of Cardiothoracic and Vascular Anesthesiologists (KSCVA), Korean Society of Transplantation Anesthesiologists (KSTA), and The Korean Spinal Pain Society (KSPS) and Korean Society of Regional Anesthesia (KSRP), and Korean Society for Airway Management (KSAM). The abbreviated title is “Anesth Pain Med.” It is published four times a year on the last day of January, April, July, and October in English.

I. Editorial Policy

The Editor assumes that all authors listed in a manuscript have agreed with the following policy of the APM on submission of manuscript. Except for the negotiated secondary publication, manuscript submitted to the APM must be previously unpublished and not be under consideration for publication elsewhere. Under any circumstances, the identities of the referees will not be revealed. Minimum publication charges and additional fee for reprints will be due on every manuscript. All published manuscripts become the permanent property of the Korean Society of Anesthesiologists (KSA) and may not be published elsewhere without written permission. APM adheres completely to guidelines and best practices published by professional organizations, including Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (http://www.icmje.org/icmje-recommendations.pdf) from ICMJE and Principles of Transparency and Best Practice in Scholarly Publishing (joint statement by COPE, DOAJ, WAME, and OASPA; http://doaj.org/bestpractice) if otherwise not described below.

II. General Information

1. Publication types

APM focuses on clinical research, experimental research, case reports, reviews, and letters to the editor, online images and various introductions.

2. Language

APM publishes articles in English. Manuscript submitted in Korean will be translated into English by the society after acceptance, Korean version will be published only on the website (www.anesth-pain-med.org). Spellings should abide by American spellings. Medical terminology should be written based on the most recent edition of Dorland’s Illustrated Medical Dictionary. Accepted manuscripts are requested to be proofread by professional English editors.

3. Submission of manuscripts

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 by using the online manuscript submission system, available at: http://submit.anesth-pain-med.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.

4. Data Availability Statement

Data sharing is encouraged by the APM, but a Data Availability Statement will be required and published with the manuscript. Authors will be provided the following options during submission or may use draft their own.

- The datasets generated during and/or analyzed during the current study are available in the [NAME] repository, [PER- SISTENT WEB LINK TO DATASETS]
- The datasets generated during and/or analyzed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.
- The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.
- Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.
- All data generated or analyzed during this study are includ-
in this published article [and its supplementary information files].

The data that support the findings of this study are available from [third party name] but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of [third party name].

5. Peer review process

APM uses double-blind review, which means that both the reviewer and author identities are concealed from the reviewers, and vice versa, throughout the review process. To facilitate this, authors need to ensure that their manuscripts are prepared in a way that does not give away their identity. If one or more of editors are involved as authors, the editor(s) should not be involved in the peer reviewer selection, evaluation, or decision process. Submitted manuscripts will be reviewed by 2 or more experts in the corresponding field. The Editorial Board may request authors to revise the manuscripts according to the reviewer’s opinion. After revising the manuscript, the author should upload the revised files with a reply to each item of the reviewer’s opinion. Additions and amendments to the revised manuscript should be highlighted in red. The author’s revisions should be completed within 60 days after the request. If it is not received by the due date, the Editorial Board will not consider it for publication. To extend the revision period to more than 60 days, the author should negotiate with the Editorial Board. The manuscript review process should be finished the second review. If the reviewers wish further review, the Editorial Board may consider it. The Editorial Board will make a final decision on the approval for publication of the submitted manuscripts and can request any further corrections, revisions, and deletions of the article text if necessary. Statistical editing is also performed if the data need professional statistical review by a statistician. The review and publication processes that are not described in the Instructions for Authors will be incorporated into the Editorial Policy Statements approved by the Council of Science Editors Board of Directors, available at: www.councilscienceeditors.org/.

6. Article processing charge and publication fee

There is no submission-related fee. Article processing charge (APC) of KRW 300,000 (USD 250) per article will be issued to the corresponding author. APC is waived if the affiliations of the first and corresponding authors are outside Korea. APC for invited articles is also waived.

7. Copyrights and secondary publication

Copyrights of all published materials are owned by the APM. On behalf of co-author(s), corresponding author must complete and submit the journal’s copyright transfer agreement, which includes a section on the disclosure of potential conflicts of interest based on the recommendations of the International Committee of Medical Journal Editors, “Uniform Requirements for Manuscripts Submitted to Biomedical Journals.” A copy of the form is made available to the submitting author within the online manuscript submission process. It is possible to republish manuscripts if ONLY the manuscripts satisfy the condition of secondary publication of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, available at: http://www.icmje.org

8. Open access

APM is an Open Access journal accessible for free on the Internet. Accepted peer-reviewed articles are freely available on the journal website for any user, worldwide, immediately upon publication without additional charge.

III. Research and Publication Ethics Guidelines

For the policies on research and publication ethics, the “Good Publication Practice Guidelines for Medical Journals” (https://www.kamje.or.kr/board/view?b_name=bo_publication&bo_id=13) or the “Ethical Guidelines on Good Publication” (http://publicationethics.org/resources/guidelines) or “Ethical Considerations in the International Committee of Medical Journal Editors” (http://www.icmje.org/recommendations) are applied.

1. Conflict-of-interest statement

The corresponding author is required to summarize all authors’ conflict of interest disclosures. Disclosure form shall be same with ICMJE Uniform Disclosure Form for Potential Conflicts of Interest (www.icmje.org/conflicts-of-interest). A conflict of interest may exist when an author (or the author’s institution or employer) has financial or personal relationships or affiliations that could influence (or bias) the author’s decisions, work, or manuscript. All authors should disclose their conflicts of interest, i.e., (1) financial relationships (such as employment, consultancies, stock ownership, honoraria, paid expert testimony), (2) personal relationships, (3) academic competition, and
(4) intellectual passion. These conflicts of interest must be included as a footnote on the title page or in the Acknowledgements section.

All sources of funding 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 original published disclosure statement, and additional action may be taken as necessary.

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

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 kept. The editor or reviewers may request copies of these documents to make potential ethical issues clear.

3. Protection of privacy, confidentiality, and written informed consent

Identifying details should not be published in written descriptions, photographs, or pedigrees unless it is essential for scientific purposes and the patient (or his/her parents or guardian) provides written informed consent for publication. Additionally, informed consent should be obtained in the event that anonymity of the patient is not assured. For example, masking the eye region of patients in photographs is not adequate to ensure anonymity. If identifying characteristics are changed to protect anonymity, authors should provide assurance that alterations do not distort scientific meaning. When informed consent has been obtained, this should be indicated in the published article.

4. Protection of human and animal rights

In the reporting of experiments that involve human subjects, it should be stated that the study was performed according to the Helsinki Declaration of 1975 (revised 2013) (Available from https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) and approved by the Institutional Review Board (IRB) of the institution where the experiment was performed. Clinical studies that do not meet the Helsinki Declaration will not be considered for publication. Identifying details should not be published (such as name, initial of name, ID numbers, or date of birth).

In the case of an animal study, a statement should be provided indicating that the experimental processes, such as the breeding and the use of laboratory animals, were approved by the Research Ethics Committee (REC) of the institution where the experiment was performed or that they did not violate the rules of the REC of the institution or the NIH Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council, https://www.nap.edu/catalog/5140/guide-for-the-care-and-use-of-laboratory-animals). The authors should preserve raw experimental study data for at least 1 year after the publication of the paper and should present this data if required by the Editorial Board.

5. Registration of the clinical research

It is recommended that all clinical trials be registered in the primary registry before submission. APM accepts registration in any of the primary registries that participate in the World Health Organization (WHO) International Clinical Trials Portal (http://www.who.int/ictrp/en), NIH ClinicalTrials.gov (http://www.clinicaltrials.gov), or Korea Clinical Research Information Service (CRiS, http://cris.nih.go.kr).

6. Reporting guidelines

The APM recommends a submitted manuscript to follow reporting guidelines appropriate for various study types. Good sources for reporting guidelines are the EQUATOR Network (www.equatornetwork.org) and the NLM’s Research Reporting Guidelines and Initiatives (www.nlm.nih.gov/services/research_report_guide.html).

7. Author and authorship

An author is considered as an individual who has made substantive intellectual contributions to a published study and whose authorship continues to have important academic, social, and financial implications.

Authorship credit should be based on: (1) substantial contributions to the conception or design of the work, or to the acquisition, analysis, or interpretation of data for the work; (2) the drafting of the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement on taking accountability for the accuracy or
integrity of the work. Authors should meet these four criteria. These criteria distinguish the authors from other contributors.

When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. When submitting a manuscript authored by a group, the corresponding author should clearly indicate the preferred citation and identify all individual authors as well as the group name. Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship. Journals generally list other members of the group in the Acknowledgments section.

8. Plagiarism and duplicate publication

Plagiarism is the use of previously published material without attribution. Prior to peer review, all manuscripts are screened for plagiarism by the Editor-in-Chief using iThenticate. When plagiarism is detected at any time before publication, the APM editorial office will take appropriate action as directed by the standards set forth by the Committee on Publication Ethics (COPE). For additional information, please visit http://www.publicationethics.org. Text copied from previously published work is interpreted using the following taxonomy:

1) Intellectual theft
   Deliberate copying of large blocks of text without attribution
2) Intellectual sloth
   Copying of “generic” text, e.g., a description of a standard technique, without clear attribution
3) Plagiarism for scientific English
   Copying of verbatim text, often from multiple sources
4) Technical plagiarism
   Use of verbatim text without identifying it as a direct quotation but citing the source
5) Self-“plagiarism”

Manuscripts are only accepted for publication if they have not been published elsewhere. Manuscripts published in this journal should not be submitted for publication elsewhere. Duplicate submissions identified during peer review will be immediately rejected. Duplicate submissions that are discovered after publication will be retracted. It is mandatory for all authors to resolve any copyright issues when citing a figure or table from a different journal that is not open access.

When duplicate publication is detected, the APM editorial office will notify the counterpart journal on this violation. Additionally, it will be notified to the authors’ affiliation and penalties will be imposed on the authors. It is possible to republish manuscripts if the manuscripts satisfy the condition of secondary publication of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, available at: www.icmje.org. If the author or authors wish to obtain a duplicate or secondary publication for reasons such as publication for readers of a different language, the author(s) should obtain approval from the Editors-in-Chief of both the first and second journal.

IV. Manuscript Preparation

APM recommends compliance with some or all of the following guidelines (www.equatornetwork.org/library).

1. Word processors and format of manuscripts

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.

2. Abbreviation of terminology

Abbreviations should be avoided as much as possible. When they are used, 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
Leave no space when using hyphen between words.
Ex) intra-operative
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.
Ex) ([ ])
4) Manuscripts in Korean should obey the rules of Korean spelling (www.korean.go.kr).

4. Citations

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

5. Arrangement of manuscript

The manuscript should be organized in the order of title, abstract, introduction, materials and 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 at 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
   ① Title
   Title should be concise and precise. The first word should be capitalized. Drug names in the title should be written with generic names, not brand names. For the title, only the first letter of the first word should be capitalized.
   Ex) Effect of smoking on bronchial mucus transport velocity under total intravenous anesthesia .......... [○] Ex) Effect of Smoking on Bronchial Mucus Transport Velocity under Total Intravenous Anesthesia .......... [×] Provide drug names as generic names, not product names.
   Ex) In CPR, Isosorbide Dinitrate is, .......... [○] Ex) In CPR, Isosorbide Dinitrate (Isoket®) is, .......... [×] Ex) In CPR, Isoket® is, .......... [×]
   ② Running title
   A running title of no more than 40 characters, including letters and spaces in Korean, or 10 words in English, should be provided. If this title is inappropriate, the Editorial Board may revise it.
   ③ Author information
   First name, middle initial, and last name of each author, with their highest academic degree(s) (M.D., Ph.D., etc.), and institutional affiliations; make sure the names of and the order of authors as they appear on the Title Page and entered in the system match exactly.
   ④ Previous presentation in conferences
   Title of the conference, date of presentation, and the location of the conference may be described.
   ⑤ Funding statement
   Disclosure of all financial support for the work, including departmental or institutional funding/support.
   ⑥ Conflicts of interest
   Any conflicts of interest for any or all authors within the 36 months of submission. If no competing interests, please add the following statement: “The authors declare no competing interests.” If any of these elements are not applicable to your submission, write “not applicable” after the number and topic; for example, “Prior Presentations: Not applicable.”

2) Manuscript
   ① Title and Running title (without author information)
   It should be the same as the Cover page.
   ② Abstract
   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 4,
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. Ex) Keywords: Carbon dioxide; Cerebral vessels; Oxygen; Spinal analgesia.

3 Introduction
The introduction should address the purpose of the article concisely and include background information that is relevant to the purpose of the paper.

4 Materials and Methods
The materials and methods section should include sufficient details regarding the design, subjects, and methods of the research in order, as well as methods used for data analysis and control of bias in the study. Sufficient details must be provided in the methodology section of an experimental study so that it can be further replicated by others.

Institute and author names should be avoided. When reporting experiments with human or animal subjects, the authors should indicate whether they received approval from the Institutional Review Board for the study. When reporting experiments with animal subjects, the authors should indicate whether the handling of the animals was supervised by the Institutional Board for the Care and Use of Laboratory Animals. Demographic data should be included in the materials and methods section if applicable. As a rule, subsection titles are not recommended. If several study designs were used, then subtitles can be used without assigning numbers.

Ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance.

• Units Laboratory information should be reported using the International System of Units [SI], available at: https://www.nist.gov/pml/special-publication-811

<Exceptions>
A. The unit for volume is “L,” while others should be written as “dl, ml, μl.”
Ex) 1 L, 5 ml
B. The units for pressure are mmHg or cmH2O, instead of Pascal.
C. Use Celsius for temperature. °C
D. Units for concentration are M, mM, μM.
Ex) μmol/L; [ × ]
E. When more than 2 items are presented, diagonal slashes are acceptable for simple units.
Negative exponents should not be used.
Ex) mg/kg/min [O], mg · kg⁻¹ · min⁻¹ [ × ]
F. Leave 1 space between number and units, except %, °C.
Ex) 5 mmHg
Ex) 5%, 36 °C
G. Units of time
Ex) hour: 1 h = 60 min = 3,600 s, day: 1 d = 24 h = 86,400 s

• Machines and equipment
Provide model name and manufacturer’s name, and country. Do not put “.” between words when writing the names of countries.
Ex) U.S.A. [O], USA [O]
For drug names, use generic names. If a brand name should be used, insert it in parentheses after the generic name. Provide® or ™ as a superscript and the manufacturer’s name and country.

• Ions
Ex) Na⁺[O], Mg²⁺[O], Mg²⁺[ × ], Mg²⁺[ × ]
Ex) Premedicated magnesium [O]
Ex) Premedicated Mg²⁺[O]

5 Results
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 of 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. Citation of tables and figures should be provided as Table 1 and Fig. 1.
Type or print each table on a separate page. Figures should be uploaded as separate tif, jpg, pdf, gif, ppt files.

6 Statistics
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 (IQR, 3Q). When displaying P values, use a capital P and do not put a “.” between “P” and “value”.

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

B. Authors should describe the objective of the study and hypothesis appropriately. The primary/secondary endpoints are predetermined sensibly according to the objective of the study.

C. The characteristics of measured variables should determine the use of a parametric or nonparametric statistical method. When a parametric method is used, the authors should describe whether the basic statistical assumptions are met. For an analysis of a continuous variable, the normality of data should be examined. Describe the name and result of the particular method to test normality.

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

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

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 comparisons, 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, or 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 docu-
ments and should not exceed 30. References should be numbered consecutively in the order in which they are first mentioned in the text. Provide citations in the body text. All references should be listed in English, including author, title, name of journal, etc.

- The format for references follows the descriptions below. Otherwise, it follows the NLM Style Guide for Authors, Editors, and Publishers (Patrias, K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling, DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007 [updated 2015 Oct 2; cited Year Month Day]. Available at: www.ncbi.nlm.nih.gov/books/NBK7256/).

- If necessary, the Editorial Board may request original documents for the references.


- Six authors can be listed. If there are more than 6 authors, only list 6 names with “et al.”

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

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

- Description format

A. Regular journal

Author name. Title of article. Name of journal published year; volume: start page-final page.


Journal article volume with supplement


Journal article issue with supplement


B. Monographs

- If reference page is only 1 page, mark ‘p’.
- Note if it is beyond the 2nd edition.


- Translated documents cannot be used as references. The original documents should be provided as references.

C. Chapter

Any separate author of a chapter should be provided.


D. Electronic documents


E. Online journal article


F. Advance access article


Tables

- 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.
• Words in the table excluding the title should use capital letters for the first word, and the following words are to be written in small letters.
• 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.
• Footnotes are to be written in the following order: “Values are mean ± SD (or SEM) or median (1Q, 3Q)” the explanations for the groups and the abbreviations in order of appearance, and statistics. Abbreviations apart from internationally recognized abbreviations are to be explained with their full spellings at the bottom of the table. Full spellings are to be presented even for repeated abbreviations for each table in order of appearance.
• 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.
⑫ Legends for figures and photographs
• All of the figures and photographs should be described in the text separately.
• The description order is the same as in the footnotes in tables and should be in recognizable sentences.
• Define all abbreviations every time they are repeated.

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

(4) Video (movie) clip(s)
The APM publishes supplemental video (movie) clip(s) that will be available online. Authors should submit videos according to our video submission guidelines.
① Each video clip should clearly illustrate the primary findings within an adequate amount of viewing time and should be discussed in the text. Authors should provide appropriate labeling (e.g., arrows, abbreviations of anatomic structures, etc.) in the video clips. However, all identifying information, including patient names and/or ID numbers, hospital names, and dates of the procedures, should be removed.
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.
③ Video clips are uploaded as the last file(s) at the time of manuscript submission and should be marked as supplementary video files.
④ The video clip(s) should have simple file names (e.g., Video 1, Video 2) and should include the appropriate extension (e.g., .mov, .mpg, .avi).
⑤ The maximum number of video clips is 20.
⑥ The video clip(s) should be playable on Microsoft Windows OS. The video clip(s) should be tested for playback before submission, preferably on computers not used for their creation, to check for any compatibility issues.
⑦ Individual video files should be a minimum of 480 × 320 pixels (smaller clips will not be accepted) and a maximum of 2 GB. Files of < 15 MB will be rejected outright unless special arrangements have been
made with the editorial board prior to submission. Approval of files of > 2 GB will be made at the end of the review process.

⑧ Supplemental still images that correspond to the respective video clip(s) should be, but are not always required to be, accompanied by legends. The video clip file name(s) should refer to the corresponding figure number(s).

⑨ The author will be able to find additional information in the Figures and photographs section.

2) Case Reports
A case report is almost never a suitable means to describe the efficacy of a treatment or a drug; instead, an adequately powered and well-controlled clinical trial should be performed to demonstrate such efficacy. The only context in which a case report can be used to describe efficacy is in a clinical scenario, or population, that is so unusual that a clinical trial is not feasible. Case reports of humans must state in the text that informed consent to publication was obtained from the patient or guardian. 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. Rarity of a disease condition is itself not an acceptable justification for a case report.

(1) Cover page: Same as that for clinical and experimental studies.

(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.

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

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

(6) References: The number of references should be less than 15. However, if necessary, the number of reference can be added in accordance with the decision of the editorial committee.

(7) Tables and figures: Proportional to those for clinical and experimental studies.

3) Reviews
Review articles synthesize previously published material into an integrated presentation of our current understanding of a topic. Review articles should describe aspects of a topic in which scientific consensus exists, as well as aspects that remain controversial and are the subject of ongoing scientific disagreement and research. Review articles should include unstructured abstracts 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, number of figures and tables can be added in accordance with the decision of the editorial committee.

4) Letters to the Editor
Letters to the Editor should include brief constructive comments that concern previously published articles and interesting cases. Letters to the Editor should be submitted no more than 3 months after the paper has been published.

(1) Cover pages should be formatted in the same way as those of clinical research papers. The corresponding author should be the first author. A maximum of five authors is allowable.

(2) The body text should not exceed 1,000 words and should have no more than 5 references. A figure or a table may be used.

(3) Letters may be edited by the Editorial Board, and if necessary, responses by the author of the subject paper may be provided.

5) Book reviews and announcements
Book reviews as well as news of scientific societies and scientific meeting dates in Korea or abroad can be included. Their formats will be same as those of Letters to the Editor.

6) Images and Videos in APM
This feature is intended to capture the sense of visual discovery and variety that anesthesiologists experience.

(1) The title should contain no more than 8 words. No more than 2 authors should be listed.

(2) The legend should contain no more than 250 words.

(3) If there is more than one panel, please label them Panel A, Panel B, etc.

(4) The legends to the images and videos should briefly present relevant clinical information, including a short description of the patient’s history, relevant physical and laboratory findings, clinical course, response to treatment (if any), and condition at the last follow-up.
Clinical Research

General instructions

1. Please note that it is unethical to submit the same manuscript to two different journals simultaneously. The paper should not have been submitted to the Anesthesia and Pain Medicine either.
2. The Anesthesia and Pain Medicine holds the copyright of published manuscripts.
3. The pages should be numbered, starting with the first page.
4. Manuscripts should be written in 10 point or larger, double-spaced, with a wide margin.
5. Should be a brief running title.

Abstract

6. The abstract should be in structured format (Background; Methods; Results; and Conclusions)
7. Should only include less than 6 keywords.
8. Should be fewer than 250 words.

Contents: (Introduction-Discussion)

9. Background (referenced), objective. The introduction should give a concise account of the background and purpose of the investigation.
10. In a clinical study, written informed consent from the patients should be obtained and a statement concerning IRB approval and informed consent procedures must appear in the methods section of paper.
11. Figures and photographs should be submitted as jpg, gif or tif files, separately from the text of the paper.
12. Legend of figure should be described on a separate page following references in sentences of present tense.
13. Tables should be included in the text.
14. Follow the instructions for citing references.
15. Conclusion or summary should be the last section.

References

16. Follow the reference format.
17. Number references (as brackets; [ ]) in the sequence they appear in the text.
18. If you cite accepted manuscripts “In Press” as references, please provide one electronic copy.

Others

19. Raw data should be presented if the committee requests.
20. Please obtain permission from the copyright holder when citing a graph, figure or table from a different journal or book.
21. The names or affiliations of the authors should be concealed in the manuscript and figures.

Experimental Research

General instructions

1. Please note that it is unethical to submit the same manuscript to two different journals simultaneously. The paper should not have been submitted to the Anesthesia and Pain Medicine either.
2. The Anesthesia and Pain Medicine holds the copyright of published manuscripts.
3. The pages should be numbered, starting with the first page.
4. Manuscripts should be written in 10 point or larger, double-spaced, with a wide margin.
5. Should be a brief running title.

Abstract

6. The abstract should be in structured format (Background; Methods; Results; and Conclusions)
7. Should only include less than 6 keywords.
8. Should be fewer than 250 words.

Contents: (Introduction-Discussion)

9. Background (referenced), objective. The introduction should give a concise account of the background and purpose of the investigation.
10. In a clinical study, written informed consent from the patients should be obtained and a statement concerning IRB approval and informed consent procedures must appear in the methods section of paper.
11. Figures and photographs should be submitted as jpg, gif or tif files, separately from the text of the paper.
12. Legend of figure should be described on a separate page following references in sentences of present tense.
13. Tables should be included in the text.
14. Follow the instructions for citing references.
15. Conclusion or summary should be the last section.

References

16. Follow the reference format.
17. Number references (as brackets; [ ]) in the sequence they appear in the text.
13. Follow the instructions for citing references.
14. Conclusion or summary should be the last section.

References

15. Follow the reference format.
16. Number references (as brackets; [ ]) in the sequence they appear in the text.
17. If you cite accepted manuscripts “In Press” as references, please provide one electronic copy.

Others

18. Raw data should be presented if the committee requests.
19. Please obtain permission from the copyright holder when citing a graph, figure or table from a different journal or book.
20. The names or affiliations of the authors should be concealed in the manuscript and figures.
Copyright transfer agreement

☐ Original Article  ☐ Case Report  ☐ Review Article  ☐ Letter to the Editor  ☐ Editorial  ☐ Others

Article title:

Author(s):

(In identical order to the electronic submission and the corresponding author should be underlined)

Journal: Anesthesia and Pain Medicine

In the event that the above manuscript is accepted for publication in the Anesthesia and Pain Medicine, the copyright is transferred to the Korean Society of Anesthesiologists.

The author shall have the right to use all or part of the Work to revise, adapt, prepare derivative works, present orally, or distribute provided that such use is for the personal noncommercial benefit of the author. With written consent from the Anesthesia and Pain Medicine, the author may use contents from the Work in other works provided that a full acknowledgment is made to the original source of the material including the journal name, volume, issue, page numbers, year of publication, title of article.

All co-authors of the Work certify that they have participated sufficiently in the intellectual content, the analysis of data if applicable, and the writing of the Work to take public responsibility for it. Each author of the Work certifies that none of the material in the Work has been previously published, included in another work, or is currently under consideration for publication elsewhere. Each author certifies that this Work has not been accepted for publication elsewhere, nor has assigned any right or interest in the Work to any third party. All funding sources supporting the Work and all institutional or corporate affiliations of the authors and commercial associations (e.g. consultancies, stock ownership, equity interests, patent-licensing arrangements, etc.) that might pose a conflict of interest in connection with the Work should be acknowledged in a footnote on the front cover of the Work.

I/we give consent to the above statements (It is THE RESPONSIBILITY of the Corresponding Author to collect the signatures of all authors before sending the form to the Editorial Office).