5 Recent updates on interscalene brachial plexus block for shoulder surgery

11 Sugammadex administration in patients with end-stage renal disease: a narrative review with recommendations

21 Mortality scoring systems for liver transplant recipients: before and after model for end-stage liver disease score
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 safety and care of patients receiving anesthesia and the quality of anesthesiologists’ clinical practice by publishing articles on anesthesia, 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 anesthesiology
- Pathophysiology, pharmacology, and all aspects of spine-related pain
- Clinical techniques of regional blocks, anatomy, patient safety issues, and basic sciences such as pharmacology of local anesthetics or sedative drugs
- All fields of airway management, including difficult airways and complications.

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

All or part of the Journal is indexed/tracked/covered by PubMed, PubMed Central (PMC), KoreaMed, KoMCI, Google Scholar, Science Central. Full text is freely available from http://anesth-pain-med.org

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Feel the difference with Ramosetron
Messages from the new Editor-in-Chief and Editorial Board, journal metrics and statistics, and appreciation to reviewers

Jun Hyun Kim¹ and Hyun Kang²

¹Department of Anesthesiology and Pain Medicine, Inje University Ilsan Paik Hospital, Goyang, ²Department of Anesthesiology and Pain Medicine, Chung-Ang University College of Medicine, Seoul, Korea

We are honored to serve as the Editor-in-Chief and Editorial Board of Anesthesia and Pain Medicine (APM). The editorial staff will continue to be committed to the success of this outstanding journal.

APM has made noteworthy advancements, gained recognition, and improved its position as an international publication in the field of anesthesiology, including perioperative management, critical care, and pain. We sincerely thank the previous editor-in-chief, Young-Cheol Woo, and the former editorial boards for their passion, vision, and commitment to the journal, which made the growth possible on behalf of the community.

Our main goals for APM in the coming years are to a) raise its profile in the clinical and research community and advance its position toward the top journal in this area; b) keep searching for and publishing excellent reviews and original articles that offer the most up-to-date clinical and research information; c) maintain the quality, standard, and transparency of our editorial and review process while fast-tracking the actual response time to submissions; and d) strengthen the regional and global network to better meet the needs of our society and the scientific community.

To accomplish these goals, the APM editorial team will actively seek the most recent and intriguing research papers and communicate with the members of the Korean Society of Anesthesiologists, subsocieties of the Korean Society of Anesthesiologists, and other global scholars in this field.

JOURNAL METRICS AND STATISTICS

APM was first indexed in the Korean Citation Index in 2015 and in PubMed Central in December 2020. The annual number of submitted articles is approximately 200 to 300, and the number of submissions from foreign countries has increased dramatically since 2020. Detailed descriptions of the authors’ countries for 2021 and 2022 are presented in Fig. 1. The number of countries that submitted articles to APM increased from 11 to 17.

APM articles published in 2020 and 2021 are cited 103 times by Web of Science articles published in 2022 (Data origin: https://www.webofscience.com/wos/woscc/summa-
The total number of original articles and reviews in 2020 and 2021 were 48 and 32, respectively. The manually calculated impact factor for 2022 in the Web of Science is 1.288 (103/[48+32]).

APM has progressed to publish 11 high-quality reviews, 29 original articles, and 25 other items, including case reports, letters to the editor, and a corrigendum in 2022.

APPRECIATION TO REVIEWERS

The APM editorial team owes tremendous gratitude to the reviewers, who willingly commit their time to reviewing manuscripts. Their contributions are crucial for preserving the quality of the journal.

The names of the reviewers are listed below. The list is in alphabetical order of the family names.

Eun-Jin Ahn       Doo Sik Kim       Jeong Soo Lee
Jiyoun Bang       Doyeon Kim       Sang Hyun Lee
Hee-Jung Baik    Eun-hee Kim       Sangseok Lee
Sung Hye Byun    Eunsoo Kim        Seung Cheol Lee
Yun Jeong Chae    Gunn Hee Kim      Sang-wook Lee
Hae Wone Chang    Ha-yeon Kim       Seung Young Lee
Jang-eun Cho     Hee-Yeong Kim     Oh Haeng Lee
Jin Sun Cho      Hee Young Kim     Woo Yong Lee
Sooyoung Cho     Hye Young Kim     Wonjin Lee
Sung-Ae Cho      Hyungtae Kim      Hyun Kyoung Lim
Byung Moon Choi  Jae hun Kim       Hyunyoung Lim
Jae Moon Choi    Jin-Tae Kim       Yun-Hee Lim
Messages from new Editorial Board

Jun Gwon Choi
So Ron Choi
Sung-uk Choi
Seung Ho Choi
Yong Seon Choi
Yoon Ji Choi
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Chan-Sik Kim
Dal-ah Kim
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Jong-Yeop Kim
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Jong Hae Kim
Jung Eun Kim
Jun Hyun Kim
Kye-Min Kim
Kyu Nam Kim
Kyung-Hoon Kim
Kyoung Ok Kim
Min-kyoung Kim
Min-soo Kim
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Wook Jong Kim
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Hanna Lee
Heeseung Lee
Hyeon Jeong Lee
Hyungmook Lee
Hyun-Yeong Lee
Je Jin Lee

Se Hun Lim
Chaeseong Lim
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Sung-Yong Park
Sungchul Park
Yong-hee Park
Yong-Seok Park
Yoo Jung Park
Ho-Geol Ryu
Junghee Ryu
Jeong Hwa Seo
Yon-Hee Shim
Yong Sup Shin
Shin Won-jung Shin
Hye-min Sohn
Ju-Tae Sohn
In-Kyung Song
Jang-Ho Song
Tae-Yun Sung
Jae Hee Woo
Chunwoo Yang
Yongjae Yoo
FUNDING

None.

CONFLICTS OF INTEREST

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

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INTRODUCTION

Interscalene brachial plexus block (ISBPB) is the most widely used postoperative analgesic technique for shoulder surgeries [1]. It not only provides excellent postoperative analgesia, but also reduce pain scores and opioid consumption [2]. However, ISBPB has several concerns, including a short duration of analgesia, rebound pain, a high incidence of unilateral diaphragmatic paresis, and potential risk of nerve damage, prompting the search for alternative techniques. Many alternatives to ISBPB have been studied to alleviate these concerns, and clinicians should choose an appropriate option based on the patient’s condition. In this mini-review, we aimed to present recent updates on ISBPB while discussing our clinical experiences in shoulder surgery.

Keywords: Brachial plexus; Interscalene brachial plexus block; Peripheral nerve block; Shoulder surgery.

STRATEGIES FOR PROLONGING THE ANALGESIC DURATION OF SINGLE-SHOT ISBPB

The average analgesic duration after single-injection ISBPB with commonly used local anesthetics is 8–12 h, which falls short of providing satisfactory postoperative pain relief on the first night of surgery. Therefore, several approaches including continuous ISBPB with a perineural catheter [9], perineural or intravenous (IV) additives [10], and liposomal bupivacaine [11] have been investigated to increase the analgesic duration after single-shot ISBPB. Here, we discuss the advantages and disadvantages of these strategies.

Continuous ISBPB

A continuous peripheral nerve block is one of the strate-
gies that can overcome the short duration of single-shot ISBPB by delivering a constant infusion of local anesthetics through a perineural catheter [12]. Clinical studies have demonstrated superior analgesia for up to 48 h after major shoulder surgery without increasing side effects [9]. However, continuous blocks with perineural catheter are labor intensive, may infringe on the surgical field, carry the risk of infection, myotoxicity, and phrenic nerve palsy, and can result in secondary failure related to catheter dislodgement [13]. Taken together, continuous ISBPB may be a useful strategy to prolong the analgesic duration; however, anesthesiologists need to weigh the risks and benefits of continuous ISBPB for shoulder surgery.

**Perineural or IV additives (dexamethasone or dexmedetomidine)**

The use of perineural or IV additives, such as dexamethasone or dexmedetomidine, is a promising strategy for prolonging the duration of analgesia. However, the safety profiles of off-label perineural injections of most additives have not yet been confirmed; therefore, caution is required [14]. Alternatively, IV administration of several additives, including dexmedetomidine and dexamethasone, can provide prolonged analgesia while avoiding the theoretical risks inherent to perineural injection [7,8,15,16]. In our previous study comparing the effective dose of IV dexmedetomidine to prolong the analgesic duration of ISBPB, we found that IV dexmedetomidine (2.0 μg/kg) significantly increased the time to first pain at the surgical site following ISBPB. However, these extended analgesic effects were not observed at a dose of 0.5 and 1.0 μg/kg [7]. In a subsequent study [8], we demonstrated that IV dexamethasone (0.11 mg/kg) significantly prolonged the time to first rescue analgesic request (1.6-fold compared with the control group) following ropivacaine ISBPB analgesia. Moreover, the co-administration of IV dexamethasone (0.11 mg/kg) and IV dexmedetomidine (1.0 μg/kg) further increased this time (3.8-fold compared with IV dexamethasone alone). This finding is clinically important because 50% of the patients receiving the two drugs did not require rescue analgesics for up to 72 h postoperatively. Taken together, IV administration of dexmedetomidine and dexamethasone may provide prolonged analgesia, but the optimal dose has not yet been determined, and further studies are warranted to clarify this point. While conducting clinical studies using additives in Korea, it should be considered that the use of IV dexamethasone, IV dexmedetomidine, perineural dexamethasone, or perineural dexmedetomidine for the purpose of prolonging the duration of analgesia must be approved by the Korean Food and Drug Administration.

**Liposomal bupivacaine**

Liposomal bupivacaine was introduced to prolong the duration of single-shot ISBPB and has recently been approved for use in interscalene blocks [11]. Its mechanism of action is due to the structural characteristics of the capsule by multivesicular liposomal lipid bilayers, which leads to a slow release and maintains a constant plasma concentration; thus, prolonging its effects for up to 72 h after a single injection [17-19]. Therefore, it may be a reasonable alternative to other analgesic techniques. However, recent evidence has demonstrated that the addition of liposomal bupivacaine appears to have no extended analgesic and opioid-sparing effects when compared with bupivacaine alone [20] or with adjuvant dexamethasone used in ISBPB [21]. However, drawing a clear conclusion from the current standpoint is complex, and further studies are needed for clarification.

**REBOUND PAIN**

Patients who receive ISBPB experience excellent pain control while the block is active, but they may experience significantly more pain than those who do not receive ISBPB 24 h after shoulder surgery [2]. This phenomenon is known as rebound pain and is defined as a dramatic increase in pain once the peripheral nerve block dissipates [22]. Recently, addition of perineural dexamethasone to ISBPB using ropivacaine led to a much smoother resolution of ISBPB and reflected in a significantly smaller increase in pain after block resolution and a significantly lower incidence of rebound pain compared with that in the control group (37.1% and 82.9%, P < 0.001) [23]. However, the perineural use of dexamethasone is not currently approved in Korea, and there have been no long-term studies on its safety. A recent retrospective study identified IV dexamethasone administration as a potentially modifiable independent risk factor associated with a lower incidence of rebound pain after peripheral nerve block [3]. Further studies using IV dexamethasone are warranted to clarify its effect on rebound pain.
DIAPHRAGM SPARING NERVE BLOCK FOR SHOULDER SURGERY

ISBPB is usually accompanied by hemidiaphragmatic paresis due to an inadvertent phrenic nerve blockade. Hemidiaphragmatic paresis has been reported to occur in up to 100% of the patients receiving ISBPB because the phrenic nerve runs close to the brachial plexus at the C5 and C6 nerve root levels [4,6]. This side effect has little impact on healthy patients, but can be dangerous in patients with pre-existing pulmonary complications [24]. This adverse effect has led to an interest in the investigation of potential phrenic nerve-sparing nerve blocks. Here, recent updates regarding the same are discussed.

Extrafascial vs. intrafascial injection for ISBPB

Extrafascial injection for ISBPB (Fig. 1) reduces the incidence of hemidiaphragmatic paresis and affects pulmonary function while providing analgesia similar to a conventional intrafascial injection [25]. Additionally, this may reduce the potential for neurologic injury inherent to ISBPB (see below section “risk of nerve damage”).

Supraclavicular brachial plexus block

The supraclavicular brachial plexus block may be considered an effective and safe alternative to ISBPB for shoulder surgery, especially in patients with preexisting pulmonary impairment [26]. When performing supraclavicular brachial plexus block, we found that the incidence of hemidiaphragmatic paresis was effectively reduced when the local anesthetic was injected primarily in the corner pocket (20 ml) and secondarily inside the neural cluster (5 ml) during the right-sided supraclavicular brachial plexus block [27].

Refining ISBPB: Superior trunk block

Injection around the superior trunk of the brachial plexus is an alternative technique that can reduce the risk of hemidiaphragmatic paresis [6,24,28]. The superior trunk is formed by fusion of the C5 and C6 nerve roots. Therefore, local anesthetic injection around the superior trunk should produce similar analgesia in the shoulder, because the major terminal nerves innervating the shoulder arise distal to the superior trunk (Fig. 2). Moreover, the injection site is farther away from the phrenic nerve, which theoretically reduces the risk of hemidiaphragmatic paresis. Based on this, we performed a non-inferiority clinical trial comparing ISBPB with a superior trunk block, in which the superior trunk block provided postoperative shoulder analgesia equivalent to ISBPB, as demonstrated by similar pain scores, duration of analgesia, and 24 h opioid consumption [6]. Our findings were confirmed by another previous study that prospectively compared ISBPB with superior trunk block [24]. They also observed less frequent hemidiaphragmatic paralysis in the superior trunk block group.

Fig. 1. Ultrasound image after extrafascial interscalene brachial plexus block. ASM: anterior scalene muscle, MSM: middle scalene muscle.

Fig. 2. Ultrasound image after superior trunk block. ASM: anterior scalene muscle, LA: local anesthetics, MSM: middle scalene muscle, ST: superior trunk.
Alternative shoulder blocks (suprascapular nerve block or axillary nerve block)

Another strategy to reduce the risk of hemidiaphragmatic paresis is to inject local anesthetic at the terminal nerves that innervate the shoulder more distal to the superior trunk [29]. A shoulder block is an alternative approach that blocks the suprascapular and axillary nerves [30]. These two nerves innervate majority of the shoulder with additional minor contributions from the subscapular and lateral pectoral nerves [31]. Theoretically, the shoulder block may spare pulmonary function and diaphragmatic movement. Compared with ISBPB, suprascapular and axillary nerve blocks reduced the incidence of hemidiaphragmatic paresis and pulmonary dysfunction, while providing similar postoperative analgesia [32-35].

OTHER STRATEGIES TO REDUCE THE INCIDENCE OF HEMIDIAPHRAGMATIC PARESIS: LIPOSOMAL BUPIVACAINE

Addition of liposomal bupivacaine is a viable option without refining the ISBPB technique. Adding liposomal bupivacaine to bupivacaine in an ISBPB resulted in statistically significant reductions in diaphragm excursion and pulmonary function tested 24 h after block placement compared with bupivacaine alone. However, this reduction was within the range of normal diaphragmatic function [36].

RISK OF NERVE DAMAGE

Other concerns when conducting ISBPB with a posterior approach include the risk of intraneural injection into the relatively unprotected roots [37,38] and injury to the dorsal scapular nerve or long thoracic nerve (Supplementary Video 1) [39]. There is growing evidence that an intraplexus injection of ISBPB can increase the potential of neurologic injury [40]. The C6 nerve root often shows intra-root splitting in the interscalene groove, which poses a risk of intraneural injection [37,38]. Unfortunately, ultrasound does not entirely protect against intraneural injections [37,38]. In addition, caution is required when advancing the needle because there are risks of encountering the dorsal scapular nerve and the long thoracic nerve crossing the middle scalene muscle [39]. To reduce the risk of nerve damage, we recommend a nerve stimulator during ultrasound-guided ISBPB using the posterior approach.

CONCLUSION

ISBPB provides optimal analgesia for shoulder surgery; however, there are concerns about the associated risks. There are several alternative techniques for ISBPB, and clinicians should select the appropriate option based on the patient’s condition.

SUPPLEMENTARY MATERIALS

Supplementary video is available at https://doi.org/10.17085/apm.22254.

FUNDING

None.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS


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REFERENCES


Superior trunk block: a phrenic-sparing alternative to the interscalene block: a randomized controlled trial. Anesthesiology 2019; 131: 521-33.


INTRODUCTION

Sugammadex, a neuromuscular blockade (NMB) reversal agent, binds strongly with neuromuscular blocking agents (NMBAs), including rocuronium, by encapsulating them in the blood and is excreted by the kidney in the form of a stable complex, resulting in the rapid and complete reversal of the NMB [1].

Concomitant renal dysfunction in patients with end-stage renal disease (ESRD) affects the pharmacokinetics (PKs) of non-depolarizing NMBAs, making neuromuscular function recovery prolonged or unpredictable. Therefore, when sugammadex is administered to patients with severe renal impairment, sugammadex or sugammadex–rocuronium complex is not excreted by the kidneys, posing a high risk of long-term exposure to the free sugammadex or complex (continuously present in high concentrations in the blood). The use of sugammadex is not currently recommended in

Due to unknown safety concerns, sugammadex should not be administered to patients with end-stage renal disease (ESRD). However, because the supply of benzylisoquinolinium-type neuromuscular blocking agents (NMBAs) has been discontinued, rocuronium is the only non-depolarizing NMA that can be used in clinical settings in some countries, including South Korea. The administration of sugammadex cannot be avoided to achieve rapid and complete neuromuscular recovery in patients with ESRD or renal transplantation after rocuronium administration. Although there has been a limited number of clinical studies involving the use of sugammadex in patients with ESRD, studies have shown that sugammadex can effectively and safely reverse rocuronium-induced neuromuscular blockade (NMB) in patients with ESRD, however recovery of neuromuscular function in patients with ESRD is slower than in patients with normal renal function. Nonetheless, safety-concerns are yet to be addressed. Considering the small number of clinical studies, high heterogeneity among studies, and insufficient safety information, more extensive data on the efficacy and safety of sugammadex in patients with ESRD are needed. In particular, it is important to secure data on safety, including residual NMB after surgery, recurarization and cardiorespiratory complications, anaphylactic reactions, and long-term morbidity and mortality. Furthermore, anesthesiologists should remember that performing proper quantitative neuromuscular monitoring and neuromuscular management based on the monitoring signs are the most essential requirements when using sugammadex in patients with ESRD.

Keywords: Chronic kidney failure; Drug-related side effects and adverse reactions; End-stage renal disease; Neuromuscular blockade; Rocuronium; Sugammadex.
Efficacy of Sugammadex in Patients with ESRD

Several prospective case-control studies, retrospective cohort studies, and case reports on the administration of sugammadex in patients with ESRD (or patients undergoing kidney transplantation) have been reported. A systematic review and meta-analysis [4], presented data analysis results on its efficacy and safety by synthesizing and integrating the results of studies reporting the use of sugammadex, and a retrospective study that investigated relatively long-term mortality [5], were reported. Table 1 shows the characteristics and results of the relevant studies.

### Table 1. Characteristics of the Main Studies Investigating the Use of Sugammadex in Patients with End-stage Renal Disease

<table>
<thead>
<tr>
<th>Study design</th>
<th>Patients in control (sample size)</th>
<th>SGX dose</th>
<th>Main results and conclusion</th>
<th>Time from SGX to recovery of TOF ratio 0.9</th>
<th>Pharmacokinetic data of SGX</th>
<th>Side effects</th>
<th>Primary outcome/main secondary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staals et al., 2008 [6]</td>
<td>Prospective clinical trial</td>
<td>ClCr &lt; 30 ml/min, TOF ratio &gt; 0.9</td>
<td>2 mg/kg</td>
<td>Time from SGX to recovery of TOF ratio 0.9 was prolonged</td>
<td>Pharmacokinetic data of SGX</td>
<td>No adverse events or evidence of recurrence of NMB</td>
<td>SGX rapidly reverses deep NMB in renal failure</td>
</tr>
<tr>
<td>Min et al., 2017 [9]</td>
<td>Open label, two parts, phase II study</td>
<td>ClCr &lt; 30 ml/min, TOF ratio &gt; 0.9</td>
<td>4 mg/kg</td>
<td>Time from SGX to recovery of TOF ratio 0.9 was prolonged</td>
<td>Pharmacokinetic data of SGX</td>
<td>No adverse events or evidence of recurrence of NMB</td>
<td>SGX rapidly reverses deep NMB in renal failure</td>
</tr>
</tbody>
</table>

This patient group due to the risk of prolonged NMB state (presence of residual NMB) and recurarization or anaphylactic reactions in the postoperative period [2]. Sugammadex is not recommended by the US Food and Drug Administration for patients with a creatinine clearance of less than 30 ml/min [3]. Furthermore, the Korean Ministry of Food and Drug Safety does not recommend the administration of sugammadex to patients with severe renal impairment (creatinine clearance of less than 30 ml/min) or patients requiring dialysis.

Nevertheless, there are cases where a combination of rocuronium and sugammadex is necessary for proper NMB management under anesthesia in surgical patients with chronic kidney disease in various clinical situations (such as surgery with very short operation time, including laryngeal microsurgery). Additionally, there are problems associated with the supply of benzylisoquinolinium-type NMBAs, their side effects and limitations. For these reasons, recently, it is common for patients with ESRD to be prescribed a combination of rocuronium and sugammadex. Therefore, considering this situation, it is necessary to comprehensively review and analyze studies on the administration of sugammadex in patients with ESRD.

Efficacy of Sugammadex in Patients with ESRD

Several prospective case-control studies on the administration of sugammadex in patients with ESRD have been reported, with some administering sugammadex 2.0 mg/kg for reversal of moderate NMB [6,7], while others administered sugammadex 4.0 mg/kg for reversal of deep NMB [8,9]. Staals et al. [6,7] reported the results of a phase III trial conducted to determine the efficacy, safety, and PKs of sugammadex in patients with ESRD by dividing them into pharmacodynamic and safety findings [6] and PK findings [7], respectively.
<table>
<thead>
<tr>
<th>Study</th>
<th>Study design</th>
<th>Patients with ESRD (sample size)</th>
<th>Patients in control (sample size)</th>
<th>SGX dose</th>
<th>Primary outcome/main secondary outcomes</th>
<th>Main results and conclusion</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adams et al., 2020 [15]</td>
<td>Two centers retrospective study</td>
<td>ESRD which is mandatory renal replacement therapy (158)</td>
<td>None</td>
<td>Median 200 mg</td>
<td>Tracheal re-intubation within 48 h/deferred tracheal extubation in the operating theatre</td>
<td>SGX appears to be safe and effective</td>
<td>Three reintubation within 48 h, no residual NMB</td>
</tr>
<tr>
<td>Paredes et al., 2020 [16]</td>
<td>Historical cohort study, three distinct geographic locations</td>
<td>eGFR &lt; 15 ml/min (219)</td>
<td>None</td>
<td>Mean 217 mg (2.7 mg/kg)</td>
<td>Any complication possibly related to SGX/patient mortality within 30 days</td>
<td>None of the outcomes appeared to be related to SGX use. SGX could be considered in patients with ESRD</td>
<td>Three reintubation, two hypoxemia not requiring reintubation, one pneumonia, nine mortality within 30 days, but none of these related to SGX use</td>
</tr>
<tr>
<td>Ono et al., 2018 [19]</td>
<td>Retrospective study</td>
<td>Severe renal failure, median eGFR 8 ml/min, underwent KT (99)</td>
<td>None</td>
<td>Median 200 mg</td>
<td>Efficacy (creatinine at postoperative day 1)/complications related to recuration</td>
<td>Serum creatinine was 2.4 mg/dl at postoperative day 1, SGX was efficacious and safe in renal transplantation</td>
<td>No adverse events were observed</td>
</tr>
<tr>
<td>Song et al., 2022 [5]</td>
<td>Retrospective propensity-score-matched study</td>
<td>ESRD dependent on haemodialysis using SGX (797 matched out of 806)</td>
<td>ESRD on haemodialysis using non-SGX (797 matched out of 1,233)</td>
<td>2–4 mg/kg</td>
<td>30-day and 1-year mortality</td>
<td>No significant difference in the 30-day or 1-year mortality rate between SGX and non-SGX before or after matching. SGX did not increase the mortality rate in ESRD</td>
<td>No adverse events clearly related to SGX were observed</td>
</tr>
<tr>
<td>Valente, 2020 [17]</td>
<td>Case report</td>
<td>A patient with acute renal failure CrCl 28.4 ml/min (1)</td>
<td>Same patient after 18 months with no renal impairment (1)</td>
<td>1,000 mg (15.5 mg/kg) vs. 200 mg</td>
<td>High dose SGX was used over 20 min to obtain TOF ratio 0.99 in renal failure, but normal need and response to the same patient with no renal impairment</td>
<td>No adverse events clearly related to SGX were observed</td>
<td></td>
</tr>
<tr>
<td>Arslantas and Cevik, 2019 [20]</td>
<td>Retrospective study</td>
<td>KT recipients reversed with SGX (14)</td>
<td>KT recipients reversed with neostigmine (28)</td>
<td>2–4 mg/kg</td>
<td>Serum creatinine/acute rejection, graft failure, length of stay, and mortality</td>
<td>SGX may be safely used in KT. Serum creatinine and graft survival rates at 28 days were not affected by SGX</td>
<td>No difference in risk of serious adverse effects. 7% rejection and 7% mortality</td>
</tr>
<tr>
<td>Vargas et al., 2021 [21]</td>
<td>Retrospective, case-control study</td>
<td>KT recipients with rocuronium-SGX (30)</td>
<td>KT recipients with cisatracurium-neostigmine (36)</td>
<td>2 mg/kg</td>
<td>Transplanted kidney function including serum creatinine, urea, and electrolyte. SGX during KT did not affect relevant kidney recovery outcomes in the first week</td>
<td>No differences in creatinine urea, and electrolyte. SGX during KT did not affect relevant kidney recovery outcomes in the first week</td>
<td></td>
</tr>
<tr>
<td>Carron et al., 2022 [22]</td>
<td>Retrospective cohort case-control study</td>
<td>KT recipients with rocuronium-SGX (175)</td>
<td>KT recipients with cisatracurium-neostigmine (175)</td>
<td>2–4 mg/kg</td>
<td>Serum creatinine/urea and eGFR</td>
<td>SGX for reversal of NMB showed a better recovery in KT than neostigmine with lower creatinine/urea and higher eGFR</td>
<td>Lower incidence of hypoxemia with SGX, no major postoperative complications</td>
</tr>
</tbody>
</table>

Administration of sugammadex 2.0 mg/kg for reversal of rocuronium-induced moderate NMB

Staals et al. [6] reported that the mean time of recovery of the train-of-four (TOF) ratio to 0.9 was not significantly different between patients with ESRD and healthy patients with normal renal function. However, reversal of NMB using sugammadex tended to be slower in patients with ESRD (a mean value of 2.0 min for recovery of the TOF ratio to 0.9 in patients with ESRD vs. 1.65 min in controls). They suggested that sugammadex 2.0 mg/kg rapidly and effectively reverses rocuronium-induced moderate NMB in patients with ESRD and healthy controls; thus, sugammadex was well tolerated by all patients.

Administration of sugammadex 4.0 mg/kg for reversal of rocuronium-induced deep NMB

First, de Souza et al. [8] reported that the mean time of recovery of the TOF ratio to 0.9 after sugammadex (4.0 mg/kg) administration was significantly prolonged in the ESRD group (5.6 ± 3.6 min) than in the control group (2.7 ± 1.3 min), and they suggested that sugammadex 4.0 mg/kg effectively and safely reversed rocuronium-induced deep NMB in patients with ESRD, although the recovery was slower than in healthy controls. Panhuizen et al. [9] reported median (95% confidence interval) time from sugammadex 4.0 mg/kg to recovery to TOF ratio of 0.9 was 3.1 (2.4–4.6) and 1.9 (1.6–2.8) min for ESRD versus control group and suggested that sugammadex 4 mg/kg provided rapid reversal of rocuronium-induced deep NMB in patients with ESRD and control patients. However, the recovery time was significantly different between patients with ESRD and healthy controls.

Efficacy of sugammadex in patients with ESRD in a systematic review and meta-analysis

A recently published systematic review found that the time required to reach a TOF ratio ≥ 0.9, 0.8, or 0.7 was significantly longer in patients with ESRD. The plasma clearance of sugammadex in patients with ESRD was significantly lower than that in healthy controls, based on meta-analysis of six prospective observational studies [4]. However, given that the difference in the recovery time is not long enough to cause a clinically significant difference (e.g., the mean difference of the time to reach a TOF ratio of 0.9:1.14 min), it is believed that the NMB reversal time in patients with ESRD is slightly longer than that in patients with normal renal function.

PHARMACOKINETIC ASSESSMENT OF SUGAMMADEX IN PATIENTS WITH ESRD

Staals et al. [7] investigated the effect of ESRD on the PKs of sugammadex and rocuronium, and on the elimination of rocuronium encapsulated by sugammadex in patients with ESRD and controls using plasma and urine sampling at various times up to 48–72 h after sugammadex administration. Panhuizen et al. [9] collected blood samples from patients with ESRD and controls to assess rocuronium and sugammadex concentrations at various times up to 24–48 h after sugammadex injection. Min et al. [10] compared PKs of a single IV dose of sugammadex in patients with moderate and severe renal impairment to healthy patients.

Total plasma clearance of sugammadex in patients with ESRD was significantly lower than that in healthy controls [7,10]. Total plasma clearance of rocuronium in patients with ESRD was significantly lower than that in healthy controls [4]. Additionally, the effect of renal impairment on total plasma clearance was found to be greater with sugammadex than with rocuronium [7].

Staals et al. [7] reported significant differences in the PKs of sugammadex and rocuronium between patients with ESRD and healthy controls, with ESRD having a greater effect on sugammadex PK variables than those of rocuronium. The reason is that extrarenal clearance of rocuronium can occur in patients with ESRD, and even after encapsulating rocuronium with sugammadex, unbound rocuronium undergoes hepatic metabolism and elimination. Therefore, the total plasma clearance of rocuronium is less affected by renal impairment than sugammadex. The greater effect of renal impairment on total plasma clearance of sugammadex compared to rocuronium suggests that plasma concentrations of sugammadex remain relatively high in patients with ESRD during the postoperative period. Therefore, the possibility of the existence of unbound rocuronium is reduced, and in this situation, if the stability of the sugammadex–rocuronium complex is guaranteed, the risk of recurarization with free rocuronium may be low [4].

In addition, the plasma concentration of rocuronium 12 h after sugammadex injection was significantly higher in patients with ESRD [7,9]; however, this was due to the limitations of liquid chromatography–mass spectrometry to mea-
Sugammadex in end-stage renal disease

sure the plasma concentration of sugammadex and rocuronium. Because this assay cannot distinguish between encapsulated rocuronium (sugammadex–rocuronium complex) and free rocuronium, high plasma concentrations of rocuronium in patients with ESRD measured after sugammadex administration do not represent plasma concentrations of pure unbound (free) rocuronium [7,9,11,12]. Fortunately, a sugammadex–rocuronium complex may exist in equilibrium with a low dissociation constant because of strong binding [13]. However, it is unknown how long sugammadex–rocuronium complexes stably exist in the blood and whether changes in the binding force occur in patients with ESRD. If the internal environment in which the binding force of the sugammadex–rocuronium complex is reduced in these patients, the risk of fatal complications, including recurarization, still exists. Furthermore, given that the sugammadex–rocuronium complex was found in the body for a longer period in patients with ESRD (when considering the report for prolonged sugammadex–rocuronium complex exposure in patients with ESRD [9]), and there are no reported clinical data for the long-term distribution and elimination of this complex in their body, further PK studies with longer follow-up periods should be conducted.

In a situation where the stability of the sugammadex–rocuronium complex and the PK process in the body are unclear in patients with ESRD, the following study results related to the dialysability of this complex by high-flux dialysis in patients with severe renal impairment are encouraging. Cammu et al. [14] evaluated the dialysability of sugammadex and the sugammadex–rocuronium complex in six patients with acute severe renal impairment in the intensive care unit (ICU). All patients received rocuronium 0.6 mg/kg, followed by sugammadex 4.0 mg/kg 15 min later. Rocuronium and sugammadex concentrations in the plasma and dialysate were measured before, during, and after high-flux dialysis. The reduction ratio (the reduction extent of the plasma concentration at the end of a dialysis episode compared to that before dialysis) and dialysis clearance in plasma and dialysate were calculated for each dialysis episode. They reported that the mean plasma concentrations of sugammadex and rocuronium were reduced by 69% and 75% during the first dialysis episode, respectively, with reductions of approximately 50% during subsequent dialysis episodes. The mean dialysis clearance of sugammadex and rocuronium in the blood were 78 and 89 ml/min, respectively. Therefore, they concluded that in patients with severe renal impairment, hemodialysis using high-flux dialysis could be effective in removing sugammadex and sugammadex–rocuronium complex. According to the findings of this study, in patients with ESRD who have been receiving renal replacement therapy, including hemodialysis before surgery, if hemodialysis using a high-flux dialysis method is performed in the patients within 24–48 h after surgery, the sugammadex–rocuronium complex can be effectively removed, which further reduces the risk of postoperative complications, such as recurarization [4].

SAFETY-RELATED RESULTS OF SUGAMMADEX IN PATIENTS WITH ESRD

Safety outcomes of sugammadex in patients with ESRD in prospective case-control studies

In prospective trials by Staals et al. [6] and de Souza et al. [8], no sugammadex-related serious adverse events (AEs) were reported in the small samples of 15 and 20 patients, respectively. A relatively larger sample of 35 patients in a prospective case-control trial by Panhuizen et al. [9] reported at least one serious AE in nine renal patients and three patients in the healthy control group; however, none were considered to be related to sugammadex, and no clinical evidence (e.g., respiratory problems) of residual NMB or recurrence of NMB was reported after extubation for any patient. As a phase 1 PK study of sugammadex performed in two parts, Min et al. [10] closely monitored the side effects of sugammadex in two parts. Drug-related AEs, including dizziness, headache, infusion site reaction, pain in the extremities, and oral paraesthesia, were reported in 1 (4.2%) of the 24 patients in their part 1 study, and no drug-related AEs were reported in the part 2 study with 18 patients. No hypersensitivity was reported in either part of this study.

Short-term safety outcomes of sugammadex in patients with ESRD in retrospective cohort studies

The short-term safety outcomes of sugammadex in surgical patients with ESRD were assessed in a retrospective study by Adams et al. [15]. The main outcomes of the study were the incidence of deferred tracheal extubation in the operating room and tracheal reintubation within 48 h of surgery in patients whose trachea was extubated at the end of surgery. Of the 158 patients with ESRD, 22 (13.9%) underwent deferred tracheal extubation due to surgical and/or
pre-existing medical conditions. Of the 136 patients who had the tracheal tube removed at the end of the surgery, three patients had tracheal reintubation within 48 h; however, two of these cases were because of pulmonary edema due to volume overload, and one case was due to deterioration of sepsis. None of the patients showed any evidence of NMB recurrence. They concluded that sugammadex is safe and effective. Paredes et al. [16] reported a cohort study of 219 patients with stage 5 chronic kidney disease who received sugammadex. No hypersensitivity reaction was observed, and reintubation was required in three patients; two patients developed hypoxemia that did not require reintubation, and one patient developed pneumonia, 9 (4.1%) patients died within 30 days of surgery. None of these events was related to the administration of sugammadex.

Long-term safety outcomes of sugammadex in patients with ESRD in a retrospective cohort study

Long-term safety outcomes were assessed in a recent retrospective propensity-score-matched study. Song et al. [5] analyzed the mortality associated with sugammadex in 2,039 surgical patients with ESRD who required hemodialysis (806 in the sugammadex group and 1,233 in the non-sugammadex group). After propensity score matching, 1,594 patients were analyzed (797 in the sugammadex group and 797 in the non-sugammadex group). No significant differences were observed in the 30-day or 1-year mortality rate between the sugammadex group and the non-sugammadex group before or after matching. They concluded that the use of sugammadex did not increase the 30-day and 1-year mortality rates after surgery in patients with ESRD. This study recommends the safe use of sugammadex in patients with ESRD with respect to long-term safety outcomes.

Safety of sugammadex in patients with ESRD in a case report

Valente et al. [17] reported a case of a 78-year-old man who weighed 66 kg with acute renal failure (estimated glomerular filtration rate [eGFR] of 28.4 ml/min) requiring a high dose of sugammadex for rocuronium reversal during general anesthesia. Sugammadex at a dose of 1,000 mg (15.5 mg/kg) was administered over 20 min to achieve NMB reversal from TOF count 1 to TOF ratio of 0.99. The patient was then extubated and transferred to the general ward. No weakness or respiratory complications were observed during the remaining hospital stays. The patient underwent another surgery with normal renal function after 18 months, and at that time, sugammadex 200 mg rapidly reversed the NMB from a TOF count of 0–2 to a TOF ratio of 0.95. In this case, no AEs related to sugammadex were observed, despite the high dose of sugammadex. This may contribute to expanding the safety profile of sugammadex and its use in patients with renal failure. In addition, this case suggests that dose modification of sugammadex may be necessary for patients with ESRD.

Taken together, although serious AEs directly related to sugammadex use were rarely observed in the abovementioned trials and case report, safety-related issues of sugammadex in patients with ESRD have not yet been resolved due to insufficient safety data.

Safety of sugammadex in patients with ESRD in a systematic review and meta-analysis

Kim et al. [4] reported that there were no significant differences between patients with ESRD and patients with normal renal function in the incidence of NMB recurrence, delayed recovery to a TOF ratio of 0.9, or other clinical signs of inappropriate neuromuscular recovery. Furthermore, in retrospective cohort studies [15,16], the possibility of residual NMB related to sugammadex was found to be insignificant. These findings suggest that sugammadex can effectively and safely reverse rocuronium-induced NMB in patients with ESRD. However, further studies are needed given the small number of included studies and the high heterogeneity of some results.

THE USE OF SUGAMMADEX IN RENAL TRANSPLANTATION PATIENTS

Reliable and sufficient reversal of NMB is important in patients with ESRD undergoing renal transplantation, to prevent microaspiration because of their perioperative immunosuppressed status. Therefore, there is no doubt about selecting a more effective and safer NMB reversal agent and providing proper NMB management using quantitative neuromuscular monitoring to measure neuromuscular function during anesthesia and to reduce postoperative residual NMB or recurarization [18].

Ono et al. [19] studied 99 consecutive patients who had undergone living renal transplantation. They investigated the efficacy and complications of sugammadex in the first
48–72 h in the surgical ICU and during 6 months follow-up period. In their study, no AEs, including recurarization, were recorded during the observation period following sugammadex administration. Although 14 (14.3%) patients had severe renal impairment (eGFR < 30 ml/min) on postoperative day 5, there were no signs of recurarization. Therefore, they concluded that the sugammadex–rocuronium complex may be excreted without detachment in their setting after renal transplantation and may remain stable for a long time in patients with renal transplants. In addition, considering that no patients required additional sugammadex injection at a dose of more than 4 mg/kg in their study, they recommended a dose of sugammadex 4 mg/kg to achieve complete recovery from deep NMB in patients with ESRD. Moreover, they emphasized that anesthesiologists should pay attention to the titrating amount of sugammadex while avoiding unnecessary overdoses, although no allergic reaction was observed in their study.

Sugammadex’s effect on grafted (transplanted) kidney function is important and warrants further investigation, in addition to its efficacy and safety in patients undergoing renal transplantation. Given that sugammadex can interact with corticosteroids, which play an important role in immunosuppression in patients undergoing renal transplantation, Arslantas et al. [20] retrospectively investigated whether there are any differences in grafted kidney function in recipients of renal transplantation when sugammadex or neostigmine is administered to the recipient. They reported no significant differences in serum creatinine values, the incidence of acute rejection episodes, graft failure, length of hospital stay, mortality, and graft survival rates until postoperative day 28 between recipients reversed with sugammadex and those reversed with neostigmine. Nevertheless, they suggested that considering the sugammadex-corticosteroid interaction and its long-term effects on immunosuppression and grafted kidney function, current safety data are insufficient to support the recommendation of routine sugammadex use in patients undergoing renal transplantation.

Vargas et al. [21] compared the effects of rocuronium and sugammadex on transplanted kidney function to cisatracurium and neostigmine. They reported that blood creatinine levels at 6, 12, and 24 h were significantly lower in the rocuronium–sugammadex group than in the cisatracurium–neostigmine group and that there were no significant differences between the two groups in blood sodium and potassium, diuresis, urinary sodium, and potassium levels before and after transplantation. They concluded that the administration of rocuronium and sugammadex during renal transplantation did not affect the grafted kidney function in the first week after transplantation.

Recently, Carron et al. [22] reported a single-center, 2014–2017 retrospective cohort case-control study that compared the impact of rocuronium–sugammadex versus cisatracurium–neostigmine on grafted kidney function in patients with renal transplants. The study included 350 patients who underwent renal transplantation and were equally divided into a sugammadex group (175 patients) and a neostigmine group (175 patients). The study showed that serum creatinine and serum urea levels were lower, while eGFR was higher in the sugammadex group than in the neostigmine group after transplantation. The sugammadex group showed a significantly lower incidence of severe postoperative hypoxemia, shorter post-anesthesia care unit stay, and reduced ICU admissions. They concluded that the rocuronium–sugammadex combination for NMB management showed a better-grafted kidney function and recovery profile and fewer AEs than cisatracurium–neostigmine in patients undergoing kidney transplantation.

**LIMITATIONS AND FUTURE CHALLENGES**

A few prospective observational studies using sugammadex in patients with ESRD have been reported [6-10]. Regarding the method of evaluating safety-related results, each study had various reporting outcomes and observation periods related to adverse reactions. In some studies, there was insufficiently detailed mention of safety results. Thus, more prospective observational studies are needed to evaluate sugammadex-related efficacy and safety in patients with ESRD. Although several high-quality retrospective cohort studies have been reported recently [15,16,19], additional large-scale retrospective studies, including more robust safety-related data, such as, data associated with recurarization, anaphylactic reactions, long-term morbidity and mortality, and sugammadex-related cardiovascular complications, including bradycardia associated with hyperkalemia, which can occur frequently in patients with ESRD, are needed.

Magoon et al. [23] hypothesized that sources of concern with sugammadex in patients with ESRD include the possible instability of rocuronium-sugammadex binding, prolonged clearance times for rocuronium and sugammadex, difficult dosing of sugammadex for deep NMB, and sugammadex-related bradycardia. The cardiovascular adverse ef-
Effects of sugammadex include corrected QT interval prolongation, atrioventricular block, atrial fibrillation, hypotension, and asystole associated with sugammadex warrant caution and further studies to examine its safety [24]. Most importantly, when administering rocuronium and sugammadex to patients with ESRD, it is essential to determine the depth of NMB during surgery using a quantitative neuromuscular monitoring device and to determine the appropriate dose of sugammadex accordingly. If such quantitative neuromuscular monitoring is not performed, it is difficult to rule out the possibility of residual NMB [23].

Comparing and observing the sugammadex-administered group and the neostigmine-administered control group in patients with ESRD would be a more efficacious for identifying sugammadex-related complications.

The use of several types of sugammadex, including many generic sugammadex, will gradually increase as only rocuronium is available in the supply of NMBAs worldwide. Considering the current limitations in terms of the effectiveness and safety of sugammadex in patients with ESRD, close patient monitoring through quantitative neuromuscular monitoring is more important. In addition, various international societies of anesthesiologists and pharmaceutical companies need to solve the supply problem of benzylisoquinolinium-type NMBAs (e.g., mivacurium, atracurium, and cisatracurium).

Recently, an experimental study showed the histochemically detectable nephroprotective effect of sugammadex in an ischemia-reperfusion rat model [25]. Considering the effect of sugammadex on renal function in patients with reduced renal function or in those undergoing renal transplantation, experimental and clinical studies on the renal protective effect of sugammadex will be valuable in the future.

RECOMMENDATIONS REGARDING THE USE OF SUGAMMADEX APPLICABLE IN PATIENTS WITH ESRD

Based on this review, we intend to present the minimum recommendations applicable to actual clinical settings for patients with ESRD undergoing general anesthesia as follows:

1. Quantitative NMB monitoring is mandatory for patients with ESRD because their responses to rocuronium and sugammadex may be more unpredictable and incomplete than those of healthy patients.

2. Considering the unresolved issue of sugammadex dosing, especially for deep NMB, moderate NMB and the corresponding sugammadex dose are recommended.

3. In patients with ESRD who have undergone hemodialysis before surgery, hemodialysis using a high-flux dialysis method within 24–48 h after surgery may be helpful. Patients who do not undergo hemodialysis require closer monitoring for a longer period to prevent postoperative complications.

4. Considering the potential risk of cardiopulmonary complications in patients with ESRD, close monitoring, including electrocardiogram, oxygen saturation, blood pressure, and blood tests for electrolytes, are required during the perioperative period.

5. A rocuronium-sugammadex combination is feasible for NMB management in patients undergoing renal transplantation. Nevertheless, routine sugammadex use is not yet recommended because of the unresolved issues of sugammadex-corticosteroid interaction and its long-term effects on immunosuppression and grafted kidney function.

CONCLUSION

Considering real clinical situations, including the discontinuation of the benzylisoquinolinium-type NMBAs, the use of sugammadex in clinical practice for NMB management cannot be avoided to achieve safe and complete neuromuscular recovery in patients with ESRD or patients with renal transplants after rocuronium administration.

Sugammadex can effectively and safely reverse rocuronium-induced NMB in patients with ESRD; however, the recovery of neuromuscular function in these patients is significantly slower than that in patients with normal renal function. However, the difference in the recovery rate was insufficient to be clinically significant. Considering the insufficient amount of reported data to date, more extensive data are required on the efficacy and safety of administration of sugammadex in patients with ESRD, especially safety-related results, including postoperative residual NMB, recurarization, and incidence of cardiopulmonary complications, and a problem in the dosing for reversal of deep NMB. Furthermore, it is important to perform appropriate quantitative neuromuscular monitoring during general anesthesia of patients with ESRD in actual clinical settings. Anesthesiologists should remember that it is essential to confirm the depth of perioperative NMB through neuromuscular monitoring, ad-
minister an appropriate dose of sugammadex, and closely monitor the recovery of neuromuscular function.

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**CONFLICTS OF INTEREST**

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

**DATA AVAILABILITY STATEMENT**

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

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Since Dr. Thomas Starzl performed the first human liver transplantation (LT) in 1963, LT has been considered the only definitive treatment for decompensated end-stage liver disease (ESLD) [1]. Several scoring systems have been proposed to predict mortality in patients with ESLD [2,3], and these scoring systems have also been used as a basis for allocating livers of brain death for LT [4]. Previously, the Child-Turcotte-Pugh (CTP) classification was used as the basis for the United Network for Organ Sharing (UNOS) organ allocation system. However, some disadvantages of CTP classification exist, such as the existence of several subjective parameters, and the final result is determined by three classes (A, B, and C) [5]. Since 2002, the Model for End-stage Liver Disease (MELD) score, which consists of all objective indicators, has replaced the CTP classification for the basis of the liver allocation system in the UNOS [5]. The Korean Network for Organ Sharing changed the basis of the liver allocation system from CTP classification to MELD in 2016 [6].

The MELD score was initially developed to predict the short-term mortality of patients undergoing the transjugular intrahepatic portosystemic shunt (TIPS) procedure for liver cirrhosis (LC) in 2000 [3]. Recently, the demographics of patients, indications for LT, and treatment options for ESLD have changed a lot [4,7]. Many studies have reported that the MELD score does not accurately reflect mortality risk in specific clinical situations, such as acute-on-chronic liver failure (ACLF) [8], hepatocellular carcinoma (HCC) [7], and sex disparity [9,10].

The prediction of mortality in patients with ESLD is closely related to donor organ allocation [4,6], and a more accurate prediction of mortality can greatly influence the perioperative management of LT recipients. In this article, we re-

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Keywords: Acute-on-chronic liver failure; End stage liver disease; Liver cirrhosis; Liver transplantation; Mortality; Organ dysfunction scores; Prognosis.

INTRODUCTION

The mortality scoring systems for patients with end-stage liver disease have evolved from the Child-Turcotte-Pugh score to the model for end-stage liver disease (MELD) score, affecting the wait list for liver allocation. There are inherent weaknesses in the MELD score, with the gradual decline in its accuracy owing to changes in patient demographics or treatment options. Continuous refinement of the MELD score is in progress; however, both advantages and disadvantages exist. Recently, attempts have been made to introduce artificial intelligence into mortality prediction; however, many challenges must still be overcome. More research is needed to improve the accuracy of mortality prediction in liver transplant recipients.
view notable scoring systems, past and present, related to the prognosis of ESLD.

**CHILD-TURCOTTE-PUGH CLASSIFICATION**

In 1964, Child and Turcotte introduced a classification that predicts the prognosis of patients undergoing portocaval shunt surgery for LC, and they suggested that their classification represents a “hepatic functional reserve” [2,5,11]. They selected five factors (serum albumin, bilirubin, ascites, encephalopathy, and nutritional status) based on their clinical experience and not on clinical trials or analysis. Finally, the classification defines each element into one of three classes (A, B, and C, Table 1) [2,5]. There was some criticism that three of the five elements (ascites, nutrition, and encephalopathy) were highly subjective, and the detailed explanation of how to integrate the five elements was ambiguous [11].

In 1972, Pugh replaced the “nutritional status,” which was considered the most subjective element with “prothrombin time,” adjusted limits for serum albumin, and defined the encephalopathy grading more clearly [12,13]. Pugh also calculated scores by assigning 1, 2, or 3 points to each of the five components, with a total score of 5–6 corresponding to class A, 7–9 to class B, and 10–15 to class C (Table 1) [12,13]. Pugh’s modification has been widely used for CTP classification [5,13].

Despite Pugh’s modification, subjective indicators (encephalopathy and ascites) remain; therefore, the attending physician can roughly grade the severity of liver disease [5]. This is often expressed by using “the gestalt method” [5,11,12]. Moreover, there are only three classes in the CTP classification, and when a certain threshold is reached, the class is fixed regardless of changes in clinical conditions [5].

**MODEL FOR END-STAGE LIVER DISEASE SCORE**

In 2000, Malinchoc et al. [3] published a “Mayo End-stage Liver Disease” model to predict the prognosis of patients undergoing TIPS procedures. They used prospectively obtained patient data and calculated scores through statistical analysis [5,14]. The score was based on serum bilirubin levels, prothrombin time (international normalized ratio [INR]), and serum creatinine levels. The name of this model was later changed to “Model for End-stage Liver Disease” [5,15]. Kamath et al. [15] validated this early MELD score and reported that the 3-month death rate in patients hospitalized for hepatic decompensation is as follows: 4% for MELD ≤ 9, 27% for MELD 10–19, 76% for MELD 20–29, 83% for MELD 30–39, and 100% for MELD ≥ 40.

In 2002, UNOS changed the liver allocation system from a state-based algorithm to an algorithm that uses a continuous, objective MELD/pediatric end-stage liver disease (PELD) score to prioritize patients needing LT [5,16,17].

The formula for the original MELD score was as follows (Table 2) [15]:

\[
\text{MELD} = 3.8 \times \log_e (\text{bilirubin} \, \text{[mg/dl]}) + 11.2 \times \log_e (\text{INR}) + 9.6 \times \log_e (\text{creatinine} \, \text{[mg/dl]}) + 6.4 \times (\text{etiology}: 0 \text{ if cholestatic or alcoholic, and } 1 \text{ otherwise})
\]

**LIMITATIONS OF THE MELD SCORE**

**Innate limitations of the MELD score**

Serum creatinine is not a good indicator for assessing renal dysfunction because it is influenced by extra-renal factors, such as muscle mass, sex, age, and ethnicity [14]. Severe muscle wasting in patients with ESLD can reduce serum

---

**Table 1. Original and Modified Child-Turcotte-Pugh Classification**

<table>
<thead>
<tr>
<th>Components</th>
<th>Original Child-Turcotte classification</th>
<th>Child-Turcotte-Pugh classification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Bilirubin (mg/dl)</td>
<td>&lt; 2</td>
<td>2–3</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>&gt; 3.5</td>
<td>3–3.5</td>
</tr>
<tr>
<td>Ascites</td>
<td>None</td>
<td>Easily-controlled</td>
</tr>
<tr>
<td>Neurological disorder</td>
<td>None</td>
<td>Minimal</td>
</tr>
<tr>
<td>Encephalopathy (grade)</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Excellent</td>
<td>Good</td>
</tr>
<tr>
<td>Prothrombin time (seconds prolonged)</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

How to integrate the five elements is unclear in original classification. In Child-Turcotte-Pugh classification: Class A (5-6 points, total scores), Class B (7–9 points), Class C (10–15 points).
creatinine levels. In this case, even if the serum creatinine level is normal, it cannot be concluded that the renal function is normal [9,14]. In the MELD-based allocation system, it has been frequently pointed out that women are less likely to receive LT than men, and that the mortality rate while waiting for LT is significantly higher in women than in men [9,10]. Several studies have suggested that glomerular filtration in women may be underestimated owing to their reduced muscle mass compared to that in men [9,14]. To overcome this, modified MELD with cystatin-C instead of creatinine [18] and MELD 3.0, with sex as an additional factor, was also announced [19]. Probable bias based on the inter-laboratory variability of measurement methods for serum creatinine, bilirubin, and INR has also been pointed out [14].

### Table 2. Equations of MELD/PELD and Updated Versions

<table>
<thead>
<tr>
<th>Score</th>
<th>Equations</th>
<th>Featuring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Original MELD [15]</td>
<td>$3.8 \times \log_e (\text{bilirubin [mg/dl]}) + 11.2 \times \log_e (\text{INR}) + 9.6 \times \log_e (\text{creatinine [mg/dl]}) + 6.4 \times \log_e (\text{age}) - 10.85 - \text{etiology}$</td>
<td>- Etiology disappeared in later versions</td>
</tr>
<tr>
<td>MELD-Na [30]</td>
<td>$\text{MELD} + 1.32 \times (137-\text{Na}) - [0.033 \times \text{MELD} \times (137-\text{Na})]$</td>
<td>- Sodium concentrations are mEq/L, values less than 125 are set to 125, and values greater than 137 are set to 137</td>
</tr>
<tr>
<td>MELD 3.0 [19]</td>
<td>$1.33 \times \text{female} + [4.56 \times \log_e (\text{bilirubin})] + [0.82 \times (137 - \text{Na})] - [0.24 \times (137 - \text{Na}) \times \log_e (\text{bilirubin})] + [9.09 \times \log_e (\text{INR})] + [11.14 \times \log_e (\text{creatinine})] + [1.85 \times (3.5 - \text{albumin})] - [1.83 \times (3.5 - \text{albumin})] \times \log_e (\text{creatinine}) + 6$</td>
<td>- Give additional points to women</td>
</tr>
<tr>
<td>PELD [31]</td>
<td>$(0.436 \times \text{age}) - [0.687 \times \log_e (\text{albumin})] + [0.480 \times \log_e (\text{bilirubin})] + [1.857 \times \log_e (\text{INR})] + [0.667 \times \text{growth failure}]$</td>
<td>- Updated interactions between parameters</td>
</tr>
</tbody>
</table>

MELD: model for end-stage liver disease, PELD: pediatric end-stage liver disease, INR: international normalized ratio.

Since the use of the MELD score in organ allocation, the demographics, epidemiology of the liver disease, and indications for LT have changed dramatically [25,26]. The widespread use of antiviral therapy against HCV has reduced the morbidity of chronic hepatitis C. In contrast, non-alcoholic fatty liver diseases are rapidly increasing, becoming a major indication for LT along with alcoholic liver disease in the USA [7,26]. Godfrey et al. [7] reported that the predictive power of MELD decreased with these demographic and epidemiologic changes. The concordance-statistic (C-statistic) of the MELD decreased from 0.80 in 2003 to 0.70 in 2015.

### Effect of demographic and epidemiologic changes in liver disease on the accuracy of the MELD score

Since the use of the MELD score in organ allocation, the demographics, epidemiology of the liver disease, and indications for LT have changed dramatically [25,26]. The widespread use of antiviral therapy against HCV has reduced the morbidity of chronic hepatitis C. In contrast, non-alcoholic fatty liver diseases are rapidly increasing, becoming a major indication for LT along with alcoholic liver disease in the USA [7,26]. Godfrey et al. [7] reported that the predictive power of MELD decreased with these demographic and epidemiologic changes. The concordance-statistic (C-statistic) of the MELD decreased from 0.80 in 2003 to 0.70 in 2015.
MELD, UKLE, MELD-AS, MELD-Plus, MELD-Cystatin C, and MELD 3.0, have been introduced as supplementary versions [4,14]. Among them, the most widely used MELD-Na and the most recently updated MELD 3.0, will be briefly described in this review.

**MELD-Na**

Serum sodium concentration is also known to be an important independent prognostic factor in patients with LC. For example, hyponatremia is strongly associated with hepatorenal syndrome, ascites, and liver-related death [27]. Several studies have reported that the incorporation of serum sodium concentration into MELD is beneficial for more accurate mortality prediction [27-29]. Accordingly, in 2016, the Organ Procurement and Transplantation Network/UNOS policy updated its MELD calculator to include serum sodium concentration [30]. The formula for MELD-Na used in the UNOS MELD calculator is shown (Table 2).

\[
\text{MELD-Na} = \text{MELD} + 1.32 \times (137 - \text{Na}) - [0.033 \times \text{MELD} \times (137 - \text{Na})] \\
\text{(Sodium concentrations are mEq/L, values less than 125 are set to 125, and values greater than 137 are set to 137).}
\]

**MELD 3.0**

Kim et al. [19] reclassified MELD to improve predictive accuracy through statistical analysis in 2021. Their final model was characterized by 1) adding sex and serum albumin, 2) considering interactions between serum albumin-sodium and albumin-creatinine, and 3) adjusting the upper bound for serum creatinine to 3.0 mg/dL. This was renamed MELD 3.0. They provided additional points to women on the basis that the MELD score of women tended to be underestimated [10]. Additionally, a significant correlation was found between bilirubin and sodium levels and between creatinine and albumin levels, which was corrected. The predictive ability for the risk of death within 90 days was slightly higher in MELD 3.0 than that in MELD-Na. The C-statistics of MELD-Na and MELD 3.0, were 0.862 and 0.869 (P < 0.01), respectively [19].

The formula for MELD 3.0 is as follows (Table 2):

\[
\text{MELD 3.0} = 1.33 \text{ (if female)} + [4.56 \times \log_2 (\text{bilirubin})] + [0.82 \times (137 - \text{Na})] - [0.24 \times (137 - \text{Na}) \times \log_2 (\text{bilirubin})] + [9.09 \times \log_2 (\text{INR})] + [11.14 \times \log_2 (\text{creatinine})] + [1.85 \times (3.5 - \text{albumin})] - [1.83 \times (3.5 - \text{albumin}) \times \log_2 (\text{creatinine})] + 6
\]

**PEDIATRIC END-STAGE LIVER DISEASE SCORE**

Similar to the development of MELD, the pediatric LT research group developed a scoring system tailored to the unique characteristics of children with chronic liver disease [31]. The PELD score was developed through statistical analysis based on the database of the “Studies of Pediatric Liver Transplantation (SPLIT),” a consortium that began recruiting children’s data from LT centers in the USA and Canada in 1995 [32]. The PELD score uses factors different from the MELD score to identify the unique growth and developmental aspects of children. Bilirubin, INR, albumin, growth failure, and age were used as the PELD score [16,31]. The PELD score has been used to allocate donor livers for children younger than 12 years in UNOS since 2002 [33]. Chang et al. [33] reported that PELD tends to underestimate the 90-day mortality compared with MELD. They suggested that children with chronic liver disease who need LT may be disadvantaged compared to adults with similar clinical conditions.

The formula for the PELD score is as follows (Table 2) [16,31]:

\[
\text{PELD} = (0.436 \times \text{age}) - [0.687 \times \log_2 (\text{albumin})] + [0.480 \times \log_2 (\text{bilirubin})] + [1.857 \times \log_2 (\text{INR})] + (0.667 \times \text{growth failure})
\]

Age: age < 1 year = 1, all other ages = 0.

Growth failure: values > 2 standard deviations from the norm = 1, all others = 0.

**ACUTE-ON-CHRONIC-LIVER-FAILURE**

ACLF is different from acute liver failure (ALF) or the progression of chronic decompensated LC [34]. ALF is defined as severe acute liver injury accompanied by coagulopathy (INR ≥ 1.5) and any degree of HE in patients without preexisting liver disease [35]. ACLF is a separate syndrome characterized by acute decompensation of chronic liver disease combined with the failure of other organs [36,37]. It has a higher short-term mortality than that predicted by the severity of the underlying chronic liver disease. It is often related to trigger events, such as exacerbation of hepatitis, bacterial infections, and active alcoholism. However, there are many cases without a definite trigger [36,38]. The systemic inflam-
flammatory response seems to be a critical factor in the development of ACLF [36]. The condition of the patient could be “reversible” through early intensive management of these reversible factors [38]. Patients with ACLF have a higher mortality rate than those without ACLF at the same MELD score [38,39]. Current management of ACLF is mainly based on support for organ failure; however, performing LT in advance at a critical time can improve prognosis [36,40]. Many studies on the pathophysiology, prognosis, and treatment of ACLF are in progress.

Since no common diagnostic criteria for ACLF have yet been established, several diagnostic criteria are being used interchangeably. In this review, we introduce the ACLF definition and scoring system of the European Association for the Study of the Liver (EASL), which is the most commonly used [36,37].

**EASL Chronic Liver Failure Consortium (EASL-CLIF-C)**

In 2013, the EASL conducted a large prospective observational study with 1343 hospitalized patients undergoing LC and acute decompensation in 29 European university hospitals to define ACLF (EASL-CLIF Acute-on-Chronic Liver Failure in Cirrhosis, CANONIC study) [37]. They modified the Sequential Organ Failure Assessment (SOFA) score into CLIF-SOFA to define organ failure in ACLF [37]. The definition of the diagnostic criteria was based on three main components (acute decompensation, organ failure, and high 28-day mortality rate) (Table 3). However, it was pointed out that the CLIF-SOFA was complex to use and did not significantly improve the prediction accuracy of MELD or MELD-Na [41]. To compensate for this, the EASL in 2014, announced the CLIF-C organ failure score (CLIF-C OFs), which simplified CLIF-SOFA [41]. The components of CLIF-C OFs are bilirubin, creatinine, the grade for HE (West-Haven), INR, mean arterial pressure, and respiratory component (PaO₂/FiO₂ or SpO₂/FiO₂) [41]. They also developed the CLIF-C ACLF score by combining the patient’s age and white blood cell count (WBC) with CLIF-C OFs to predict the short-term and long-term mortality of ACLF [41]. The equation of the CLIF-C ACLF score ranges from 0 to 100 and is as follows [36,41]:

\[
\text{CLIF-C ACLF score} = 10 \times [0.33 \times \text{CLIF-C OFs} + 0.04 \times \text{age} + 0.63 \times \ln (\text{WBC count}) - 2]
\]

The CLIF-C ACLF score can be easily calculated using a website (http://www.eclfif.com) [36]. It has been reported that the ability of the CLIF-C ACLF score to predict mortality

<table>
<thead>
<tr>
<th>Grade</th>
<th>Subgroups</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ACLF</td>
<td>1) Pt with no OF</td>
<td>28-day: 4.7%</td>
</tr>
<tr>
<td></td>
<td>2) Pt with a single “non-kidney” OF (a single failure of the liver, coagulation, circulation, or respiration) (sCr &lt; 1.5 mg/dl and no HE)</td>
<td>90-day: 14%</td>
</tr>
<tr>
<td></td>
<td>3) Pt with single cerebral failure (sCr &lt; 1.5 mg/dl)</td>
<td></td>
</tr>
<tr>
<td>ACLF grade 1</td>
<td>1) Pt with single kidney failure</td>
<td>28-day: 22.1%</td>
</tr>
<tr>
<td></td>
<td>2) Pt with single failure of the liver, coagulation, circulation, or respiration (sCr 1.5–1.9 mg/dl and/or mild to moderate HE)</td>
<td>90-day: 40.7%</td>
</tr>
<tr>
<td></td>
<td>3) Pt with single cerebral failure (sCr 1.5–1.9 mg/dl)</td>
<td></td>
</tr>
<tr>
<td>ACLF grade 2</td>
<td>Pt with 2 OFs</td>
<td>28-day: 32.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90-day: 52.3%</td>
</tr>
<tr>
<td>ACLF grade 3</td>
<td>Pt with ≥ 3 OFs</td>
<td>28-day: 76.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>90-day: 79.1%</td>
</tr>
</tbody>
</table>

**Definition of Organ Failure (CLIF-SOFA)**

1. Liver failure: serum bilirubin ≥ 12.0 mg/dl
2. Kidney failure: serum creatinine ≥ 2.0 mg/dl or the use of renal replacement therapy
3. Cerebral failure: grade III or IV HE (West Haven)
4. Coagulation failure: INR ≥ 2.5 and/or a platelet count ≤ 20 × 10^9/L
5. Circulatory failure: use of dopamine, dobutamine, or terlipressin
6. Respiratory failure: PaO₂/FiO₂ ≤ 200 or SpO₂/FiO₂ ≤ 214

**Table 3. Diagnostic Criteria and Grades of ACLF (EASL-CLIF-C)**

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25
was significantly higher (approximately 25 to 28%) than that of the MELD, MELD-Na, and CTP scores in patients with ACLF [41].

As ACLF is a dynamic process, the severity of ACLF can rapidly change during hospitalization. Investigators of the CANONIC study reported that ACLF resolved or improved in 49.2%, steady or fluctuating in 30.4%, and worsened in 20.4% of the patients. Most patients (81%) reached their final ACLF grade within one week of diagnosis. If patients with more than four organ failures or CLIF-C ACLF score > 64 did not undergo LT, the mortality rate was 100% after 28 days. They suggested that the assessment of patients with ACLF at 3–7 days after diagnosis provides a more accurate prediction of mortality [40].

FUTURE PERSPECTIVES OF MORTALITY PREDICTION

With the recent developments in computer science, most patient information is stored through electronic health records (EHR). Many studies have been published to introduce machine learning or (in a broader sense) artificial intelligence (AI) methods using EHR in the field of LT [4,42,43]. Banerjee et al. [44] created a prediction model using an artificial neural network technique in 2003 and published a study that predicted 1-year mortality better than the CTP score. Recently, many studies have suggested that machine learning is superior to MELD score in predicting mortality [45,46] or graft failure [42]. However, in some cases, these technologies do not show significant improvements over the current methods [47,48]. Many researchers are attempting to use AI in a wide range of fields, including optimizing organ allocation, donor-recipient pairing, and even automated immunosuppressant regimens based on transplant pathology [43,47].

Although AI enables accurate prediction, the parameters used in these studies are significantly different, and it is unclear whether the accuracy of any model can be reproduced in cohorts with different characteristics [43]. The predictive ability of these models is ultimately related to the quality of the clinical dataset [48]. AI is still considered to have limitations in comprehensively considering other clinical factors to determine the complexity, possibility, and urgency of surgery [4,43,47]. Further research is needed for the use of AI in clinical practice.

CONCLUSION

Many studies have been published to supplement the weaknesses of the MELD score, which is widely used for predicting mortality in patients with LT and organ allocation. However, the disadvantages of this approach remain. With the development of computer technology such as AI, there have been attempts to use it for prognosis prediction and organ distribution in those with LT. However, these also seem insufficient for practical use. Accurate prognosis prediction is important, as it is used not only for patient treatment but also for more efficient organ allocation. In the future, more studies should be conducted to predict mortality in patients with LT more accurately.

FUNDING

None.

CONFLICTS OF INTEREST

Yang-Hoon Chung has been an editor of the Anesthesia and Pain Medicine since 2019. He is a reviewer for several international journals, including Korean Journal of Anesthesiology, and Journal of Korean Medical Science. 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

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

AUTHOR CONTRIBUTIONS


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Sang Hyun Kim, https://orcid.org/0000-0001-6267-7365
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24. Yoo HY, Edwin D, Thuluvath PJ. Relationship of the model for end-stage liver disease (MELD) scale to hepatic encephalopathy, as defined by electroencephalography and neuropsychometric testing, and ascites. Am J Gastroenterol 2003; 98: 1395-9.


1018-26.
INTRODUCTION

Neoadjuvant chemotherapy is a type of cancer treatment in which chemotherapeutic drugs are administered before surgical extraction. It is recommended for locally advanced breast cancer without distant metastasis (especially in human epidermal growth factor receptor 2 [HER2]-positive and triple-negative breast cancer). Neoadjuvant chemotherapy not only increases the rate of breast conserving surgery by reducing tumor size but also enables precision medicine (e.g., adjuvant capecitabine or trastuzumab emtansine [T-DM1] for early breast cancer with residual disease) [1-5].
However, it has risks and side effects such as hair loss, extreme fatigue, weight loss, loss of appetite, nausea and vomiting, oral sores, constipation or diarrhea, neuropathy, decreased cognitive function, increased risk of infection, infertility, osteoporosis, leukemia, and heart disease. The systemic toxicities of chemotherapy in the nervous, hepatorenal, and cardiopulmonary systems have important implications in general anesthesia [6,7]. In particular, the neurotoxicity of chemotherapy, which induces pathophysiologic changes in the central and peripheral nervous systems, can influence sensitivity to anesthetics and the depth of sedation [8-10]. Some studies have demonstrated that there is a difference in the requirement for anesthetics between patients who did and did not receive chemotherapy [11-14]. A study by Wu et al. [12] on patients with breast cancer showed that propofol demand was lower in the neoadjuvant chemotherapy group than in the non-chemotherapy group. In addition, He et al. [14] reported that in patients with breast cancer, the median effective effect-site concentration (Ce50) of intravenous anesthetics (i.e., propofol and etomidate) causing loss of consciousness (LOC) in the neoadjuvant chemotherapy group was lower than that in the non-chemotherapy group. However, Ki et al. [15] had contrasting results, reporting that in colorectal cancer patients, no difference was observed in the Ce values of propofol for loss of verbal contact (LVC) and LOC between those who did and did not receive chemotherapy. Therefore, studies must confirm whether chemotherapy affects the pharmacodynamics (PD) of propofol. We recruited only female patients with breast cancer because the Ce of propofol for LOC showed a significant sex-dependent difference in the study by Ki et al. [15].

This study aimed to examine the Ce of propofol for each sedation level in female patients who received neoadjuvant chemotherapy for the treatment of breast cancer and to determine whether there is a difference in the Ce of propofol for sedation between those who received neoadjuvant chemotherapy and those who did not. In addition, we explored a PD model that determines the amount of propofol required for an appreciable depth of sedation.

**METHODS**

**Study design**

This prospective observational study was approved by the Institutional Review Board of our hospital (BP IRB 2019-01-171). We explained the study methods to each patient the day before surgery and obtained written informed consent from them. Clinical research was conducted in accordance with the Declaration of Helsinki of 1975 (revised 2013). Patients aged between 19 and 75 years, with a body mass index between 18 and 29.9 kg/m² and an American Society of Anesthesiologists physical status class between 1 and 3, who were scheduled to undergo breast cancer surgery under general anesthesia were enrolled in this study. Patients with a history of receiving chemotherapy for the treatment of diseases other than breast cancer, chronic alcoholism, difficulty in communicating, difficulty in maintaining the airway during anesthesia induction, and taking sedatives or neuro-psychiatric drugs were excluded. Among the included patients, those who received neoadjuvant chemotherapy for breast cancer were assigned to group C and those who did not were assigned to group N. We conducted a pilot study with nine patients (three patients in group C and six in group N), which revealed that the mean Ce value of propofol for LOC was $2.57 \pm 0.50 \mu g/ml$ in group C and $2.92 \pm 0.13 \mu g/ml$ in group N. On the basis of the results of the pilot study, effect size was calculated using “Cohen’s $d$” formula, and a sample number of 40 was calculated (20 patients per group) using G*power (version 3.1.9.2, Franz Faul, University Kiel, Germany) with the following settings: $t$-test; mean—difference between two independent means (two groups); tails—two; effect size—1.2006; power—0.95; $\alpha$—0.05; and allocation ratio—1:1. In total, we enrolled 50 patients (25 per group).

Vital signs (electrocardiogram, heart rate, noninvasive blood pressure, and pulse oximetry) and Bispectral Indextm (BIS, Coviiden, USA) were monitored throughout the surgery. End-tidal CO₂ was monitored and 100% oxygen (6–8 L/min) was supplied using a facial mask for airway management during the study period. For anesthesia induction, propofol (Fresofol MCT inj. 2%, Fresenius Kabi Korea, Korea) was administered as an effect-site target-controlled infusion (Effect-site TCI; Orchestra® Base Primea, Fresenius Kabi Company, France), using the Schnider model [16]. The initial target Ce was 1.5 $\mu g/ml$. One investigator, who was blinded to the study, assessed the depth of sedation using the Modified Observer’s Assessment of Alertness/Sedation (MOAA/S) scale which was evaluated every 30 s [17], and the BIS value at that time point was also recorded. When the plasma concentration (Cp) and Ce became equal to the target Ce and if the MOAA/S score remained unchanged, the target Ce was increased by 0.2 $\mu g/ml$. However, if the MOAA/S score decreased, the target Ce was not increased.
immediately but was maintained for 2 min and then increased. This process was repeated until the MOAA/S score became 0. An MOAA/S score of 2 or 3 was defined as LVC, and an MOAA/S score of 0 or 1 was defined as LOC.

**Statistical analyses**

Statistical analyses were performed using MedCalc (version 20.110, MedCalc Software Ltd., Belgium) and GraphPad Prism (version 9.4.0, GraphPad Software, USA). A t-test was performed to compare the mean values of two independent samples (group C vs. group N). Quantitative data are expressed as mean ± standard deviation or median ± 95% confidence interval. A P value of < 0.05 was considered statistically significant.

**Population PD analysis**

The relationship between the probability of response (MOAA/S score) and the Ce of propofol and the relationship between the Ce of propofol and the BIS (effect, E) were explored using PD modeling with a nonlinear mixed-effects modeling software (NONMEM, NONMEM® 7.5, ICON Development Solution, Ireland).

\[
P(\text{MOAA/S} \leq n) = \frac{\text{Ce}^{\gamma}}{\text{Ce50} (n)^{\gamma} + \text{Ce}^{\gamma}}
\]

where \( P(\text{MOAA/S} \leq n) \) is the probability of the sedation level being equal to or less than a given MOAA/S score \( n \), Ce50 \( (n) \) is the Ce of propofol with a 50% probability of the MOAA/S score \( n \), and \( \gamma \) (Hill coefficient) is the slope steepness of the Ce versus the response (MOAA/S score) curve.

\[
E = E_0 + \frac{(E_{\text{max}} - E_0)}{\text{Ce}^{\gamma} + \text{Ce50}^{\gamma}}
\]

where \( E_0 \) is the BIS value at no effect, \( E_{\text{max}} \) is the BIS value at maximal effect, Ce50 is the Ce of propofol associated with a 50% response, and \( \gamma \) is the slope steepness of the Ce versus the response (BIS) curve. The covariates that were analyzed were age and history of neoadjuvant chemotherapy. NONMEM computed the minimum objective function value (MOFV), which is a statistical equivalent to the –2log likelihood of the model. An \( \alpha \) level of 0.05, which corresponds to a reduction in the MOFV of 3.84 (chi-square distribution, degree of freedom = 1 and \( P < 0.05 \)), was used to distinguish between the hierarchical models [18,19].

**RESULTS**

We analyzed the data of 49 patients, of whom 24 were in group C, with one dropout due to the low signal quality index (SQI) of BIS, and 25 were in group N. Patient characteristics are summarized in Table 1. The period between the last neoadjuvant chemotherapy session and the start of the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group C (n = 24)</th>
<th>Group N (n = 25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>54.08 ± 12.05</td>
<td>54.52 ± 9.58</td>
<td>0.889</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>157.48 ± 5.54</td>
<td>158.76 ± 4.94</td>
<td>0.400</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.69 ± 8.18</td>
<td>59.04 ± 6.96</td>
<td>0.229</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.83 ± 2.90</td>
<td>23.43 ± 2.70</td>
<td>0.088</td>
</tr>
<tr>
<td>Menopause (n)</td>
<td>17</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Total propofol* (mg)</td>
<td>126.35 ± 26.91</td>
<td>117.06 ± 25.23</td>
<td>0.219</td>
</tr>
<tr>
<td>Total propofol/weight† (mg/kg)</td>
<td>2.06 ± 0.43</td>
<td>1.99 ± 0.38</td>
<td>0.539</td>
</tr>
<tr>
<td>Total time‡ (min)</td>
<td>12.37 ± 1.89</td>
<td>11.66 ± 2.15</td>
<td>0.226</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy§</td>
<td>9</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>AC</td>
<td>9</td>
<td>7</td>
<td></td>
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<tr>
<td>TC</td>
<td>7</td>
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</tr>
<tr>
<td>TCHP</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number only. BMI: body mass index, AC: adriamycin + cyclophosphamide, TC: docetaxel + cyclophosphamide, TCHP: docetaxel + carboplatin + trastuzumab + pertuzumab, ED: epirubicin + docetaxel. Group C = patients who received neoadjuvant chemotherapy for the treatment of breast cancer. Group N = who had never received chemotherapy. *Amount of propofol administered until the Modified Observer’s Alertness Sedation score was 0 or 1, which was defined as “loss of consciousness (LOC)”. †Total propofol divided by body weight. ‡Time to LOC after administration of propofol. §The regimens of neoadjuvant chemotherapy in group C. P value = Group C vs. Group N, t-test.

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study was an average of 25.89 ± 12.30 days (the longest period was 62 days, and the shortest period was 6 days). In our study, neoadjuvant chemotherapy regimens were determined according to the molecular type (gene-based) of breast cancer: 1) luminal type and triple-negative type—adriamycin + cyclophosphamide or docetaxel + cyclophosphamide; 2) HER2-enriched type—docetaxel + carboplatin + trastuzumab + pertuzumab; and 3) palliative type—epirubicin + docetaxel.

As the target Ce of propofol increased, both the MOAA/S scores and the BIS values decreased (Fig. 1A). The BIS values with MOAA/S scores of 3 and 1 were lower in group C than in group N. When the MOAA/S score was 3, the BIS values in groups C and N were 70.54 ± 9.10 and 75.12 ± 5.62, respectively (P = 0.037). When the MOAA/S score was 1, the BIS values for groups C and N were 63.83 ± 6.99 and 68.68 ± 5.63, respectively (P = 0.010). Fig. 1B shows the Ce of propofol for each MOAA/S score. There was no difference in the Ce values for each MOAA/S score between the two groups. The Ce values with a MOAA/S score of 3 in groups C and N were 2.68 ± 0.27 and 2.60 ± 0.24, respectively (P = 0.289). The Ce values with a MOAA/S score of 1 in groups C and N

Fig. 1. (A) BIS value for each MOAA/S score (B) Ce of propofol for each MOAA/S score. Orange: group C (those who received neoadjuvant chemotherapy for the treatment of breast cancer), Green: group N (those who never received chemotherapy). In this box-and-whisker plot, the center line of the box represents the median value, whiskers are 2.5-97.5 percentiles, and the plus sign (+) represents the mean value. BIS: Bispectral Index, Ce: effect-site concentration of propofol, MOAA/S: Modified Observer’s Alertness/Sedation scale. *Group C vs. Group N, t-test, P value < 0.05.

Fig. 2. (A) BIS values at LVC and LOC (B) Ce of propofol for LVC and LOC. Orange: group C (those who received neoadjuvant chemotherapy for the treatment of breast cancer), green: group N (those who never received chemotherapy), middle bold line and error bar: median and 95% CI, gray circle: individual’s value. BIS: Bispectral Index, Ce: effect-site concentration of propofol, CI: confidence interval, LVC: loss of verbal contact (when the Modified Observer’s Alertness/Sedation [MOAA/S] score was 3 or 2), LOC: loss of consciousness (when the MOAA/S score was 1 or 0).
were 2.76 ± 0.29 and 2.67 ± 0.27, respectively (P = 0.285).

The BIS and Ce values at LVC and LOC are shown in Fig. 2. Comparisons of the BIS and Ce values at LVC and LOC and the time taken to reach LVC and LOC are summarized in Table 2. There was no difference in Ce values between the LVC and LOC groups, but the BIS value at LOC was lower in group C than in group N (P = 0.018). Table 3 summarizes the PD parameter estimates, along with the standard error and median parameter values (2.5% and 97.5%, respectively) of the nonparametric bootstrap replicates of the final PD model for each MOAA/S score. Table 4 summarizes the PD parameter estimates along with the standard error and median parameter values (2.5% and 97.5%, respectively) of the nonparametric bootstrap replicates of the final PD model for BIS. A history of neoadjuvant chemotherapy was not a significant covariate. The relationship between the Ce of propofol and BIS is shown in Fig. 3.

### DISCUSSION

This study found no difference in the Ce of propofol for each sedation level between groups C (patients who received neoadjuvant chemotherapy for breast cancer) and N (patients who never received chemotherapy). The Ce values for LVC in groups C and N were 2.68 ± 0.28 and 2.60 ± 0.24 μg/ml, respectively (P = 0.289). The Ce values for LOC in

| Table 2. Comparisons of BIS and Ce of Propofol at LVC and LOC, and Time Spent on LVC and LOC |
|----------------------------------|-------------|-------------|-------------|
| LVC*                          |
| BIS                           | 70.79 ± 9.02 | 75.04 ± 5.69 | 0.053 |
| Ce                            | 2.68 ± 0.28  | 2.60 ± 0.24  | 0.268 |
| Time (min)                    | 8.69 ± 1.48  | 7.94 ± 1.43  | 0.076 |
| LOC†                          |
| BIS                           | 63.87 ± 7.04 | 68.44 ± 6.01 | 0.018 |
| Ce                            | 2.76 ± 0.29  | 2.67 ± 0.27  | 0.285 |
| Time (min)                    | 10.94 ± 1.63 | 10.25 ± 1.49 | 0.129 |

Values are presented as mean ± SD. LVC: loss of verbal contact, LOC: loss of consciousness, BIS: Bispectral Index, Ce: effect-site concentration of propofol. Group C = patients who received neoadjuvant chemotherapy for the treatment of breast cancer. Group N = never received chemotherapy. *When the Modified Observer’s Alertness/Sedation [MOAA/S] score was 3 or 2. †When the MOAA/S score was 1 or 0. The time in minutes from start to LVC or LOC.

| Table 3. Results of PD Modeling for the Relationship between Ce of Propofol and MOAA/S Score |
|----------------------------------|-------------|-------------|-------------|
| Parameters                      | All patients | Group C    | Group N    |
|                                | Estimate (RSE*) | Median (2.5%, 97.5%) | Estimate (RSE*) | Median (2.5%, 97.5%) | Estimate (RSE*) | Median (2.5%, 97.5%) |
| Ce50 (4)                        | 2.29 (1.85)   | 2.29 (2.23, 2.35) | 2.29 (3.21)  | 2.28 (2.19, 2.39)  | 2.28 (2.02)  | 2.30 (2.24, 2.37)  |
| Ce50 (3)                        | 2.51 (1.73)   | 2.52 (2.46, 2.57) | 2.58 (2.48)  | 2.58 (2.49, 2.67)  | 2.45 (2.20)  | 2.45 (2.39, 2.52)  |
| Ce50 (2)                        | 2.69 (1.77)   | 2.69 (2.62, 2.75) | 2.74 (2.36)  | 2.74 (2.65, 2.82)  | 2.62 (2.50)  | 2.62 (2.54, 2.70)  |
| Ce50 (1)                        | 2.97 (2.00)   | 2.96 (2.89, 3.87) | 3.06 (2.97)  | 3.05 (2.93, 3.15)  | 2.86 (2.81)  | 2.85 (2.75, 2.85)  |
| Ce50 (0)                        | 3.54 (3.20)   | 3.54 (3.45, 3.67) | 3.68 (4.67)  | 3.66 (3.50, 3.89)  | 3.37 (3.38)  | 3.34 (3.19, 3.48)  |
| γ                              | 9.65 (7.95)   | 10.00 (8.73, 10.00) | 9.28 (15.84) | 9.74 (7.79, 10.00) | 11.10 (10.45) | 11.50 (10.00, 13.40) |

Values are presented as median (1Q, 3Q). Estimates of population PD parameters and median parameter values (2.5% and 97.5%) of nonparametric bootstrap replicates of the final PD model for each MOAA/S score. No interindividual random variability was assumed. Nonparametric bootstrap analysis was repeated 1,000 times. PD: pharmacodynamic, Ce: effect-site concentration, BIS: Bispectral Index, RSE: relative standard error. Group C = patients who received neoadjuvant chemotherapy for the treatment of breast cancer. Group N = patients who never received chemotherapy. *BIS value at no effect. †BIS value at maximal effect. γ of Ce of propofol associated with 50% response. Slope steepness of the Ce vs. BIS curve. SE/mean×100 (%).
groups C and N were 2.76 ± 0.29 and 2.67 ± 0.27 μg/ml, respectively (P = 0.285). These results are similar to those reported by Ki et al. [15], who determined whether chemotherapy drugs used to treat colorectal cancer influenced the Ce of propofol for sedation, reporting that chemotherapy had no effect on the Ce of propofol for LVC and LOC in patients with colorectal cancer. The Ce values of propofol for LVC in the chemotherapy and non-chemotherapy groups were 2.40 ± 0.39 and 2.29 ± 0.39 μg/ml (P = 0.286), respectively, and those for LOC in the chemotherapy and non-chemotherapy groups were 2.69 ± 0.43 and 2.50 ± 0.36 μg/ml (P = 0.069), respectively [15].

However, some studies have reported different results [12,14]. He et al. [14] compared the differences between the three groups (non-adjuvant chemotherapy group [group NP], taxol group [group TP], and cyclophosphamide + adriamycin + 5-fluorouracil [group CP]) and calculated Ce50 at LOC (defined as loss of eyelash reflex and loss of response to a verbal command) by probit analysis. He et al. [14] reported that the Ce50 values of propofol for LOC in the TP and CP groups were lower than that in the NP group (NP: 4.11 μg/ml, group TP: 3.41 μg/ml, CP: 3.60 μg/ml). In our study, the values of Ce50 for MOAAS/S score = 1 (MOAAS/S score = 1 means that a patient responds only after painful trapezius squeeze, and MOAAS/S score ≤ 1 means LOC in our study) in groups C and N were 3.06 and 2.86 μg/ml, respectively. These contrasting results may be explained by the following. First, the methods used for propofol administration are different. We used the Schinider model [16], which is the most commonly used model for propofol effect-site TCI infusion, whereas He et al. [14] used the Arden model. In addition, we initiated propofol infusion at 1.5 μg/ml Ce, increasing it by 0.2 μg/ml, whereas He et al. [14] initiated infusion at 3.0 μg/ml Ce, increasing it by 0.3 μg/ml. Second, the neoadjuvant chemotherapy regimen administered to the enrolled patients was different in each study. Kesler and Blayney [20] compared the effects of anthracycline (adriamycin) and non-anthracycline regimens on cognitive status and functional brain connectivity in breast cancer survivors. In their results, the anthracycline group demonstrated significantly lower verbal memory performance, including immediate recall, delayed recall, and lower left precuneus connectivity, than the other two groups (non-anthracycline and non-chemotherapy groups) [20]. Among the 24 patients, 9 received the anthracycline regimen in our study. If the study had been subdivided according to the type of chemotherapy regimen, the results of our study may differ. Third, there were differences between the statistical methods used. While we compared the Ce (the target Ce value we set during the study) of the two groups using the t-test and calculated Ce50 by PD modeling with the sigmoid Emax model using the NONMEM software, He et al. [14] only calculated Ce50 by probit analysis without direct comparison of Ce values. In the results of He et al. [14], although the calculated Ce50 values in TP and CP were lower than that in NP, it was uncertain whether the differences were statistically significant.

Moreover, our results demonstrated that the BIS value at the LOC in group C was lower than that in group N. The BIS values in groups C and N were 63.87 ± 7.04 and 68.44 ± 6.01, respectively (P = 0.018). However, there was no difference in the amount of propofol infused until LOC between the two groups. Ki et al. [15] also reported that the BIS values for LOC in the chemotherapy and non-chemotherapy groups were 66.93 ± 8.82 and 71.75 ± 5.77 (P = 0.018), respectively. Several studies have revealed the influence of chemotherapy on brain structure and functional brain connectivity, which is termed as “chemobrain” [8,10,20-22]. We suspected that these chemotherapy-induced changes might be related to the low BIS value in the neoadjuvant chemotherapy group. Kesler and Blayney [20] studied the neurotoxic effects of anthracycline in breast cancer survivors using resting-state functional magnetic resonance imaging (MRI)
and high-resolution anatomic MRI, as well as a clinical cognitive status test. They found that the patients treated with anthracycline demonstrated significantly lower left precuneus connectivity within the frontal, hippocampal, and lateral parietal regions and indicated that disrupted intrinsic connectivity decreased the efficiency of information processing and reduced the brain network’s capacity for a dynamic functional response. In addition, Inagaki et al. [21] reported that in breast cancer survivors, compared with the non-chemotherapy group, the adjuvant chemotherapy group had smaller gray matter and white matter volumes, including the prefrontal, parahippocampal, and cingulate gyri and precuneus, on MRI scans taken within 1 year after cancer surgery. In a study by Yun et al. [22], the consistent findings of MRI studies on breast cancer survivors who received chemotherapy were as follows: 1) brain volume loss in the frontal and temporal regions; 2) impaired connectivity of the default mode network, especially the superior frontal gyrus and the medial prefrontal cortex, and abnormal small-world properties; 3) altered perfusion in the precentral gyrus and bilateral frontal and parietal lobes; 4) altered resting brain activity in the prefrontal lobe, posterior cingulate gyrus, precuneus, and cerebellum; and 5) different activations in the bilateral frontoparietal network, cerebellum, anterior cingulate, and occipitotemporal cortex in different tasks.

Our study had several limitations. First, we did not analyze the data according to chemotherapy regimen because of the insufficient number of enrolled patients. As neoadjuvant chemotherapy regimens vary (the treatment regimen becomes more diverse when considering endocrine and hormonal therapies), future studies must increase the number of participants for each chemotherapy regimen. Second, stimulating the patient to check the MOAA/S score may have caused a bias in the BIS values. Third, MRI and electroencephalogram could have been used to demonstrate changes in the brain structure and functional connectivity.

In conclusion, in this study, no significant differences were observed in the Ce values of propofol at each sedation level between the neoadjuvant chemotherapy and non-chemotherapy groups. We do not recommend reducing the dose of propofol for the induction of anesthesia in patients who have received neoadjuvant chemotherapy for breast cancer. Moreover, even at the same level of sedation, the BIS value may be lower in patients who received neoadjuvant chemotherapy for breast cancer than in those who did not.

**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 due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.

**AUTHOR CONTRIBUTIONS**

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**REFERENCES**


INTRODUCTION

As video-assisted thoracoscopic surgery is preferentially employed for thoracic surgery, one-lung ventilation (OLV) is mandatory for surgical exposure [1]. Obviously, proper placement of the bronchial limb of the double-lumen endobronchial tube (DLT) is a vital part of the OLV procedure. The depth of DLT, an important indicator for DLT placement, is reportedly known to be directly proportional to patient height [2,3] and several height-based formulae have been suggested in literature [2,4–8]. Although statistical significance was obtained, those formulae were shown to have

Depth of double-lumen endobronchial tube: a comparison between real practice and clinical recommendations using height-based formulae

Background: The depth of double-lumen endobronchial tube (DLT) is reportedly known to be directly proportional to height and several height-based recommendations have been suggested. This retrospective study was designed to find out the difference between calculated depths using height-based formulae and realistic depths in clinical practice of DLT placement by analyzing pooled data from patients intubated with left-sided DLT.

Methods: The electronic medical records of adults, intubated with DLT from February 2018 to December 2020, were reviewed. Data retrieved included age, sex, height, weight, and size and depth of DLT. The finally documented DLT depth (depth final, DF) was compared with the calculated depths, and the relationship between height and DF was also evaluated. A questionnaire on endobronchial intubation method was sent to anesthesiologists.

Results: A total of 503 out of 575 electronic records of consecutive patients were analyzed. Although the relationship between height and DF was shown to have significant correlation (Spearman’s rho = 0.63, \( P < 0.001 \)), DF was shown to be significantly greater than calculated depths (\( P < 0.001 \)). Despite 57.1% of anesthesiologists have knowledge of clinical recommendations to anticipate size and depth of DLT, no one routinely utilizes those recommendations.

Conclusions: Anesthesiologists tend to place DLTs in a deeper position than expected when depths are calculated using height-based recommendations. Although such discrepancies may not be clinically meaningful, efforts are needed to standardize the methods of endobronchial intubation to prevent potential complications associated with malposition.

Keywords: Depth; Double-lumen endobronchial tube; Endobronchial intubation; Height.
a less than “moderate” correlation between height and depth of DLT (i.e., correlation coefficient < 0.6). Furthermore, those formulae were not clinically recommended in adults with short stature (<155 cm) [9].

This retrospective study aimed to analyze data from patients whose tracheas were intubated with a left-sided DLT for operations requiring OLV. Additionally, the anesthesiologists whose practices were included into the analysis were asked to complete a simple questionnaire on how they perform the endobronchial intubation. The current investigation was designed to find out the difference between calculated depths using height-based formulae and realistic depths in clinical practice of DLT placement at two institutions.

**METHODS**

After receiving approval from the local ethics committees of participating hospitals to waive informed consent, the electronic medical records (EMR) of adult patients (≥ 20 years old), who required endobronchial intubation with DLT for OLV over a three-year period from February 2018 to December 2020, were reviewed. The exclusion criteria included no documentation of DLT depth and/or documentation of failure in maintaining OLV from desaturation, hypercarbia, or elevated peak airway pressure. When a patient had undergone more than two consecutive operations requiring OLV during the study period, only the more recent operation was included. The data retrieved included age, sex, height, weight, and size and depth of DLT. The current investigation was registered with the Clinical Research Information Service of the Republic of Korea (no. KCT 0005966).

The DLT intubation procedures were as follows. The size and anticipated depth of DLT was selected at the discretion of a board-certified anesthesiologist who oversaw the anesthesia care of a given patient. Anesthesia was administered using intravenous (IV) midazolam (1–3 mg), fentanyl (50–100 μg) and propofol (2 mg/kg) and muscle relaxation was provided with IV rocuronium (0.6 mg/kg). The trachea of the patient was intubated with a left-sided DLT, which was provided by two different manufacturers (Shiley™, Covidien, USA for 32, 35 and 37 Fr and Human-Broncho™, Insung Medical, Korea for 33 and 35 Fr). The methods used to confirm bronchial placement of the DLT were at the discretion of the assigned anesthesiologist, including auscultation and fiberoptic bronchoscope (FOB). The DLT was fixed at either corner of the mouth depending on the surgical requirement and its depth was measured at the upper incisor level using centimeter markings on the external surface of the DLT. The EMR template required the depth of DLT to be documented as follows. Initially, the depth of DLT was recorded at the discretion of the assigned anesthesiologist when it was finally considered to be adequate for OLV. In the middle of the study period, the requirement for documentation of DLT depth was changed to be two times; first, in the supine position and then in the decubitus position, designated as depth supine and depth decubitus, respectively. For comparison, the finally documented depth of the DLT, irrespective of the position in which it had been recorded, was designated as depth final (DF). If depths in both the supine and decubitus positions were available, the authors left the following remarks about the depth adjustment and adjustment distance as follows: no adjustment and zero (when both depths were the same), pull and negative distance (when DLT was withdrawn from the initially indwelt position), and push and positive distance (when DLT was advanced beyond the initial depth). The anticipated depth of DLT placement was calculated using height-based formulae suggested in previous studies [2,4–8]. The size of DLT was compared to the anticipated size based on sex and height [10]. The following qualifiers were used: match, smaller or bigger for same, smaller, or bigger size of DLT (size discrepancy). The patients included in the analysis were further categorized into four different height ranges, based on overall and sex-specific 25, 50, and 75 percentiles from Size Korea Database [11].

We surveyed the anesthesiologists whose practices were included in the current retrospective investigation about their methods to decide the size and depth of DLT. The first question was whether they had prior knowledge about recommendations to anticipate the size and depth of DLT based on the patient’s height and sex. The second was about how they chose the size of DLT, and then about how they decide the depth of DLT (Supplementary Table 1).

Categorical data are shown as number (percent) and continuous data are represented as mean ± SD or median (1Q, 3Q), as appropriate. Based on the normality test, parametric or non-parametric test was done appropriately. Correlation and simple linear regression were calculated to evaluate the relationship between height and DF producing coefficients of correlation and determination (R²), respectively. A P value of < 0.05 was considered significant. Statistical analyses were performed with R studio (1.4.1103, R, RStudio, Inc., USA; http://www.rstudio.com/) and R version 4.0.3 (R foundation for Statistical Computing, Austria; https://www.R-project.org/).
**RESULTS**

A total of 575 electronic records of consecutive patients whose tracheas were intubated with left-sided DLT for operations requiring OLV over the study period were reviewed. 52 records from patients who were less than 20 years old, 19 initial records of patients who had undergone duplicate operations over the study period and 1 record from a patient who had required bronchial blocker were excluded from analysis (Fig. 1). No failure in maintaining the OLV was documented.

Table 1 represents the demographic and DLT-related data of the 503 patients. Compared to the calculated depths, the DF (29.1 ± 1.9 cm) was shown to be significantly greater (P < 0.001). Data on the adjustment of DLT depth after turning to the lateral position were available for 361 patients. The DLT was left in place in most patients (75.9%, 274/361). Although it was done in a relatively small number of patients, further advancement was more frequently done than withdrawal was (60 vs. 27, respectively). A DLT smaller than that anticipated using the Slinger method [10], was used in most patients (81.7%). Fig. 2 represents the relationship between height and DF for overall patients with significant correlation (Spearman’s rho = 0.63, P < 0.001) and the regression equation of DF = 8.36 + 0.13 × Height (Adjusted R² = 0.394, P < 0.001).

Tables 2 and 3 represent the demographic and DLT-related data, categorized by height range (HR, HR1, < 158 cm; HR2, ≥ 158 and < 165 cm; HR3, ≥ 165 and < 172 cm and HR4, ≥ 172 cm) and sex, respectively. The DF was shown to be significantly greater than the calculated depths (P < 0.05), except for those calculated by some formulae in HR1, HR4 and in female patients. Fig. 3A and 3B illustrates the relationship

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**Table 1.** Demographic and DLT-related Data of Entire Patients (n = 503)

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<td>Age (yr)</td>
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<td>Height (cm)</td>
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<tr>
<td>Brodsky et al. [2]</td>
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<td>Bahk and Oh [6]</td>
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<tr>
<td>Takita et al. [8]</td>
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<td>Measured depth (cm)</td>
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<td>Adjustment distance (cm)</td>
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<td>Size of DLT determined by Slinger’s method (Fr)</td>
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</table>

Values are presented as number (%) or mean ± SD. DLT: double-lumen endobronchial tube, HR1–4: height ranges for overall patients (HR1: < 158 cm, HR2: ≥ 158 and < 165 cm, HR3: ≥ 165 and < 172 cm, HR4: ≥ 172 cm). *P < 0.001, compared to depth final.

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**Fig. 1.** Flow diagram of patient enrollment.

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between height and DF in female and male patients, respectively, revealing a significant correlation between height and DF in both female and male patients ($P < 0.001$).

A questionnaire about personal knowledge and methods of endobronchial intubation, consisting of four questions (Supplementary Table 1) was sent to 18 anesthesiologists, and 14 anesthesiologists of whom (77.8%) successfully completed it. Of the anesthesiologists, 57.1% (8/14) had knowledge of the recommendations to anticipate the size and depth of DLT based on height and/or sex. However, none reported routinely using those recommendations when performing endobronchial intubation. Most anesthesiologists (13/14, 93%) reported empirically choosing the DLT size based on a patient’s height and weight. Only one anesthesiologist reported referring to the diameter of the left bronchus retrieved from radiological evaluations. Regarding how to decide the depth of DLT, 57.1% (8/14) of anesthesiologists advance the DLT until moderate resistance is encountered, and then confirm the placement with FOB. Only 28.6% (4/14) of anesthesiologists place the DLT at the anticipated depth based on the literature. One anesthesiologist reported consistently deciding the depth of DLT using FOB, while another anesthesiologist adopted an arbitrary depth of DLT based on sex, which was subsequently confirmed using auscultation and FOB. The anesthesiologists preferentially (12/14, 85.7%) use auscultation to check the proper placement of the DLT, and subsequent FOB to confirm the placement. The remaining anesthesiologists prefer the FOB, and auscultation is only used to check bilateral symmetry. No one reported using only FOB to confirm the proper placement of DLT.

**DISCUSSION**

The current investigation on retrospectively pooled data from anesthetic practices with DLT for OLV demonstrated that the anesthesiologists working in the participating hospitals placed smaller DLTs at deeper levels than those anticipated using clinical recommendations based on height and sex. This tendency to place a smaller DLT at a deeper level was apparently demonstrated regardless of sex and height range.

A preoperative radiograph, such as a chest posteroanterior radiograph or chest computed tomography (CT), has been known to be little help to predict difficulty to be encountered during left endobronchial intubation [3,12]. It is commonly performed that a DLT is advanced until moderate resistance is encountered. As evidenced in the answers to the questionnaire in the current investigation, most anesthesiologists use such a “blind” method for initial placement of DLT. However, this method is known to easily produce DLT mal-

![Fig. 2. The relationship between patient’s height and depth final for overall patients.](image-url)
Table 2. Demographic and DLT-related Data of Entire Patients Categorized by Height Ranges

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR1 (n = 127)</th>
<th>HR2 (n = 112)</th>
<th>HR3 (n = 149)</th>
<th>HR4 (n = 115)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female</td>
<td>109 (85.8)</td>
<td>45 (40.2)</td>
<td>17 (11.4)</td>
<td>2 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>18 (14.2)</td>
<td>67 (59.8)</td>
<td>132 (88.6)</td>
<td>113 (98.3)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>64.2 ± 11.6</td>
<td>61.9 ± 14.2</td>
<td>57.9 ± 17.3</td>
<td>43.8 ± 18.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>152.9 ± 3.9</td>
<td>161.6 ± 2.0</td>
<td>168.2 ± 2.1</td>
<td>177.0 ± 4.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>56.7 ± 8.4</td>
<td>61.8 ± 10.2</td>
<td>66.6 ± 9.3</td>
<td>71.0 ± 11.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Calculated depth (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eldawlaty et al. [4]</td>
<td>24.9 ± 0.6*</td>
<td>26.2 ± 0.3*</td>
<td>27.2 ± 0.3*</td>
<td>28.5 ± 0.6*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lin and Cheng [5]</td>
<td>26.0 ± 0.8*</td>
<td>27.7 ± 0.4*</td>
<td>29.0 ± 0.4*</td>
<td>30.8 ± 0.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Brodsky et al. [2]</td>
<td>27.3 ± 0.4</td>
<td>28.3 ± 0.2*</td>
<td>29.0 ± 0.2*</td>
<td>30.0 ± 0.4*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Bahk and Oh [6]</td>
<td>26.9 ± 0.6†</td>
<td>28.2 ± 0.3*</td>
<td>29.2 ± 0.3*</td>
<td>30.5 ± 0.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Chow et al. [7]</td>
<td>26.4 ± 0.6*</td>
<td>27.7 ± 0.3*</td>
<td>28.7 ± 0.3*</td>
<td>30.0 ± 0.6*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Takita et al. [8]</td>
<td>27.8 ± 0.4</td>
<td>28.7 ± 0.2†</td>
<td>29.3 ± 0.2†</td>
<td>30.2 ± 0.4†</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Measured depth (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depth supine</td>
<td>27.5 ± 1.8</td>
<td>28.7 ± 1.7</td>
<td>29.7 ± 1.2</td>
<td>30.2 ± 1.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Depth decubitus</td>
<td>27.4 ± 1.8</td>
<td>29.0 ± 1.5</td>
<td>29.7 ± 1.3</td>
<td>30.4 ± 1.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Depth final</td>
<td>27.4 ± 1.8</td>
<td>28.9 ± 1.7</td>
<td>29.7 ± 1.3</td>
<td>30.4 ± 1.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Size of DLT (Fr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>32</td>
<td>17 (13.4)</td>
<td>4 (3.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>31 (24.4)</td>
<td>9 (8.0)</td>
<td>3 (2.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>75 (59.1)</td>
<td>64 (57.1)</td>
<td>43 (28.9)</td>
<td>15 (13.0)</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>4 (3.1)</td>
<td>35 (29.2)</td>
<td>103 (69.1)</td>
<td>100 (87.0)</td>
<td></td>
</tr>
<tr>
<td>Depth adjustment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.428</td>
</tr>
<tr>
<td>Non-applicable</td>
<td>34 (26.8)</td>
<td>30 (26.8)</td>
<td>43 (28.9)</td>
<td>35 (30.4)</td>
<td></td>
</tr>
<tr>
<td>Not adjusted</td>
<td>74 (58.3)</td>
<td>57 (50.9)</td>
<td>86 (57.7)</td>
<td>57 (49.6)</td>
<td></td>
</tr>
<tr>
<td>Pull</td>
<td>7 (5.5)</td>
<td>6 (5.4)</td>
<td>9 (6.0)</td>
<td>5 (4.3)</td>
<td></td>
</tr>
<tr>
<td>Push</td>
<td>12 (9.4)</td>
<td>19 (17.0)</td>
<td>11 (7.4)</td>
<td>18 (15.7)</td>
<td></td>
</tr>
<tr>
<td>Adjustment distance (cm)</td>
<td>0.1 ± 0.9</td>
<td>0.2 ± 0.7</td>
<td>–0.0 ± 0.6</td>
<td>0.2 ± 0.6</td>
<td>0.123</td>
</tr>
<tr>
<td>Size of DLT determined by Slinger’s method (Fr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>32</td>
<td>29 (22.8)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>80 (63.0)</td>
<td>11 (9.8)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>18 (14.2)</td>
<td>48 (42.9)</td>
<td>17 (11.4)</td>
<td>2 (1.7)</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>0 (0.0)</td>
<td>53 (47.3)</td>
<td>87 (58.4)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>45 (30.2)</td>
<td>113 (98.3)</td>
<td></td>
</tr>
<tr>
<td>Size difference (Fr)</td>
<td>–0.4 ± 1.7</td>
<td>–2.4 ± 1.2</td>
<td>–3.0 ± 1.3</td>
<td>–4.2 ± 0.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Size discrepancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Bigger</td>
<td>20 (15.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Match</td>
<td>62 (48.8)</td>
<td>9 (8.0)</td>
<td>0 (0.0)</td>
<td>1 (0.9)</td>
<td></td>
</tr>
<tr>
<td>Smaller</td>
<td>45 (35.4)</td>
<td>103 (92.0)</td>
<td>149 (100.0)</td>
<td>114 (99.1)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean ± SD. DLT: double-lumen endobronchial tube, HR1–4: height ranges for overall patients (HR1: < 158 cm, HR2: ≥ 158 and < 165 cm, HR3: ≥ 165 and < 172 cm, HR4: ≥ 172 cm). *P < 0.001, compared to depth final. †P < 0.01, compared to depth final, ‡P < 0.001, compared to depth final, §P < 0.05, compared to depth final.

Position, and even induce tracheobronchial damage, especially when a smaller-than-anticipated tube is used [13,14]. Therefore, a clinical guide to predict the depth of DLT prior to endobronchial intubation is required.

As the direction of DLT movement during lateral positioning or head rotation is almost always out of the bronchus [3,15], anesthesiologists tend to place the DLT as deep as possible to prevent dislodging. While most anesthesiologists agree that a bronchial cuff must be placed immediately below the carinal bifurcation, others suggest that the bronchial
cuff must be advanced by 0.5–1.0 cm deeper into the bronchus because the DLT is easily moved proximally when the patient’s body or head is turned [16]. In a study on fiberoptic bronchoscopic measurements in Korean patients, the distance between the upper incisor and the upper margin of left mainstem bronchial carina was demonstrated to be 32.0 ± 2.1 cm in male, and 28.5 ± 2.0 cm in female [17]. The height of patients included in that FOB investigation (169.4 ± 6.1 cm in male, 158.4 ± 5.3 cm in female) was similar to that identified in the current investigation [17]. Therefore, the DF identified in the current investigation (29.1 ± 1.9 cm for overall patients, 27.6 ± 1.7 cm and 29.9 ± 1.3 cm for female and male patients, respectively) would not be considered too deep. Furthermore, recent investigations on the measurement of tracheobronchial tree in the Asian patients using chest CT demonstrated that the average length of left

### Table 3. Demographic and DLT-related Data of Entire Patients Categorized by Sex

<table>
<thead>
<tr>
<th>Variable</th>
<th>Female (n = 173)</th>
<th>Male (n = 333)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>59.1 ± 14.7</td>
<td>56.2 ± 18.6</td>
<td>0.056</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>156.4 ± 6.5</td>
<td>169.3 ± 7.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>58.3 ± 9.5</td>
<td>67.1 ± 10.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Calculated depth (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eldawlatly et al. [4]</td>
<td>25.5 ± 1.0*</td>
<td>27.4 ± 1.1*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lin and Cheng [5]</td>
<td>26.7 ± 1.3*</td>
<td>29.2 ± 1.4*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Brodsky et al. [2]</td>
<td>27.7 ± 0.7</td>
<td>29.2 ± 0.8*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Bahk and Oh [6]</td>
<td>27.4 ± 1.0</td>
<td>29.4 ± 1.1*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Chow et al. [7]</td>
<td>26.9 ± 1.0*</td>
<td>28.9 ± 1.1*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Takita et al. [8]</td>
<td>28.1 ± 0.7*</td>
<td>29.4 ± 0.7*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Measured depth (cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depth supine</td>
<td>27.6 ± 1.8</td>
<td>29.8 ± 1.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Depth decubitus</td>
<td>27.6 ± 1.7</td>
<td>29.9 ± 1.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Depth final</td>
<td>27.6 ± 1.7</td>
<td>29.9 ± 1.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Size of DLT (Fr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>20 (11.6)</td>
<td>1 (0.3)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>33</td>
<td>38 (22.0)</td>
<td>5 (1.5)</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>114 (65.9)</td>
<td>83 (25.2)</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>1 (0.6)</td>
<td>241 (73.0)</td>
<td></td>
</tr>
<tr>
<td>Depth adjustment</td>
<td></td>
<td></td>
<td>0.470</td>
</tr>
<tr>
<td>Non-applicable</td>
<td>43 (24.9)</td>
<td>99 (30.0)</td>
<td></td>
</tr>
<tr>
<td>Not adjusted</td>
<td>98 (56.6)</td>
<td>176 (53.3)</td>
<td></td>
</tr>
<tr>
<td>Pull</td>
<td>12 (6.9)</td>
<td>15 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Push</td>
<td>20 (11.6)</td>
<td>40 (12.1)</td>
<td></td>
</tr>
<tr>
<td>Adjustment distance (cm)</td>
<td>0.1 ± 0.9</td>
<td>0.1 ± 0.6</td>
<td>0.343</td>
</tr>
<tr>
<td>Size of DLT determined by Slinger’s method (Fr)</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>32</td>
<td>29 (16.8)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>91 (52.6)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>53 (30.6)</td>
<td>32 (9.7)</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>0 (0.0)</td>
<td>140 (42.4)</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>0 (0.0)</td>
<td>158 (47.9)</td>
<td></td>
</tr>
<tr>
<td>Size difference (Fr)</td>
<td>-0.9 ± 1.7</td>
<td>-3.3 ± 1.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Size discrepancy</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Bigger</td>
<td>20 (11.6)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Match</td>
<td>64 (37.0)</td>
<td>8 (2.4)</td>
<td></td>
</tr>
<tr>
<td>Smaller</td>
<td>89 (51.4)</td>
<td>322 (97.6)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number (%). DLT: double-lumen endobronchial tube. *P < 0.001, compared to depth final.
mainstem bronchus (tracheal bifurcation to the second carina) was 48.3 ± 6.5 mm [18]. The authors measured the length of the bronchial limb of the DLT used in the current investigation including bronchial balloon. It was 24–28 mm for Human-Broncho™ and 30-31 mm for Shiley™. Therefore, the left bronchial limb of the DLT has a safety margin of approximately 15–20 mm, which had been demonstrated in previous investigations on the measurement using FOB and CT scan in Korean patients [19,20]. The differences between the average values of measured and calculated depths in the current investigation was < 20 mm. Therefore, statistically significant differences between the measured and calculated...
depths would not be “clinically” significant.

When the chest cavity is assumed to be a column, the sitting height is known for an important parameter to predict lung volume, estimating the height of the chest cavity [21]. The length of the tracheobronchial tree would be related to the sitting height. Asians have a relatively higher sitting height-to-leg length ratio, compared to the ratios in non-Asians [22], indicating that they have relatively longer torsos for a given height. Therefore, the previously suggested height-based formulae could underestimate the depth of DLT in Asians.

The depth of DLT would not be vital because the DLT depth is easily affected by postural changes of the head and neck. Furthermore, the optimal length of DLT is difficult to predict, along with intra-manufacturer variability in the dimensions of the bronchial cuff and tip, on which the margin of safety for insertion of the DLT depends [23]. However, DLT’s inserted too deep could predispose patients to tracheobronchial damage and potential barotrauma or pneumothorax [14]. Therefore, the anticipation of optimal depth matters to prevent the malposition of the DLT. Although FOB can help correct the position of the DLT, bronchoscopic misinterpretation of the carinal cascade can occur, especially in a patient with short stature; the second carina could be misidentified as the main carina, resulting in the obstruction of the left upper lobe. This may be attributed to the fear of DLT dislodgement by movement of the head and neck, wherein anesthesiologists tend to place a DLT at a relatively deeper position as the current investigation revealed. To prevent potential complications stemming from insertions that are too deep, the DLT position should be confirmed using FOB with standardized criteria. An institution’s own formula to predict the size or depth of the DLT based on its own patient characteristics would be suggested as a method of standardization, as demonstrated by Eldawlatly et al. [4,24].

The limitations of the current investigation are as follows. Although DF was measured after confirmation with FOB as an EMR template, unified criteria for FOB evaluation of DLT placement were not adopted. Thus, inter-practitioner variation might have occurred. Additionally, the DLT’s used in this investigation were from multiple manufacturers, which might have caused subtle differences in the detailed dimensions of the DLT, including the length of the bronchial limb and/or cuff, thus inter-manufacturer variation must be considered. Those inter-practitioner variations in FOB evaluation criteria and inter-manufacturer variations in DLT dimensions are, however, not considered clinically significant because all anesthesiologists uniformly confirmed the DLT placement using FOB with safety margin of approximately 20 mm in the bronchial limb of DLT irrespective of manufacturer. Although no documentation of failure in maintaining OLV was found, various record of non-fatal desaturation/hypoxia, hypercarbia or ventilatory difficulty could have been missed in the current retrospective investigation.

In conclusion, anesthesiologists working in the participating hospitals tend to place a smaller DLT at a deeper position, when compared to the size and depth calculated by clinical recommendations based on height. Such a discrepancy may not be clinically meaningful; however, efforts are needed to standardize the methods of endobronchial intubation to prevent potential complications associated with malposition.

SUPPLEMENTARY MATERIALS

Supplementary data including a questionnaire can be found online at https://doi.org/10.17085/apm.22214.

FUNDING

None.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

Conceptualization: Jae Hee Woo, Jong Wha Lee. Data curation: Jae Hee Woo, Sooyoung Cho, Yongju Choi, Jong Wha Lee. Formal analysis: Sooyoung Cho, Jong Wha Lee. Methodology: Jae Hee Woo, Sooyoung Cho, Jong Wha Lee. Visualization: Sooyoung Cho. Writing - original draft: Jae Hee Woo, Sooyoung Cho, Youn Jin Kim, Dong Yeon Kim, Yongju Choi, Jong Wha Lee. Writing - review & editing: Jae Hee Woo, Sooyoung Cho, Youn Jin Kim, Dong Yeon Kim, Yongju Choi, Jong Wha Lee. Investigation: Yongju Choi. Resources: Youn

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REFERENCES

Secondary migration of a pre-existing central venous catheter due to a Swan-Ganz catheter insertion - A case report -

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Background: The entanglement of multiple central venous catheters is a rare and serious complication. The Swan-Ganz catheter is a responsible for various cases.

Case: A 66-year-old male patient was under general anesthesia for a coronary artery bypass graft surgery. As he had a pre-existing Perm catheter in the right subclavian vein, a Swan-Ganz catheter was inserted into the left internal jugular vein. Chest radiograph after catheter placement revealed that the Perm catheter had migrated to the left brachiocephalic vein. The surgeon attempted to reposition it manually, but postoperative radiograph showed that it had rolled into a loop. On postoperative day 1, radiological intervention was performed to untangle the loop, which was successful.

Conclusions: After placing a Swan-Ganz catheter in patients with a pre-existing central venous catheter, the presence of entanglement should be assessed. In such cases, radiology-guided correction is recommended, as a blind attempt to disentangle can aggravate the condition.

Keywords: Anesthesia, cardiac procedures; Catheterization, Swan-Ganz; Catheters, indwelling; Central venous catheters; Equipment failure; Intraoperative complications.

The role of Swan-Ganz catheterization in cardiac surgery and perioperative intensive care management has come into doubt over the years. Considering its extremely low rate of serious complications, its use in cardiac surgery remains justified [1]. One of the complications is knotting or entanglement of the catheter, which may require radiological intervention or surgical removal. Of the numerous cases of intravascular catheter knotting, more than two-thirds involved pulmonary artery catheters [2]. In contrast, cases of knotting or entanglement of multiple central venous catheters are few. Here, we report the entanglement of a Swan-Ganz catheter with a pre-existing central venous catheter, and the subsequent migration and ultimately looping of the central venous catheter after an attempt to reposition it.

CASE REPORT

Written informed consent was obtained for the publication of this case report. A 66-year-old male patient (weight, 67 kg; height, 173 cm) was scheduled for coronary artery bypass grafting under general anesthesia for the management of 3-vessel coronary artery occlusive disease. The patient...
had coexisting end-stage renal disease with regular hemodialysis 3 times a week, dyslipidemia, mildly uncontrolled diabetes mellitus and hypertension. Preoperative laboratory tests revealed mild anemia with a hemoglobin of 9.1 g/dl, an increased white blood cell count of 19.18 × 10³/μl, a prolonged activated partial thromboplastin time of 54.8 seconds, and elevated blood urea nitrogen/creatinine levels of 26.3/2.36 mg/dl. Results from other laboratory tests, electrocardiography, transthoracic echocardiography, and pulmonary function tests, were within normal limits. Preoperative chest radiograph showed an appropriately positioned HemoSplit (BD, USA) catheter, a split-tip form of the Perm catheter, inserted through the right subclavian vein (Fig. 1).

On arrival in the operating room, general anesthesia was induced and maintained with an effect-site target-controlled infusion of propofol and remifentanil. Atracurium was used for the neuromuscular blockade. To avoid catheter crowding at the entrance of the right brachiocephalic vein, a MAC™ Two-Lumen Central Venous Access Device (Arrow International Inc., USA) for use with 7–8 Fr. catheters, 10 cm in length, was inserted into the left jugular vein using ultrasonography. The Swan-Ganz CCOmbo V (Edwards Lifesciences LLC, USA) was prepared and inserted via MAC catheter. The Swan-Ganz catheter was advanced, considering the curvature of the catheter and the relevant anatomy. In the initial attempt, ballooning was done after advancing the catheter to approximately 20 cm. Even after advancing to 50 cm, no right ventricular pressure wave was observed. Thus, the balloon was deflated, and the catheter was retreated to a 20 cm point. No significant resistance was felt during catheter advancement or retrieval, except for a slight rubbing sensation, which was assumed to be due to minor friction between the previously inserted Perm catheter and the Swan-Ganz catheter. On retracting the Swan-Ganz catheter to a 20 cm point, the tip was ballooned again, and the catheter was advanced once more. At the advancement to the 40 cm point, the same rubbing feeling was evident. Thus, the balloon was deflated, and the catheter was retrieved completely. The retrieved catheter was examined for damage or defects and confirmed to be intact. On the third attempt at inserting the Swan-Ganz catheter, the tip was ballooned at the 20 cm point. As gradually advancing the catheter, the waveforms of the right ventricle and pulmonary artery were observed. After confirming the waveforms of pulmonary capillary wedge pressure, the catheter was slightly retrieved and fixed at 50 cm. A chest radiograph taken to confirm the appropriate positioning of the Swan-Ganz catheter revealed migration of the pre-existing Perm catheter. The mid- to distal portion of the Perm catheter was positioned in the left brachiocephalic vein, with a flexure in the middle and the tip in the superior vena cava (Fig. 2). Being aware of this preoperative catheter migration, the surgeon manually attempted to reposition the catheter during cardiopulmonary bypass. The remainder of the intraoperative period was uneventful. However, a postoperative chest radiograph revealed that manual repositioning of the Perm catheter was incomplete and the tip remained looped (Fig. 3). One day after the operation, the patient underwent a radiology-guided repositioning of the Perm catheter. An Amplatz guidewire was successfully inserted through each lumen of the looped catheter to carefully straighten the catheter and reposition the tip in the right atrium (Fig. 4). The repositioned Perm catheter functioned properly throughout the hemodialysis without further complications.

**DISCUSSION**

The entanglement of the central venous catheter causing a loop or knot has been repeatedly reported over the years.
Its incidence has increased with the increased use of intravascular devices, such as inferior vena cava filters, indwelling catheters, and pacemakers [1,2]. Over two-thirds of the reported entanglements are attributed to Swan-Ganz catheters [3]. While entanglement was limited to the catheter itself in most cases, eight existing reports have described the entanglement of a Swan-Ganz catheter with at least one other central venous catheter. The form of the entanglement varied from case to case. There were four cases of tight knots [4-7], two reports of a loose knot [8,9], and one case of a catheter transecting the other [10].

In our patient, we suspect that entanglement occurred by a loop in the Swan-Ganz catheter, formed by its course in the right ventricle, encircling the central venous catheter during the retrieval attempt. The angle between the catheters was suggested to be a contributing factor in creating a knot. Although the role of angulation between catheters is unclear, it has been reported that central venous catheter misplacement can often occur when inserted from the left side [11]. We also assumed that the loose knot in our case may have untangled spontaneously during the advancement and retrieval of the Swan-Ganz catheter for proper placement.
Migration of two central catheters

However, the maneuver of unaware loose knot resulted in secondary migration of the previously well-positioned Perm catheter. According to other reports, initial suspicion of entanglement is usually associated with resistance during an attempt to remove the catheters after malfunctioning. In our case, there was little evidence to suspect entanglement except for a minor rubbing sensation. Thus, when handling a Swan-Ganz catheter in the presence of multiple central venous catheters, one should be aware of the possibility of multiple catheter entanglement, as well as the risks of inserting the Swan-Ganz catheter itself.

With the occurrence of catheter entanglement, forceful maneuvers to untangle the catheter may result in lethal conditions, such as vascular tearing or catheter rupture, leading to a remnant foreign body within the venous system [1]. Thus, various methods using interventional radiological or surgical approaches have been developed to safely remove the entangled catheter [1,2,12]. When entanglement occurs between multiple central catheters, attempts to untangle it may become much more complicated. A tight knot can make it impossible for radiologic intervention to untangle, and surgical removal may be required [4,5,7]. In one reported case, a tight knot was successfully removed through the insertion site after spontaneous breakage at the knot [6]. In two other cases, the catheters were freed apart using an introducer with a larger lumen [10,13], whereas loosely knotted catheters were untangled with gentle maneuvers [8].

Contrary to the previously reported cases, in our patient, both catheters were left in place after freeing the entanglement, as we were under the impression that the function of both catheters was still intact. Although the Perm catheter was not used during the operation to confirm this, we suspected that its function did not deteriorate, considering that the knot was loose, and the tip of the catheter remained within the vascular lumen. Were it not for the postoperative chest radiograph, the Perm catheter loop formed by the surgeon may have gone unnoticed and could have been used postoperatively, remaining to be potentially hazardous. Importantly, when placing multiple central venous catheters, radiographs should be taken between handling catheters, even if they are functional, to ensure that the catheters are not entangled.

The fact that the tip of the central venous catheter was rolled into a loop after the surgeon’s blind maneuver to reposition it must also be considered. We suspected that the tip of the catheter was pressed against the vascular wall and subsequently rolled into a loop. This could have been potentially harmful, and may have led to vascular damage. In such cases, it may be advisable to leave the migrated catheter in place until interventional radiologic procedure can be performed. As our case demonstrated, a blind maneuver to reposition the catheter did not resolve the problem successfully, nor did it prove to be safe.

As shown in Fig. 1, the hemodialysis catheter was split. A split catheter with unequal lengths may increase the risk of entanglement, especially if the entanglement involved another guidewire or if the catheter was passing through the space between the split catheters. In our patient, both tips were displaced in unison. Therefore, we suspect that entanglement did not occur between the split catheters.

In conclusion, although the incidence may be low, the insertion of a Swan-Ganz catheter can lead to entanglement, a potentially serious complication, especially when there are also multiple central catheters present. It should be noted that the entanglement of catheters can be present even when they are functional. Therefore, proper placement should be radiographically verified before and after handling the catheters. In addition, when an entangled or looped catheter is present, it may be advisable to disentangle it using interventional radiology, as blind attempts may be potentially harmful.

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

REFERENCES

INTRODUCTION

Airway management is a challenging task in children and a variety of devices have been developed precisely for this purpose. A safer alternative to endotracheal intubation was brought to the fore by Archie Brain, namely a supraglottic airway (SGA) [1]. The advent of SGAs has reduced perioperative airway-related side effects and they have become a more popular device for securing the airway, as reported by the National Audit Project-4 (NAP-4) [2].

Pediatric-size SGAs are limited, and these devices have been innovated and modified from their adult counterparts.
although their efficacy and safety in this subset of the population are limited [3]. A network meta-analysis on the use and evaluation of different SGAs in pediatric patients concluded that I-gel™ (Intersurgical Ltd., UK) is one of the most studied SGAs in children with a high oropharyngeal leak pressure (OPLP) and the lowest risk of blood staining among 16 SGAs studied [4]. Another second-generation laryngeal mask airway (LMA) is Blockbuster™ LMA (Touren Medical Instrument Co., Ltd., China), invented in 2012 by Professor Ming Tian, made of silicone with an inflatable cuff [5]. Till now no study was available in literature that compared efficacy and safety of these devices in pediatric population.

Therefore, we designed this study to compare the clinical performance of Blockbuster™ LMA with that of I-gel™ in pediatric patients with the hypothesis that LMA-Blockbuster would have comparable efficacy to I-gel when used in pediatric patients.

**METHODS**

This study was conducted in tertiary care centre after approval from Institutional Ethics Committee (no. SNMC/IEC/2020/Plan/313) and registration in the Clinical Trial Registry of India (no. CTRI/2020/09/028079). Informed written consent was taken from the parents of all patients. Children of age 1–5 years, weighing between 5 and 25 kg, belonging to the American Society of Anesthesiologists- physical status I or II, scheduled for elective surgery under general anesthesia were included in this study. The syndromic babies, upper respiratory tract infections, silicone allergy, emergency surgery, abnormal anatomy of pharynx and larynx, those at increased risk of aspiration and patients who have received oxygen support or mechanical ventilation in the past one month were excluded from the study.

Children were randomized to either group- the I-gel™ group (Group I) or the Blockbuster™ LMA group (Group B) using a computer-generated random number table. To ensure the confidentiality of the assignment, random numbers were placed in a sealed opaque envelope which was opened upon the child’s arrival in the operating room.

Patients were kept nil per oral as per standard fasting guidelines. Monitoring consisted of electrocardiography, non-invasive blood pressure (NIBP), and pulse oximetry, and baseline vital parameters were recorded. Children were premedicated with midazolam 0.05 mg/kg intravenously (IV), and anesthesia was induced with fentanyl 2 µg/kg and and propofol 2–3 mg/kg IV. Intravenous atracurium 0.5 mg/kg was administered after confirmation of satisfactory mask ventilation. The airway was secured with one of the airway devices as per group allocation. The airway device size was chosen according to body weight and manufacturer recommendations. The lubricated device was inserted in a neutral head position. Both these devices were inserted along the hard palate with the airway device shafts held approximately parallel to the patient’s chest until resistance was felt. The Blockbuster™ LMA cuff was inflated with the appropriate amount of air according to the manufacturer’s instructions. The ventilator was attached to the device and effective placement was assessed by bilateral equal chest movements, square wave capnograph, absence of gastric insufflations epigastrium auscultation and delivery of adequate tidal volume. The insertion time was calculated as the time from picking up the device to the appearance of the first capnographic waveform on the monitor. The number of insertion attempts was also calculated. Insertion failure was marked if the airway could not be secured in three attempts and the patient was intubated via direct laryngoscopy with an appropriate size endotracheal tube. The primary outcome of the study was the comparison of the OPLP and secondary outcomes were insertion parameters such as ease of insertion, time of insertion and number of attempts, as well as hemodynamic changes and incidence of postoperative complications.

The OPLP was determined one minute after securing the airway by closing the circle system’s expiratory valve at a fixed gas flow of 3 L/min. The airway pressure at which equilibrium was reached and a gas leak occurs as determined by an audible leak or by detection of an audible noise with a stethoscope placed directly lateral to the thyroid cartilage was the OPLP [6].

Ease of insertion was assessed by an objective rating depending on the number of airway manipulations required to introduce the LMA with no manipulation, only one manipulation and more than one manoeuver rated as very easy, easy and difficult respectively. Hemodynamic parameters including heart rate, NIBP and peripheral oxygen saturation (SpO₂) were recorded at baseline, immediately after device insertion and every 5 min until surgery was completed. Anesthesia was maintained with sevoflurane in an O₂-air mixture with a targeted FiO₂ of 40%. Anesthetics were discontinued at the end of the operation; 0.05 mg/kg neostigmine was administered together with 0.01 mg/kg glycopyrrolate to reverse the effect of the neuromuscular blocking agent. Upon return of adequate spontaneous breathing and muscle
strength, the device was removed as soon as the child was awake. The device was examined for blood stains and the child was evaluated for other postoperative complications.

All patients’ SGAs were inserted by anesthesiologists, who had at least 3 years of SGAs insertion experience or had at least 50 SGAs insertions before the start of the study. The OPLP, SGA insertion time, hemodynamic parameters, and postoperative complications were noted and recorded by an independent observer who was unaware of the inserted device.

The sample size was calculated on previous study by Kim et al. [7] The oropharyngeal leak pressure for I-gel™ was mean ± SD; 27.1 ± 6.1 cmH₂O. Assuming a minimum difference of 3 cmH₂O to be clinically significant, the minimum sample size calculated to be 66 in each group at type I error of 0.05 and power of 80%. To account for potential dropouts, we enrolled 70 patients in each group.

The Kolmogorov–Smirnov test was used to determine the distribution of all continuous variables. An independent t-test was used for the normally distributed variables. Fisher’s exact test and chi-square test were used for comparison of qualitative data. The continuous variables were described in mean ± SD, while categorical variables were described in numbers and percentages. Differences were considered significant at P < 0.05.

RESULTS

A total of 149 patients were evaluated for eligibility, of which 5 patients were excluded due to symptoms of upper respiratory tract infection on the day of surgery and the parents of 4 children refused to participate, so the remaining 140 patients were included in the final analysis. Selected children were randomly assigned to Group I and Group B (Fig. 1). Children included in both groups had comparable demographic variables (Table 1).

The mean OPLP was significantly higher for I-gel™ (27.97 ± 1.65) than for Blockbuster™ LMA (26.04 ± 2.12) (P < 0.001) (Fig. 2). Total insertion time was comparable between I-gel™ and Blockbuster™ LMA at 15.51 ± 1.62 and 15.92 ±
Table 1. Demographic Variables

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Parameter</th>
<th>Group I (n = 70)</th>
<th>Group B (n = 70)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age (yr)</td>
<td>3.40 ± 1.36</td>
<td>3.16 ± 1.44</td>
<td>0.320</td>
</tr>
<tr>
<td>2</td>
<td>Sex (M/F)</td>
<td>59/11</td>
<td>61/9</td>
<td>0.629</td>
</tr>
<tr>
<td>3</td>
<td>Weight (kg)</td>
<td>12.81 ± 3.82</td>
<td>12.54 ± 3.66</td>
<td>0.673</td>
</tr>
<tr>
<td>4</td>
<td>ASA-PS (I/II)</td>
<td>70/0</td>
<td>70/0</td>
<td>1.000</td>
</tr>
<tr>
<td>5</td>
<td>Duration of surgery (min)</td>
<td>31.49</td>
<td>32.09</td>
<td>0.190</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number. n: number, M: male, F: female, ASA-PS: American Society of Anesthesiologists-physical status. Independent t-test or chi-square test used.

Table 2. Comparison of Oropharyngeal Leak Pressure, Ease of insertion, Number of Attempts and Time for Insertion

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Parameter</th>
<th>Group I (n = 70)</th>
<th>Group B (n = 70)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Oropharyngeal leak pressure (cmH2O)</td>
<td>27.97 ± 1.65</td>
<td>26.04 ± 2.12</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>2</td>
<td>Ease of insertion (easy/very easy/difficult)</td>
<td>68/2/0</td>
<td>63/7/0</td>
<td>0.066</td>
</tr>
<tr>
<td>3</td>
<td>Number of attempts for insertion (1/2/3)</td>
<td>68/2/0</td>
<td>63/7/0</td>
<td>0.066</td>
</tr>
<tr>
<td>4</td>
<td>Time for insertion (s)</td>
<td>15.51 ± 1.62</td>
<td>15.92 ± 3.02</td>
<td>0.314</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number. Independent t-test or chi-square test used. *P < 0.05.

![Fig. 2. Comparison of oropharyngeal leak pressure. OPLP: oropharyngeal leak pressure.](image)

3.02 s respectively. Both groups were found to be comparable in terms of ease of SGA insertion. The devices were successfully inserted on the first attempt in 97.14% and 90% of the I-gel™ group and Blockbuster™ LMA groups respectively (Table 2). All hemodynamic parameters and cases of post-operative complications were comparable between both groups.

DISCUSSION

The main results of the study show that both I-gel™ and Blockbuster™ LMA provide adequate sealing pressure around the laryngeal inlet. However, the I-gel™ provides a comparatively better airway seal than the Blockbuster™ LMA.

Effective and adequate sealing around the glottis becomes important when SGAs are used during surgery to prevent loss of tidal volume, avoidance of operative room air contamination, repeated airway switching and reduce the risk of regurgitation. To ensure adequate ventilation, an ideal SGA should have an OPLP higher than ventilation airway pressure or greater than 20 cmH2O [8]. In the literature pediatric counterparts of various first-generation SGA such as classic LMA, flexible LMA, LMA unique, etc. have reported OPLP of 16 to 20 cmH2O [9]. Second-generation devices such as the LMA Proseal, Air-Q, I-gel™, and LMA Supreme are also available in pediatric sizes and have better seal pressure compared to first-generation devices [7,9–11].

In our study, the OPLP of Blockbuster™ LMA has been reported to be lower than I-gel™ (26.04 ± 2.12 mmHg and 27.97 ± 1.65 mmHg respectively), although both these devices provide adequate seal pressure when used for positive pressure ventilation. I-gel™ has a non-inflatable thermoplastic polymer cuff that is known to conform itself to the glottis to provide an effective seal around the glottis. The cuff is said to respond to body temperature to create an adequate seal around the glottis to resist leakage during positive pressure ventilation [11,12]. With the Blockbuster™ LMA, the 95-degree angled breathing tube and the cuff shape of the BlockbusterTM LMA can be responsible for the high sealing pressure [5]. In most studies, the OPLP of I-gel™ was reported to be greater than 20 cmH2O in pediatric patients [13–15]. While studies using Blockbuster™ LMA in pediatric patients are limited. Endigeri et al. [16] reported an OPLP of Block-
buster™ LMA of 33.7 ± 1.8 cmH₂O in adult patients, which is higher than observed in our study. Though a higher OPLP doesn’t always guarantee an appropriate placement, it is commonly used objective test to guide correct placement. A higher OPLP suggests proper placement of device around perilaryngeal structure and ability of the device to sustain leak during positive pressure ventilation. Though in our study a statistically significant difference was observed between two devices, with I-gel™ reported to have higher seal pressure, but clinically this difference was not very significant as if SGA is achieving an OPLP more than 20 cmH₂O, it can sustain leak during spontaneous or controlled ventilation in pediatric patients. There are plenty of studies in I-gel™ in pediatric patients and I-gel™ is considered to be a prototype second generation LMA but Blockbuster™ LMA is newly introduced with limited studies available on its use in children. So, our study finding support the use of Blockbuster™ LMA for pediatric airway management, however further randomized controlled trial are required to confirm and support our study findings. We inflated the Blockbuster™ LMA as per manufacturer specification but further study of inflation pressures and positioning may help optimize the Blockbuster™ LMA.

There was no case of failed insertion of the LMA in either group, with airways secured in 97% and 90% of the first attempts in the I-gel™ and Blockbuster™ LMA groups respectively. Studies have reported a greater than 95% first-attempt success rate for I-gel™ [17]. Ease of insertion was comparable for both I-gel™ and Blockbuster™ LMA with 100% of both groups having “easy” and “very easy” insertion. Total insertion time was comparable between I-gel™ and Blockbuster™ LMA at 15.51 ± 1.62 and 15.92 ± 3.02 s respectively. All insertions were performed in < 30 s which is acceptable given the time required to secure an airway. Both I-gel™ and the Blockbuster™ LMA had a sleek and streamlined design that could be deployed quickly, even considering the anatomical challenges presented by pediatric airways. Previous studies have found that I-gel™ took a longer time to insert and this was attributed to I-gel™ straight shape which showed frequent displacements. It has also been shown that the I-gel™ requires consistent downward mechanical pressure to stay in place with close contact with the glottis. We had no such difficulties in our study and were able to promptly fix I-gel™ in place. The Blockbuster™ LMA with its inflatable cuff and the angled tube, did not cause any difficulties worth mentioning during insertion.

All hemodynamic variables were comparable in both groups with no significant change in parameters at different intervals in the study. Similarly, the incidence of postoperative complications was zero in I-gel™ and one incidence of blood stains in Blockbuster™ LMA. All insertions were performed by trained individuals and therefore the optimal safety seen with both SGA devices was to be expected.

Limitations of our study include enrolling subjects with normal airways with no prior anatomical pathology. Second, we did not evaluate the additional features of both LMAs such as gastric channels and the ability to be used as a channel for intubation. Third, we have not confirmed the fiberoptic position of any of the LMA after insertion and we have not evaluated the inflation cuff pressure in the Blockbuster™ LMA.

To conclude, the I-gel™ delivered significantly higher OPLP than Blockbuster™ LMA, otherwise, both LMAs are comparable in terms of performance. Both I-gel™ and Blockbuster™ LMA are appropriate devices for positive pressure ventilation in pediatric patients undergoing short surgical procedures under general anesthesia with minimal pharyngolaryngeal morbidity.

**FUNDING**

None.

**CONFLICTS OF INTEREST**

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

**DATA AVAILABILITY STATEMENT**

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

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REFERENCES
INTRODUCTION

As coronavirus disease 2019 (COVID-19) was declared a global pandemic, vaccines are being developed rapidly, and mass vaccination has been performed in a short time. Vaccination is an efficient and safe way to resolve the COVID-19 pandemic; however, its adverse reactions have been continuously reported [1]. The most common adverse reactions associated with vaccines include injection site pain, fever, myalgia, headache, and fatigue, which can be treated easily in a short period [2,3]. However, rare, fatal postvaccination adverse reactions, such as myocarditis, thrombosis, and Guillain–Barré syndrome, have been reported [4–7].

Herpes zoster (HZ) is one of the adverse reactions of COVID-19 vaccination and is being continuously reported up to now [8–12]. HZ is caused by the reactivation of varicella-zoster virus (VZV), which remains latent in the dorsal root ganglia. It is characterized by severe pain along the area of the affected nerve with a unilateral skin lesion appearing around its cutaneous distribution [13,14]. HZ, which was reported in relation to COVID-19 vaccination, has been investigated from the perspective of dermatology regarding skin...
lesions [15–17]. However, HZ may induce severe acute pain from nerve damage by the virus and postherpetic neuralgia (PHN), in which pain persists even after skin lesions improve [18]. PHN can affect patients’ daily lives and may cause depression, decreased quality of life, and social withdrawal [13,18]. In this regard, HZ should not only be considered a cutaneous adverse effect associated with COVID-19 vaccination. However, to the best of our knowledge, there have been no reports or studies of HZ from the perspective of pain medicine. Therefore, we conducted this study to compare the clinical features of HZ related to COVID-19 vaccination with those of other HZ from the perspective of pain medicine by retrospectively reviewing medical records.

**METHODS**

This was a retrospective single-center study. This study was approved by the institutional review board of our hospital (no. 2021-11-046) and registered with the Clinical Research Information Service (no. KCT0006864). The present study was conducted according to the ethical principles for medical research of the Declaration of Helsinki 2013.

Patients who visited the pain clinic of our hospital from August 1, 2021, to October 31, 2021, were screened. During the study period, 475 patients visited the pain clinic, of whom 53 were diagnosed with HZ. Patients whose COVID-19 vaccination history was not clearly verified (n = 8), whose medical records were unreliable (n = 2), and who were referred to dermatologists because of chilblain-like lesions (n = 1) were excluded from this study (Fig. 1). Patients were divided into two groups based on 6-week (42-day) postvaccination [1]. Patients who were vaccination-naive or had received a vaccine more than 6 weeks before were allocated to the control group (n = 28), and those who developed HZ within 6 weeks after vaccination were allocated to the COVID-19 vaccination-related HZ (CV-related HZ) group (n = 14).

In the pain clinic of our hospital, we recognize the association between COVID-19 vaccination and HZ [11], and we have been documenting the history of COVID-19 vaccination in patients with HZ since approximately August 2021. The following data were collected from the patients’ medical records and analyzed: demographic information: (age and sex), COVID-19 vaccination-related information (vaccination status, types of vaccines, vaccination dose associated with HZ, and time from vaccination to development of HZ), and HZ-related information (time to development of prodromal pain and skin lesions, pain score, location of lesions, treatment methods, treatment duration, and development of PHN). PHN was defined as dermatomal pain persisting for > 90 days after the onset of acute HZ rash [18]. The time

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**Fig. 1.** Study flowchart. COVID-19: coronavirus disease 2019, CV-related HZ: coronavirus disease 2019 vaccination-related herpes zoster.
from vaccination to the development of HZ was defined as the time of onset of pain, not the time of onset of skin lesions. The vaccination date was not included in the calculation. An 11-point numerical rating scale was used to measure pain. In terms of treatment methods, the use of antiviral agents or anticonvulsants and application of nerve blocks were investigated.

Data are presented as mean (standard deviation) or median (interquartile range). The normality of the quantitative data was tested using the Shapiro–Wilk test, and data were analyzed using the independent t-test or Mann–Whitney U test. The chi-squared or Fisher’s exact test was used for categorical data. Statistical significance was set at P < 0.05. Statistical analyses were performed using the Statistical Package for the Social Sciences version 23 (IBM Corp., USA).

RESULTS

This study included 42 patients with HZ. Of the 32 patients who received COVID-19 vaccination, 14 developed HZ within 6 weeks after the vaccination. Ten patients did not receive any vaccination. The median age of the patients was 63.5 (34.5, 73.3) years, with 17 (40.5%) male and 25 (59.5%) female patients. Patients in the CV-related HZ group (52.0 [30.8, 62.3] years) were significantly younger than those in the control group (66.5 [54.3, 78.8] years) (P = 0.005). Prodromal pain was reported in 26 (61.9%) patients; thereafter, skin lesions developed after a median day of 3.0 (0.0, 4.0). The median pain scores were 3.0 (3.0, 4.0) and 4.0 (3.0, 4.0) in the CV-related HZ and control groups, respectively (P = 0.834). The most common locations of the lesion were the thoracic (64.3%) and cranial (14.3%) nerves. Antiviral agents (100%), anticonvulsants (87.2%), and nerve blocks (43.6%) were used. Moreover, 87.2% of the patients completely recovered within 12 weeks (Table 1). The other data did not show any statistical difference. In the CV-related HZ group, eight (57.1%) patients completely recovered within 4 weeks after symptom development. Although the difference was not statistically significant, five (12.8%) patients in the control group progressed to PHN (P = 0.092) (Fig. 2).

In the CV-related HZ group, five patients received BNT1 62b2 (Pfizer), five received mRNA-1273 (Moderna), and four received ChAdOx1 nCov-19 (AstraZeneca). Ten patients developed symptoms after the second dose. Nine (64.3%) patients developed symptoms within 21 days of vaccination (Table 2).

The clinical information of patients with CV-related HZ and PHN is presented in Tables 3 and 4.

DISCUSSION

In total, 42 patients with HZ were included in the present study, of whom 14 (33.3%) developed HZ within 6 weeks after COVID-19 vaccination. Except for age, demographic and HZ-related data did not show statistically significant differences between the groups. However, five patients in the control group developed PHN, whereas none of the patients in the CV-related HZ group progressed to PHN, but the difference was not statistically significant.

VZV, which remains latent in the ganglia, can be reacti-vated and replicated, inducing neuritis that directly damages the nerves. It is transported along the microtubules within the sensory axons in the affected nerve to infect the epithelial cells of the skin. This results in severe pain and skin lesions along the cutaneous distribution. Weakened VZV-specific T-cell-mediated immunity reactivates VZV. Its risk factors include immunosenescence, immunocompromised conditions due to disease, trauma, drug use, and psychological stress [14,19]. The outbreak of the COVID-19 pandemic and COVID-19 vaccination have been reported to be associated with the development of HZ [20–23]. Its mechanism of action has been reported to be lymphopenia and T-cell dysfunction due to COVID-19 infection, and immunomodulation associated with COVID-19 vaccination weakens T-cell-mediated immunity, which inhibits VZV from being reactivated. However, its mechanism of action remains unclear [20,23].

Although HZ is accompanied by severe pain and is likely to progress to PHN, a neurological complication, most published cases of HZ after COVID-19 vaccination have been approached from the aspect of dermatology regarding skin lesions [15–17]. Many studies have mentioned HZ in view of skin complications that occur after vaccination [24,25]. Even in studies that directly reported HZ, most described the association between HZ and vaccination or the mechanism [15,16]. In studies published from the aspect of dermatology, it was rare for the treatment and progress of HZ to be clearly described, as in the present study. In cases that clearly described the treatment for HZ and its progress, most treatment outcomes were highly good. Most patients improved with antiviral therapy, and there were no cases lasting >6 weeks [165]. However, five (35.7%) of the 14 patients with HZ required treatment for 6 weeks or longer (6–11 weeks) in the present study (Fig. 1). The reason that the treatment period of the
Table 1. Demographic Data and Characteristics of Herpes Zoster-related Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>CV-related HZ (n = 14)</th>
<th>Control (n = 28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic data</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>52.0 (30.8, 62.3)</td>
<td>66.5 (54.3, 78.8)</td>
<td>0.005</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td>6 (42.9)/8 (57.1)</td>
<td>11 (39.3)/17 (60.7)</td>
<td>0.824</td>
</tr>
<tr>
<td><strong>Medical history</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>9 (64.3)</td>
<td>20 (71.4)</td>
<td>0.447</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>3 (21.4)</td>
<td>12 (42.9)</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>3 (21.4)</td>
<td>8 (28.6)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1 (7.1)</td>
<td>2 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Nephrotic</td>
<td>0 (0.0)</td>
<td>2 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>0 (0.0)</td>
<td>5 (17.9)</td>
<td></td>
</tr>
<tr>
<td>Allergy</td>
<td>3 (21.4)</td>
<td>3 (10.7)</td>
<td></td>
</tr>
<tr>
<td>Malignant</td>
<td>0 (0.0)</td>
<td>4 (14.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Characteristics of herpes zoster</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prodromal pain</td>
<td>9 (64.3)</td>
<td>17 (60.7)</td>
<td>0.822</td>
</tr>
<tr>
<td>Interval between prodromal pain and rash (d)</td>
<td>3.0 (0.0, 4.0)</td>
<td>3.0 (0.0, 4.75)</td>
<td>0.661</td>
</tr>
<tr>
<td>Pain score, NRS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial pain</td>
<td>3.0 (3.0, 4.0)</td>
<td>4.0 (3.0, 4.0)</td>
<td>0.843</td>
</tr>
<tr>
<td>Peak pain</td>
<td>4.0 (3.0, 4.3)</td>
<td>4.0 (3.3, 5.0)</td>
<td>0.535</td>
</tr>
<tr>
<td><strong>Location</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cranial</td>
<td>2 (14.3)</td>
<td>4 (14.3)</td>
<td>0.689</td>
</tr>
<tr>
<td>Cervical</td>
<td>2 (14.3)</td>
<td>2 (7.1)</td>
<td>0.407</td>
</tr>
<tr>
<td>Thoracic</td>
<td>9 (64.3)</td>
<td>18 (64.3)</td>
<td>0.629</td>
</tr>
<tr>
<td>Lumbar</td>
<td>1 (7.1)</td>
<td>1 (3.6)</td>
<td>0.561</td>
</tr>
<tr>
<td>Sacral</td>
<td>0 (0.0)</td>
<td>3 (10.7)</td>
<td>0.285</td>
</tr>
<tr>
<td><strong>Patients number</strong></td>
<td>14</td>
<td>25*</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiviral agents</td>
<td>14 (100)</td>
<td>25 (100)</td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>12 (85.7)</td>
<td>22 (88.0)</td>
<td>0.600</td>
</tr>
<tr>
<td>Nerve block</td>
<td>6 (42.9)</td>
<td>11 (44.0)</td>
<td>0.945</td>
</tr>
<tr>
<td><strong>Recovery time (wk)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–4</td>
<td>8 (57.1)</td>
<td>10 (40.0)</td>
<td>0.303</td>
</tr>
<tr>
<td>5–8</td>
<td>4 (28.6)</td>
<td>7 (28.0)</td>
<td>0.624</td>
</tr>
<tr>
<td>8–12</td>
<td>2 (14.3)</td>
<td>3 (12.0)</td>
<td>0.600</td>
</tr>
<tr>
<td>&gt; 12</td>
<td>0 (0.0)</td>
<td>5 (20.0)</td>
<td>0.092</td>
</tr>
<tr>
<td>Postherpetic neuralgia</td>
<td>0 (0.0)</td>
<td>5 (20.0)</td>
<td>0.092</td>
</tr>
</tbody>
</table>

Values are presented as median (1Q, 3Q) or number (%). CV-related HZ: coronavirus disease 2019 vaccination-related herpes zoster, NRS: numerical rating scale. *Three patients were excluded: one patient was transferred to another hospital, one was lost to follow-up, and one was transferred to the emergency room at the second visit due to a high fever.

The present study was longer than those of previous studies is considered to be the additional treatment for persistent pain that occurs even after skin lesion improvement. We can deduce that such difference can be caused by the possibility of visiting the pain clinic rather than the dermatology department when patients mainly complained of severe pain. Generally, skin lesions of HZ completely recover within 2–4 weeks, and pain is known to last for an average of 45 days [26].

Antiviral therapy is important for the treatment of HZ. Antiviral therapy provided in the acute phase inhibits progression to PHN by inhibiting viral replication and reducing injury to nerve fibers and can also reduce the severity and duration of PHN. In addition, a decreased incidence of PHN was reported when antivirals were administered with gabapentin [27]. On the contrary, nerve blocks are effective in pain control in a short period of time, but their effects on PHN have not yet been clarified [19]. In the present study, all patients received antiviral therapy (100%) for the treatment...
Recovery time for herpes zoster. The recovery rates within 8 weeks in the CV-related HZ and control groups are 85.7% and 68.0%, respectively. CV-related HZ: coronavirus disease 2019 vaccination-related herpes zoster.

Table 2. Characteristics of Vaccination-related Herpes Zoster (n = 14)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>1st dose</th>
<th>2nd dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine and dose</td>
<td>Pfizer</td>
<td>Moderna</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Time of symptom onset after vaccination</td>
<td>1–21 days</td>
<td>22–42 days</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

of HZ, and anticonvulsants, such as gabapentin or pregabalin, were used in 87.2% of the patients. Moreover, 43.6% of the patients underwent nerve blocks. Nevertheless, five patients (male/female: 2/3; age, 66.0 [61.0, 77.5] years) in the control group developed PHN. Although the incidence of PHN in the two groups was not statistically significant, the reason for the absence of PHN in the CV-related HZ group can be deduced from the age of the two groups. Older age is the most potent risk factor for PHN because the nervous systems in the elderly may be less tolerant of the damage associated with HZ. In this study, it can be inferred that progression to PHN was absent in the CV-related HZ group because the patients were significantly younger. However, a large-scale additional study using such a large dataset is required to confirm this because this study has a small sample size.

The window in which the risk of HZ increases remains unclear. The risk window for HZ significantly varied, ranging from 21 days to 3 months, depending on the studies reported [1,22,23,28]. Barda et al. [1] set a follow-up period of 42 days after vaccination in a safety study on the COVID-19 vaccine. They believed that 42 days would be sufficient to identify medium-term adverse events without diluting the incidence of short-term adverse events. In their study, the risk of HZ was substantially higher in the vaccinated group than in the unvaccinated group (risk ratio, 1.43; 95% confidence interval [CI], 1.20–1.73; risk difference, 15.8 events per 100,000 persons; 95% CI, 8.2–24.2). Based on this, the present study used a 42-day risk window [1].

Of COVID-19 vaccines, an association between mRNA COVID-19 vaccination and HZ has been reported more frequently [7,9,16], but postvaccination HZ has been reported in almost all types of vaccines [8,10,29]. In the present study, five patients were in the Pfizer group, five in the Moderna group, and four in the AstraZeneca group. In Korea, there were approximately 75,287,995 vaccination cases by the end of October 2021, and there were 42,927,605 patients receiving Pfizer vaccine, 20,296,861 receiving AstraZeneca vaccine, 10,586,677 receiving Moderna vaccine, and 1,476,852 receiving Janssen vaccine. Since approximately 1.1 million cases in a specific occupational group received the Janssen vaccine in June 2021, the number of vaccination cases was small. Accordingly, there were no cases of Janssen vaccination in the present study.

The association between COVID-19 vaccination and HZ remains controversial. A meta-analysis by Chu et al. [30] reported that there was no evidence that COVID-19 vaccination increased the incidence of HZ (risk ratio, 1.06; 95% CI, 0.91–1.24). Patil et al. [28] also reported that there was no
### Table 3. Characteristics of Patients with COVID-19 Vaccination-related Herpes Zoster and Herpes Zoster-associated Data

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>COVID-19 vaccination</th>
<th>Time interval of HZ onset after vaccination (d)</th>
<th>Comorbidities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td>Age (yr)</td>
<td>Sex, M/F</td>
<td>Types</td>
</tr>
<tr>
<td>Patient 1</td>
<td>30</td>
<td>F</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Patient 2</td>
<td>71</td>
<td>M</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>Patient 3</td>
<td>63</td>
<td>F</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>Patient 4</td>
<td>57</td>
<td>F</td>
<td>Moderna</td>
</tr>
<tr>
<td>Patient 5</td>
<td>21</td>
<td>F</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Patient 6</td>
<td>54</td>
<td>M</td>
<td>Moderna</td>
</tr>
<tr>
<td>Patient 7</td>
<td>59</td>
<td>M</td>
<td>Moderna</td>
</tr>
<tr>
<td>Patient 8</td>
<td>50</td>
<td>M</td>
<td>Moderna</td>
</tr>
<tr>
<td>Patient 9</td>
<td>31</td>
<td>M</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Patient 10</td>
<td>66</td>
<td>F</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>Patient 11</td>
<td>62</td>
<td>F</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>Patient 12</td>
<td>50</td>
<td>M</td>
<td>Moderna</td>
</tr>
<tr>
<td>Patient 13</td>
<td>28</td>
<td>F</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Patient 14</td>
<td>32</td>
<td>F</td>
<td>Pfizer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Herpes zoster-associated data</th>
<th>Interval between prodromal pain and rash (d)</th>
<th>Pain score, NRS (0–10)</th>
<th>Skin lesion severity</th>
<th>Location</th>
<th>HZ treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Peak</td>
<td></td>
<td></td>
<td>Antiviral agents</td>
</tr>
<tr>
<td>Patient 1</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>Mild</td>
<td>T1, T2</td>
</tr>
<tr>
<td>Patient 2</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>Mild</td>
<td>T10</td>
</tr>
<tr>
<td>Patient 3</td>
<td>3</td>
<td>6</td>
<td>6</td>
<td>Mild</td>
<td>L4, L5</td>
</tr>
<tr>
<td>Patient 4</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>Mild</td>
<td>T6, T7</td>
</tr>
<tr>
<td>Patient 5</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>Severe</td>
<td>T7, T8</td>
</tr>
<tr>
<td>Patient 6</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>Mild</td>
<td>T10</td>
</tr>
<tr>
<td>Patient 7</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>Mild</td>
<td>V1</td>
</tr>
<tr>
<td>Patient 8</td>
<td>0</td>
<td>4</td>
<td>4</td>
<td>Mild</td>
<td>C2</td>
</tr>
<tr>
<td>Patient 9</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>Mild</td>
<td>V1</td>
</tr>
<tr>
<td>Patient 10</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>Mild</td>
<td>T10, T11</td>
</tr>
<tr>
<td>Patient 11</td>
<td>7</td>
<td>4</td>
<td>4</td>
<td>Mild</td>
<td>T6, T8</td>
</tr>
<tr>
<td>Patient 12</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>Mild</td>
<td>T11</td>
</tr>
<tr>
<td>Patient 13</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>Mild</td>
<td>T5</td>
</tr>
<tr>
<td>Patient 14</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>Mild</td>
<td>C3</td>
</tr>
</tbody>
</table>


difference in the frequency of HZ before and 3 months after vaccination. In contrast, a case-control study by Alhasawi et al. [22] reported a significant association between COVID-19 vaccination and varicella zoster activation (odds ratio, 4.87; 95% CI, 2.40–9.89). Hertel et al. [23] also reported that the risk increased in the group who received vaccination, with a risk ratio of 1.802 (95% CI, 1.680–1.932). Temporal compatibility and biological plausibility should be confirmed to evaluate the causal association between HZ and COVID-19 vaccination in terms of adverse events following immunization. Future studies should investigate temporal compatibility and biological plausibility.

The present study has a strength in that it was conducted from the aspect of pain medicine, but its limitations are clear as it was a single-center, retrospective study that included a small sample size. Another limitation of this study is that the incidence of HZ associated with COVID-19 vaccination could not be evaluated. To overcome this limitation, a multicenter, prospective, large-scale study targeting a large population must be conducted in the future.

In the present study, patients with HZ associated with COVID-19 vaccination showed similar manifestations to
general patients with HZ. They recovered after treatment with antiviral agents, anticonvulsants, and nerve blocks, and none of the patients developed PHN.

**FUNDING**

None.

**CONFLICTS OF INTEREST**

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

**DATA AVAILABILITY STATEMENT**

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

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INTRODUCTION

When a patient presents with intractable chest pain, physicians commonly consider potentially life-threatening disorders, such as pulmonary embolism, myocardial infarction, aortic dissection, pericardial effusion, pneumothorax, and malignancy [1]. Pneumonia, rheumatoid arthritis, tuberculosis, rib fractures, and trauma can be other causes of chest pain [2]. A complete medical history, physical examination, serologic studies including cardiac enzymes, electrocardiography (EKG), simple chest radiologic studies, echocardiography, computed tomography (CT), magnetic resonance imaging, and bone scans are useful for the differential diagnosis of intractable chest pain [3]. In addition, ultrasonography (US) is also a useful diagnostic tool [4]. Herein, we present a case of unusual intractable chest pain caused by playing golf, diagnosed and treated using US, in which the underlying pathology had not been found over 4 months despite various diagnostic tests.

CASE REPORT

The patient in this case was informed regarding the study and written consent was obtained for the publication of this
case report.

A 64-year-old woman presented with intractable left anterior chest pain. Two years prior to the consultation, transforalional interbody fusion and posterior spinal fusion at L5-S1 had been performed. Pain developed 4 months prior, while playing golf, characterized as a sudden stabbing type of pain; it persisted and worsened even with small movements of the arm. The intensity of pain was rated as 7–10/10 on the numerical rating scale (NRS). At that time, she consulted a private orthopedic surgeon and underwent radiological examination, which revealed no significant findings. She was administered trigger point injections and intercostal nerve blocks, which did not improve the pain. The patient was referred to a tertiary general hospital for further evaluation, as the pain persisted.

Two months earlier, she had consulted a thoracic surgeon, cardiologist, pulmonologist, and gastroenterologist. The patient underwent various examinations, such as cardiac enzyme level determination, EKG, echocardiography, coronary angiography, simple radiologic studies of the chest and bony thorax, lung high-resolution computed tomography (HRCT), esophagogastroduodenoscopy, and bone scan; however, there were no significant findings (Fig. 1).

The patient had difficulties and severe limitations in her daily life activities due to continuous and intractable pain; thus, she was transferred to our pain clinic for further evaluation and management. Physical examination revealed two painful areas on the left anterior chest (T3, T5), which were non-tender and there was no redness or swelling that indicated an infection. The pain was aggravated by flexion and extension, but there was no increased intensity or relief associated with change in position and respiration. On US examination, a linear transducer (4–18 MHz, eL18-4 Linear Probe, EPIQ 5, Philips, USA) was placed over the two painful areas, and a small pleural effusion was found (Fig. 2).

The US probe was placed transversely on the areas in which the patient felt the pain. After confirming focal pleural effusion, a 23-gauge 5 cm needle was inserted using the in-plane technique from the lateral to the medial side of the left anterior chest at a point approximately 1 cm from the probe. US-guided intralesional injection at the left T3 and

![Fig. 1](A) High-resolution computed tomography image of the chest, which was initially read as normal, but upon reexamination, was found to show focal pleural effusion (white arrow). (B) Magnified view of the left anterior chest showing focal pleural effusion (white arrow).

![Fig. 2](An ultrasonographic image of the focal pleural effusion asterisk (*). A long axis view of the anterior intercostal space at T5–6 with 4–18 MHz linear transducer (EPIQ 5, Philips, USA).)
T5 anterior chest was administered. A mixture of 0.75% ropivacaine hydrochloride (5.5 ml), triamcinolone acetonide (20 mg), and hyaluronidase (1,500 IU), total 6 mL was injected (Fig. 3). Pain was reduced from 8–9/10 to 0/10 based on NRS immediately after injection, and no pain was reported for approximately 1 week on telephone follow-up. Naproxen (1,000 mg/D) was prescribed to control pain and inflammation.

At the one-month follow-up, the pain was found to have reduced from 7/10 to 1–2/10 based on the NRS. An US-guided intralesional injection at the left T3 and T5 anterior chest was re-administered per the patient’s request. Two months after the first dose of intralesional injections, the patient was pain-free and had no impairment in daily life activities; thus, further follow-up was advised only if pain recurred.

**DISCUSSION**

Pleurisy, also called pleuritis, is an inflammation of the parietal pleura [1]. Pleuritic chest pain is characterized by sudden and intense sharp, stabbing, or burning pain in the chest and is exacerbated by forceful movements such as deep breathing and coughing [3]. The parietal pleura of the outer rib cage and lateral aspect of each hemidiaphragm are innervated by the intercostal nerves. Trauma or inflammation in these regions results in pain localized to the cutaneous distribution of these nerves [3].

Pleuritic chest pain can be caused by several factors. Life-threatening disorders, such as pulmonary embolism, myocardial infarction, aortic dissection, pericardial effusion, and pneumothorax, must first be identified [1]. Viral or bacterial pneumonia, rheumatoid arthritis, malignancy, tuberculosis, rib fractures, and trauma can be other causes [2,5]. If a cardiac or vascular source is considered, EKG, cardiac enzyme studies, and echocardiography are required [3]. When infection is considered, a complete blood count, serology, and cultures of the blood or sputum may be indicated [3].

If pleurisy is suspected, a chest X-ray examination may be performed first. This is because a chest X-ray examination, which is the least expensive and time-consuming examination available, makes it simple to screen for additional causes like pneumonia or fractures [6]. In the postero-anterior view, pleural effusion is detectable when the volume of accumulated fluid is more than 200 ml, and the lateral decubitus view can be used to check the free flow of an effusion of more than 50 ml around the lung [6]. Chest CT shows pleurisy, which is not visible in chest X-ray examinations and helps to identify the causes of effusions such as pneumonia, cancer, and pulmonary embolism [6]. However, it is difficult to distinguish small effusions from pleural thickening, dependent atelectasis, or tumors [6]. US is a useful tool for physicians managing pleural diseases, and it is particularly sensitive because of its superficial location on the body [4]. The advantages of US are rapidity, ease of use, repeatability, and no radiation exposure [6].

The higher the transducer frequency, the better the resolution, but the lower the penetration; thus, the 7.5–10 MHz probe is employed to view the pleura, and the 3.5–5 MHz probe is used to view the pleural effusion.
probe is used to observe structures deeper in the thorax or adjacent abdominal structures in addition to the normal lung surface [7]. US images of the chest wall show soft-tissue echogenicity with multiple layers of muscle and fascia [7]. Beneath the chest wall, the parietal pleura lining the bony thorax and the visceral pleura covering the lungs are seen as two thin, bright echogenic lines, and normally, they are smooth and less than 2 mm in thickness [7].

Pleurisy is well visualized on pleural US. The parietal pleura is thickened and hypoechoic and standing within pleural effusion may develop [5]. Pleural US identifies undulating, threadlike bands that float freely in the pleural effusion [5]. US is suitable for the identification of fluid collections throughout the body because fluid is relatively echo-free between the visceral and parietal pleura, compared with other body tissues; thus, the sonographer may readily identify even small-sized pleural effusions [7]. Pleural US can even detect small physiologic amounts of pleural fluid (less than 5 ml) and detects septations within the pleural fluid with greater sensitivity than CT scanning [6]. Furthermore, US is helpful to identify effusions based on sonographic characteristics, which include anechoic, septation, homogenously echogenic, or complex [4]. Pleural thickening, pleural tumors, pleuritis, and pneumothorax can also be detected easily and accurately with chest US [4]. Moreover, US guidance improves the rate of successful pleural aspiration [4]. Therefore, chest US can supplement other imaging modalities for the chest and guide a variety of diagnostic and therapeutic procedures [7]. The pitfall of lung US is that image artifacts are common. Bone shadowing and lung air reflection artifacts are predictable problems [7]. The probe should be moved in transverse or longitudinal directions along the intercostal spaces to avoid interference by the bony ribs [7].

In this case, the patient underwent various examinations, such as echocardiography and coronary angiography, HRCT of the lung, and bone scan, which showed no specific findings. However, focal pleural effusion was found using US of the localized painful areas; therefore, pleural US was the key for evaluation. In this case, none of the above test results are specific, and if a patient complains of persistent localized chest pain, performing US on the painful area may be helpful in the diagnosis and treatment.

Considering that the golf swing is an action that uses the maximum possible rotational force, several causes of chest pain can be associated with it. First, injuries to the chest from continuous, repetitive rotational movements can cause costochondritis, which is an inflammation of the cartilage that connects the ribs to the sternum [8]. Second, athletes may also experience Tietze’s syndrome, which is an inflammatory disorder that affects the chest wall cartilage [9]. Third, stress fractures of the ribs are common and can be diagnosed using a bone scan [10]. Fourth, slipping rib syndrome, which is an intercostal nerve impingement resulting from abnormal movement of false ribs related to unstable costal cartilage attachments, can be caused by the maximum possible rotation of the thoracic spine [11]. Fifth, intercostal muscle strain or pull can occur when the muscle is stretched or torn due to excessive rotation, which may also cause sharp chest pain.

In this case, we postulated three hypotheses that could have caused focal pleural effusion that led to intractable chest pain. First, as the pain began while playing golf, we assumed that the microfracture on the inferior side of the rib adjacent to the parietal pleura may have occurred four months prior to the consultation. It may have continued to stimulate the pleura and caused inflammation, a small effusion, and chronic chest pain. However, the bone scan that was performed did not reveal significant findings. The second possible theory is interposition of the costal cartilage. Considering the swing-rotation posture used by golfers, the rib-costal cartilage and costal cartilage-costal cartilage would overlap each other, and focal pleural inflammation may be caused by pinching or friction of the pleura. Third, because of excessive rotation, costochondral inflammation due to costosternal joint deformity may have resulted in a costochondral degenerative change and progressed to costochondral osteoarthritis. Persistent costochondral inflammation may have led to pleural irritation, resulting in focal pleural effusion.

After excluding life-threatening causes of pleuritic chest pain that require emergent treatment, pain control and treatment of the etiology of underlying conditions should be performed [3]. Nonsteroidal anti-inflammatory drugs are commonly prescribed as the initial therapy for pain control, since side effects with these are significantly less frequent than those with opioids, which are centrally acting analgesics [1]. Corticosteroids inhibit many of the initial events in an inflammatory response and promote the resolution of inflammation by inhibiting vasodilation, so that leukocyte emigration into inflamed sites is decreased [12]. In addition, there are case reports in which inflammation and pain improved after intrapleural corticosteroid injection in eosinophilic pleural effusion and tuberculous pleural effusion [13,14]. In this case, the cause of focal pleural effusion, which
caused persistent pain in the patient, was probably inflammation in that area, and the patient wanted improvement in intractable chest pain urgently. An intralesional injection was administered by US for diagnostic and therapeutic purposes. In this process, a small amount of colorless fluid was aspirated, but due to the risk of pneumothorax, we could not obtain enough fluid for pleural fluid examination. The regimen selected for administration by injection was a local anesthetic for pain control and a steroid for inflammation control.

In conclusion, this case demonstrates that US should be considered as a diagnostic modality for unusual chest pain that has not been diagnosed despite various examinations, since pleurisy could be well visualized by pleural US. US-guided intralesional injection can be a treatment option for patients with focal pleural effusions.

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.

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Complex regional pain syndrome (CRPS) is known as one of the most severe and disabling conditions which significantly impair the quality of life with psychologic distress. The diagnosis and treatment of CRPS are challenging due to the lack of confirmative diagnostic test and definitive treatment tools [1]. The Budapest criteria, which shows greatly improved diagnostic specificity compared to international association of study of pain criteria, is widely used to diagnose CRPS [2]. Earlier detection and an interdisciplinary cooperation for treatment seem to be essential in alleviating the symptoms of CRPS, although one single treatment has not been found to be effective definitely.

Lymphedema is characterized by localized tissue swelling due to excessive interstitial space retention of lymphatic fluid caused by obstructed lymphatic drainage. Primary lymphedema is rare and it is caused by genetic or developmental lymphatic vascular anomalies. Most of lymphedema which we encounter is secondary and this disorder is caused by an underlying carcinoma, parasite infection, trauma, or surgery. Lymphedema is easy to be misdiagnosed frequently since it resembles other conditions of extremity swelling [3].

We present a case of CRPS type I which was combined with secondary lymphedema and successfully managed with spinal cord stimulation (SCS).

Case Report

Treatment experience in a patient of complex regional pain syndrome combined with secondary lymphedema of lower extremity-A case report-

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Background: Lymphedema is characterized by localized tissue swelling due to excessive interstitial space retention of lymphatic fluid. Lymphedema is easy to be misdiagnosed since it resembles other conditions of extremity swelling. We present a case of complex regional pain syndrome (CRPS) type I with secondary lymphedema that was successfully managed with spinal cord stimulation (SCS).

Case: A 39-year-old female patient came to our pain clinic with complaints of lower extremity pain and edema. To find out reason of leg edema, computed tomography of extremity angiography and blood test were performed. However, all of evaluations were normal. Lastly performed lymphoscintigraphy showed secondary lymphedema. SCS was performed and it showed dramatic reduction subsequent to implantation of SCS.

Conclusions: We could successfully manage the intractable pain and edema in CRPS combined with lymphedema. If a patient presents different nature of edema, coexistence of other disease needs to be considered.

Keywords: Complex regional pain syndrome; Leg edema; Lymphatic fluid; Lymphedema; Lymphoscintigraphy; Spinal cord stimulation.

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CASE REPORT

The authors certify that written informed consent for publication was obtained from the patient or guardian. The potential risks and benefits were discussed with the patient before the spinal cord stimulation.

A female patient of 39 years old, who complained of severe right side lower extremity pain, visited our pain clinic. Her right side extremity pain started one month ago and her numerical rating scale (NRS) was 7. In addition to severe pain, she felt redness, heat, tenderness, and weakness of right leg during her walking. Mild edema was also present. The color of right leg was more reddish compared to left leg. She had a prior history of fracture of right foot and subsequent cast maintenance for one month. Because of her severe pain, color change, local heat and hypoesthesia, we suspected her CRPS. For the diagnostic work up of CRPS, electromyography (EMG), nerve conduction velocity (NCV), 3-phase bone scan, and quantitative sudomotor axon reflex test (QSART) were performed. The result of EMG and NCV was normal. QSART demonstrated skin temperature asymmetry, with the affected right leg being warmer than the left leg. The greatest temperature difference (2.0°C) was observed in an ankle area. Resting sweat out was normal, but Q-sweat output was greater on right side. The 3-phase bone scan showed increased tracer uptake in delayed skeletal phase. According to the clinical feature and the results of diagnostic work up, we diagnosed her CRPS type I of lower extremity. For her pain relief, medication was started including pregabalin 150 mg/day, oxycodone 20 mg/day, and amitriptyline 10 mg/day. However, those medications showed minimal effect in relieving her pain. Lumbar sympathetic ganglion block was performed 3 times for the temporary relief of pain.

Two weeks after treatment of CRPS, she started to complain of both side leg pain. At first, only right side was painful, but left side leg became painful gradually. In addition to pain, both legs presented severe edema. Since one of important clinical feature of CRPS is edema, we just observed her leg edema using medication to improve edema without further evaluation. Lumbar sympathetic ganglion block improved her leg pain and edema, but it lasted only 2–3 days. She felt severe heaviness and discomfort of leg. Also, she was very difficult to walk due to severe leg edema.

Although CRPS can present the symptom of edema, we thought that edema of this patient is somewhat different from that of CRPS. As a reason of such suspicion, this edema showed pitting edema, and over time, the skin became indurated with hard and leathery texture. Lower extremity elevation during sleep did not improve the edema. Due to a different nature of leg edema, we suspected venous edema, drug induced swelling, cellulitis, and lymphedema for the possible cause of edema.

To find out possible reason of leg edema, computed tomography (CT) of extremity angiography and laboratory blood test were performed. The result of CT angiography was completely normal. Blood test including C reactive protein and erythrocyte sedimentation rate was also within normal limit except for mildly increased liver enzyme. She was not taking any medications which are known to cause swelling.

To evaluate lymphedema as a reason of leg edema, she was consulted to rehabilitation department. Both leg girths were measured at 5 regions at proximal 10 cm and 20 cm of patella upper border and distal 10 cm, 20 cm, and 30 cm of patella lower border to assess the severity of edema. The edema was more severe in right side and upper thigh than left side and lower calf. Lastly, lymphoscintigraphy was performed and it showed secondary lymphedema of both lower extremities (Fig. 1). We assessed her both leg CRPS type I combined with lymphedema.

Since her leg edema and pain were still intractable in opioid medication and lumbar sympathetic ganglion block, SCS was performed subsequent to an admission to hospital. After local infiltration of skin with 1% lidocaine, a 14-gauge needle was inserted into the L2-3 interlaminar space using fluoroscopic guidance. When loss of resistance was felt using distilled water, a steerable guide wire was inserted to confirm the epidural space. When the position of guide wire was in posterior epidural space by fluoroscopy, bilateral octapolar lead was inserted and advanced up to superior endplate of T11, which covers posterior epidural space from T12 to T11 (Fig. 2).

After placement of electrode into the epidural space, tonic mode SCS test stimulation was performed with pulse frequencies of 40–60 Hz, pulse width of 200–500 μs and an intensity of 1.7–2.7 mA at the operating room. After this test stimulation, she was sent to an admission room to observe the proper electrical stimulation for 5 days. The first day of test stimulation period, she was lying in bed all day long to minimize the lead migration and the intensity and the location of electrical stimulation were similar to that of test stimulation at operating room. Sitting was permitted beginning on the third day of test stimulation. However, the stimulation was relatively weak when she was in sitting position com-
pared to lie in bed. The pulse frequencies and pulse width were similar with that of settings at the operating room but the intensity was maintained with 2.5 mA. With such intensity, she could not feel any weakness and differences between sitting and lying position were minimal. We made a programming so that a patient could feel maximal electrical sensation at both upper thigh which corresponds to the most painful site. During 5 days of trial period of SCS, her pain was reduced to NRS 1–2. After confirming successful reduction of pain and edema, left lower subcutaneous abdominal pocket was made to insert implantable pulse generator (Intellis™, Medtronic, USA) for permanent SCS. Following permanent SCS, we set the pulse frequency to 50 Hz, the pulse width to 450 μs, and the intensity to 2.5 mA.

For the evaluation of edema, she was consulted to the rehabilitation department and both leg girths were measured at 5 regions again. Among the 5 regions of measured leg girth, dramatic reduction of edema was observed at upper thigh (proximal 20 cm of patella upper border) and calf (distal 10 cm of patella lower border). Therefore, serial changes of leg girth at those two regions before and after SCS were presented (Fig. 3A, B). In addition to reduction of leg girth, her fibrotic and leathery texture became normalized and disappeared leg hair due to leathery and hard skin started to grow again.

Two months after SCS, NRS was maintained within 1–2 during rest in bed, but NRS increased slightly when she walked around.

**DISCUSSION**

This case report demonstrated dramatic improvement of lymphedema using SCS which was combined in CRPS.

Patients diagnosed with CRPS present their symptoms after minor or moderate trauma or tissue injury. The injured extremity shows extremely painful, red, warm, and swollen during the acute phase. Other features which are observed in CRPS include allodynia, hyperalgesia, changes in sweating, hair, nail growth, and muscle weakness. As the disorder persists, pain does not subside but often spreads proximally and can even emerge on the contralateral extremity [4] like a patient of this case report.

If a patient presents severe edema which results from oth-
er disease, it is not easy to suspect other reasons because edema in an affected extremity of CRPS is commonly found during their clinical course [4]. At first, we also did not suspect other disease as a cause of edema and just observed it without any further evaluation. However, as the day progressed, her edema became worse. Moreover, edema of this patient was different from that of CRPS. There are little clinical studies showing specific characteristic of edema which is usually observed in CRPS. It is known that the skin of edematous extremity of CRPS demonstrates a glossy pattern [4]. However, if an edema develops due to lymphedema, the skin becomes hard and fibrotic, and presents even leathery texture with loss of hair [3]. The reason of suspicion that this patient might have other disease was its severity and different nature of edema described above. However, if an edema is combined with trophic change of CRPS, we think that it is hard to differentiate it from lymphedema. Generally, trophic change is usually found in later stage of CRPS, which presents an edema infrequently [1].

Lymphedema is more commonly found in females than in males. Also, lower extremity lymphedema is more frequent than that of upper extremity. Patients diagnosed with lymphedema mostly have a secondary cause. It is reported that the incidence of secondary lymphedema is 1 in 1000 individuals, with the mean age at the time of diagnosis between 50 to 58 years old [3]. Lower extremity lymphedema is usually associated with filariasis (parasite infection), chronic venous insufficiency, obesity, rapamycin treatment in patients with decreased renal function, and malignancies such as lymphoma, uterine cancer, and melanoma. Among causes of secondary lymphedema, parasite infection caused by mosquito-borne nematode is most common. It infects patients who have traveled to endemic area with this disease, usually in India and sub-Saharan Africa [3,5]. However, she did not travel any endemic area, nor have been diagnosed with malignancy. Also, she did not have a history of rapamycin treatment. The obesity was suspected for the reason of development of secondary lymphedema, since her body mass index was 28 kg/m².

For many years, the primary tool to confirm the presence of lymphedema was lymphoscintigraphy. It visualizes the functional status of the lymphatic system and helps to differentiate between partial and complete obstruction of lymphatic system. Moreover, it can guide a further strategy plan of treatment [3,6]. The advantage of this imaging method is that it is a noninvasive technique which is available at most hospitals. Also, it is easy to perform involving a subcutaneous injection of particulate radiotracer attached to technetium-99m in the distal aspect of the swollen extremity with subsequent imaging of the lymphatic vessel [3,6].

Widely accepted conservative treatment for lymphedema is complex decongestive therapy, which means manual lymphatic drainage massage [7]. Although there is no study suggesting effective management of lymphedema using SCS, this patient experienced effective pain and edema reduction. The exact mechanism of action why the extremity edema caused by lymphedema is improved by SCS is uncertain. The composition of lymphatic system is tonsil, spleen, lymph nodes, and the thymus, all of which are interconnected via a network of lymphatic vessels that run parallel to the

![Fig. 3. The changes of right (green) and left (yellow) side leg girth at the upper thigh (A) before and after spinal cord stimulation (SCS). The changes of right (green) and left (yellow) side leg girth at the lower calf (B) before and after SCS.](image-url)
venous circulation. Most of interstitial fluid (> 90%) which leaks from capillaries into the tissue is reabsorbed via the venous microcirculation and returns to the blood stream. Remaining interstitial fluid (< 10%) has a high protein concentration and this interstitial fluid (lymph) in drained in blind-ended lymphatic capillaries [3,8]. Once the protein rich interstitial fluid comes into the lymphatic capillaries, it ultimately reenters the circulatory system via collecting lymphatic vessels. In contrast to lymphatic capillaries, collecting lymphatic vessel have smooth muscle walls which has the potential to contract and propel the lymphatic fluid forward [3]. It is assumed that SCS might affect the smooth muscle of collecting lymphatic vessel, ultimately resulting in increasing the ability of lymphatic fluid drainage. Similarly, the restoration and improvement of pulsatile blood flow to the distal extremity in patients of chronic limb ischemia has been reported previously [9-11].

In conclusion, we could successfully manage the intractable pain and edema in patients of CRPS combined with lymphedema. If a patient presents different nature of edema, we need to consider the possibility of coexistence of other disease.

**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: Ji Hee Hong. Data curation: Seung Ju Kim. Writing - original draft: Ji Hee Hong. Investigation: Ji Hee Hong.

**REFERENCES**

INTRODUCTION

Peripheral nerve blocks are commonly used in regional anesthesia. In recent years, it has become a reliable technique owing to the low complication and high success rates of application using ultrasound (US) [1–3]. However, there are certain difficulties such as inaccurate evaluation of block success because available evaluation techniques (cold sensation, pinprick, muscle force, etc.) are composed of subjective tests [4,5]. Additionally, a cooperative patient is an

Evaluation of distal skin temperature and tissue oxygen saturation determined by near-infrared spectroscopy for predicting ultrasound-guided lateral infraclavicular block success

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Background: Changes in tissue oxygen saturation determined by near-infrared spectroscopy (NIRS) may help predict and determine the success of a lateral infraclavicular (LIC) block. We investigated whether evaluation of tissue oxygen saturation determined by NIRS could be an indicator of LIC block success.

Methods: Forty patients scheduled for hand or forearm surgery under LIC block were studied. NIRS sensors were placed on the ventral aspect of both mid-forearms, and the contralateral hand was used as the control group. NIRS values were recorded before the block and at regular intervals during the following 30 min.

Results: NIRS values were significantly higher in the successfully blocked patients when compared to the complete failure, partial failure, and contralateral hand groups at the 10th min. In the successfully blocked patients, NIRS values (mean ± SD [change in %]) increased by 11.09 ± 4.86 (16.03%), 15.00 ± 4.53 (21.76%), 16.35 ± 5.14 (23.77%), 16.38 ± 4.88 (23.85%), 16.67 ± 5.04 (24.29%), and 16.96 ± 5.71 (24.78%), respectively, from baseline to 5, 10, 15, 20, 25, and 30 min. ΔTs values were significantly higher in the successfully blocked patients than in the complete failure patients and contralateral hand at the 30th min. However, there was no statistically significant difference when comparing ΔTs values of successful block and partial failure block patients at the 30th min.

Conclusions: We conclude that measurement of tissue oxygen saturation by NIRS within the scope of evaluation of the lateral infraclavicular block is a rapid, effective, and applicable technique.

Keywords: Local anesthetics; Near-infrared spectroscopy; Peripheral nerves; Skin temperature; Sympathetic nervous system.
essential requirement, as well as anatomic information and experience, for the successful applicability of these tests [4,5]. A rapid, reliable, and noninvasive assessment method is needed to accurately evaluate block success.

It has been shown that sympathetic blockade which develops due to peripheral nerve block causes vasodilatation and increased peripheral blood flow and consequently leads to elevated distal skin temperature [6–8]. Although elevated skin temperature has been demonstrated, there is no absolute conclusion regarding the advantage of skin temperature in evaluating and predicting the success rate of nerve block.

Near-infrared spectroscopy (NIRS) is a novel, continuous, and non-invasive method for monitoring regional tissue oxygenation of cerebral and somatic beds by providing real-time feedback [9]. NIRS, which was initially used for the assessment of cerebral oxygen saturation, is commonly used nowadays to evaluate somatic tissue perfusion [9].

Assuming that sympathetic blockage can affect tissue oxygen saturation due to vasodilation and increased peripheral blood flow, we hypothesized that the evaluation of tissue oxygen saturation determined by NIRS would be a predictor of peripheral nerve block success.

**METHODS**

Institutional ethics committee approval (Necmettin Erbakan University Meram School of Medicine, no. 2016/464) and written consent from the patients were obtained for this prospective, observational study. It has been registered in the Australian New Zealand Clinical Trial Registry (ACTRN12616600656437). Forty patients between the ages of 18–65 years, American Society of Anaesthesiologists physical status I and II, scheduled for acute or elective hand or forearm surgery under lateral infraclavicular block, were studied. Exclusion criteria were age < 18 years, morbid obesity defined as a body mass index (BMI) > 40, international normalized ratio > 1.4, platelet count < 80 × 10^9 L^-1, coagulopathy, medication with vitamin K antagonists, high-dose or fractionated heparin treatment, allergy to local anesthetics, infection at the site of needle insertion, peripheral neurological disease, Raynaud's phenomenon, and patient refusal. In all patients, a 20-gauge intravenous (IV) cannula was inserted into the radial vein at the wrist of the non-blocked hand for IV fluid and medication administration.

Routine monitoring (consisting of a pulse oximeter, 3-lead electrocardiogram, and non-invasive blood pressure cuff) was performed.

**Skin temperature assessment**

The patients were placed in a supine position in the recovery ward at a room temperature of 21°C. Direct sunlight was avoided, all bandages and clothing were removed from the forearms and hands, and the patients were allowed to acclimatize for 10 min. Both hands remained in a neutral position while the block was performed and during the following 30 min of measurements. A blinded anesthesia nurse recorded skin temperature (Ts) of both hands at baseline, immediately after lateral infraclavicular (LIC) block and at 5 min intervals for 30 min, starting immediately after performing LIC block (LIB). A VeraTemp® V32035 (Lotus Global Co., UK) device was used for skin temperature assessment.

Many studies have stated that blocking the sympathetic nerves causes vasodilation, increased peripheral blood flow, and an increase in Ts, and that Ts can be used as an outcome in peripheral nerve blocks [6,7].

**Ultrasound-guided lateral infraclavicular block**

Using a high-frequency linear US transducer (LA435/13–6 MHz, Esaote My Lab Five Mobile Ultrasound System, Esaote, USA), the axillary artery and vein were located in the cross-section of the LIC region and the position of the three nerve cords. After disinfection with ethanol-chlorhexidine (83% and 0.5%, respectively), a sterile transparent drape was placed over the planned injection site, and the attending anesthesiologist performed the LIC block previously described [10] as a triple injection technique, and 10 ml of bupivacaine 0.25% and prilocaine 0.05% was injected into the three nerve cords. We used a lateral and sagittal in-plane US-guided approach to position the needle tip (SonoPlex Stim cannula 22 G 80–100 mm, Pajunk, USA). When correctly positioned, spread of local anesthetics was observed. The blocks were performed by experienced (>100 performed LIC blocks) and less experienced (between 20 and 100 performed LIC blocks) anesthesiologists.

**Clinical block assessment**

Immediately after the injection of the local anesthetic, two investigators blinded to the study evaluated the block until the 30th min after the injection. Sensory block was evaluated with sensation to cold elicited by applying ice cubes on the dermatomes of the median (palmar aspect of second finger), radial (dorsum of the hand between thumb and sec-
ond finger), ulnar (fifth finger), and musculocutaneous (lateral aspect of forearm) nerves, if the patient’s hand was eligible for evaluation. The sensation of the patients was recorded as either cold or not cold.

Motor function was assessed by the ability of the patients to extend the wrist (radial nerve), oppose the first digit (median nerve), flex the distal interphalangeal joint of the fifth digit (ulnar nerve), and flex the elbow joint (musculocutaneous nerve). Motor block of each nerve was recorded as either normal or compromised compared with the non-blocked side. Lateral infraclavicular block was categorized as successful when all four nerves were affected by both sensory and motor functions, as described above. In contrast, the block was categorized as failed when any part of the evaluated sensory or motor function remained intact. Patients with successful blocks were transferred directly to the operating room, whereas those with unsuccessful blocks were given a complementary US-guided nerve block (peripheral individual musculocutaneous, ulnar, median, or radial nerve blocks) depending on the failure.

**Tissue oxygen saturation assessment by near-infrared spectroscopy**

Two sensors (Small Adult SomaSensors, Somanetics, USA) were placed on each patient: one on the side of the peripheral nerve block and another at a similar site on the contralateral side, as described by the manufacturer. The ventral aspect of the mid-forearm area was preferred for sensor placement, as described in a previous study [11]. The sensors were connected to a two-channel monitor (Invos 5100 B monitor, Somanetics) that automatically recorded digital data approximately every 7 s for a maximum of 30 min. A blinded anesthesia nurse recorded bilateral tissue oxygen saturation values from the monitor at baseline, immediately after LIB and at 5 min intervals for 30 min, starting immediately after performing LIB.

**Statistical analysis**

Our study was designed to have an 80% power at the 95% significance level to detect an increase in the Ts when the successful block was reached, as reported by Lange et al. [12]. On the basis of this study evaluating Ts (ΔTs = 2.5°C, SD = 3.8), we calculated that 20 patients were required. However, we included 40 patients in the study because the main purpose of the study was to evaluate tissue oxygen saturation with NIRS to predict the success of the LIC block. NIRS values that could have been used in previous studies for sample size calculations could not be determined. Therefore, the sample size was calculated according to skin temperature, which is the secondary outcome of our study.

Statistical analysis was carried out by a statistical software package (SPSS 20.0®, SPSS, USA). Data are expressed as mean ± SD or number of patients. The Wilcoxon signed-rank test was used to analyze changes in mean NIRS values and Ts between baseline and the other measurement times (5, 10, 15, 20, 25, and 30 min) within the blocked and non-blocked hands. To analyze the effects of time (measurement times = 0, 5, 10, 15, 20, 25, and 30 min) and block (successful block, partial failure, complete failure, or contralateral hand) on NIRS values, two-way repeated-measures analysis of variance was used. P values were Bonferroni-corrected. Statistical significance was set at P < 0.05.

**RESULTS**

Forty patients were enrolled in the study, and all completed the study. Twenty-seven patients underwent elective surgery, and 13 patients were scheduled emergently. No patient withdrew from the study after the LIC block. Thirty-one of the performed LIC blocks were successful, 5 were partial failures, and 4 were complete failures. In a total of 9 failed blocks (complete and partial), the LIC block was successfully repeated preoperatively. Successful block patients did not require additional intraoperative analgesics, and visual analogue scale scores were 0 for 12 h postoperatively. Patient demographic data are summarized in Table 1. There were no significant differences between the three groups regarding sex, age, weight, height, BMI, and American Society of Anaesthesiologists physical status (P = 0.436, P = 0.459, P = 0.906, P = 0.774, P = 0.826, and P = 0.459, respectively).

The NIRS values from the baseline to 30th min are shown in Fig. 1. Baseline NIRS values were 70.84 ± 6.79, 70.20 ± 6.72, 65.75 ± 3.77, and 69.63 ± 8.14 in successful, partial failure, complete failure patients and contralateral side, respectively, and showed no statistical difference (P = 0.834). NIRS values were significantly higher in the successfully blocked patients than in the complete failure patients and contralateral side (P = 0.003 and P < 0.001, respectively) at the 5th min. However, there was no statistically significant difference between NIRS values of successful block patients (81.94 ± 6.82) and partial failure patients (73.80 ± 6.30) at 5 min (P = 0.164). NIRS values were significantly higher in the suc-
cessfully blocked patients from the complete failure, partial failure, and contralateral sides (P < 0.001, P = 0.008, and P < 0.001, respectively) at the 10th min. There was no statistically significant difference when comparing NIRS values at all measurement times (5th, 10th, 15th, 20th, 25th, 30th min) between complete failure and partial failure block patients (P =0.996, P =0.467, P =0.373, P =0.321, P =0.183, and P =0.261, respectively).

The changes in the Δ NIRS values are shown in Fig. 2. In the successfully blocked patients, NIRS values (mean ± SD [Change in %]) increased by 11.09 ± 4.86 (16.03%), 15.00 ± 4.53 (21.76%), 16.35 ± 5.14 (23.77%), 16.38 ± 4.88 (23.85%), 16.67 ± 5.04 (24.29%) and 16.96 ± 5.71 (24.78%), respectively, from baseline to 5, 10, 15, 20, 25, and 30 min (P < 0.001). Δ NIRS values were significantly higher in the successfully blocked patients than in the partial failure patients, complete failure patients, and contralateral side (P = 0.047, P = 0.002, and P < 0.001, respectively) at the 5th min. Δ NIRS values were significantly higher in the successfully blocked patients from the complete failure, partial failure, and contralateral groups (P < 0.001, P < 0.001, and P = 0.008, respectively) at the 10th min. NIRS values increased by 21.76% in the successfully blocked patients at 10th min according to baseline, whereas this increase was 8.54% in partial failure patients (P = 0.003). NIRS values increased by 24.78%, 10.83%, 1.14%, and -5.26%, respectively, in the successfully blocked, partial failure, complete failure patients and contralateral, from baseline to 30th min (P < 0.001, P = 0.225, P = 0.996, and P = 0.448).

The Ts values from baseline to 30th min are shown in Fig. 3. Ts increased from 31.77 ± 1.28 to 32.19 ± 1.54, 33.07 ± 1.56, 33.74 ± 1.27, 34.15 ± 1.18, 34.41 ± 1.10 and 34.46 ± 1.20 in the successfully block patients from baseline to 5th, 10th, 15th, 20th, 25th, 30th min (P = 0.054, P < 0.001, P <

Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Successful (n = 31)</th>
<th>Partial failure (n = 5)</th>
<th>Complete failure (n = 4)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>33.16 ± 5.88</td>
<td>27.00 ± 6.63</td>
<td>36.75 ± 7.22</td>
<td>0.459</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>5/26</td>
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<td>0/4</td>
<td>0.436</td>
</tr>
<tr>
<td>ASA (I/II)</td>
<td>28/3</td>
<td>5/0</td>
<td>3/1</td>
<td>0.459</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>171.13 ± 7.10</td>
<td>171.40 ± 6.98</td>
<td>172.75 ± 3.77</td>
<td>0.906</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.52 ± 14.70</td>
<td>69.40 ± 15.45</td>
<td>75.00 ± 10.80</td>
<td>0.774</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.66 ± 4.54</td>
<td>23.50 ± 4.45</td>
<td>25.07 ± 2.82</td>
<td>0.826</td>
</tr>
</tbody>
</table>

Values are given as mean ± SD or number. ASA: American Society of Anesthesiologists, BMI: body mass index.

Fig. 1. NIRS values from baseline to 30th min of lateral infraclavicular block. NIRS: near-infrared spectroscopy.
0.001, P < 0.001, P < 0.001, and P < 0.001, respectively). In the three patients with completely failed blocks, Ts decreased from baseline to 30th min (–0.9°C, –1.5°C, and –0.9°C). However, in one of the patients with complete failure, block Ts increased from baseline to 30th min (0.6°C). In complete failure block patients, skin temperature and Δ skin temperature did not show statistically significant difference from baseline to 30th min (P = 0.366 and P = 0.252, respectively).

Ts in one of the patients with partial failure decreased from baseline to 30th min (–3.9°C). Ts in the remaining four patients with partial failure block Ts increased from baseline to 30th minute (+3.2°C, +2.1°C, +3.6°C, and +1.9°C). In partial failure block patients, skin temperature and Δ skin temperature did not show statistically significant difference from baseline to 30th min (P = 0.162 and P = 0.156, respectively).

There were no statistically significant differences when comparing Ts values of complete failure and partial failure block patients at all measurement times (5th, 10th, 15th, 20th, 25th, 30th min) (P = 0.992, P = 0.996, P = 0.588, P =

**Fig. 2.** Changes in Δ NIRS values from baseline to 30th min of lateral infraclavicular block. NIRS: near-infrared spectroscopy.

**Fig. 3.** Ts values from baseline to 30th min of lateral infraclavicular block. Ts: skin temperature.

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0.185, P = 0.155, and P = 0.063, respectively).

The changes in ΔTs values are shown in Fig. 4. Δ Ts (baseline to 30 min) values were 2.69 ± 1.40, 2.20 ± 1.39, 1.47 ± 2.89, and −0.43 ± 1.11, in the successful block, partial failure, and complete failure patients and contralateral side (P < 0.001, P = 0.223, P = 0.996, and P = 0.102, respectively). Δ Ts values were significantly higher in the successfully blocked patients than in the complete failure patients and contralateral side (P < 0.001 and P = 0.008, respectively) at the 30th min. However, there was no statistically significant difference when comparing Δ Ts values of the successful block and partial failure block patients at the 30th min (P = 0.162).

**DISCUSSION**

To the best of our knowledge, this is the first study to evaluate tissue oxygen saturation changes in the forearm and hand according to NIRS responses after US-guided LIC blocks. The essential purpose of this study was to comprehensively evaluate these changes and assess the efficacy of NIRS in predicting blockade success. We planned to define the amount and timing of the changes in NIRS values for evaluation. Beginning from the 10th min after the LIC block, NIRS values in the successful block patients were significantly different compared with partial failure, complete failure patients, and contralateral hand. In the successful block patients, NIRS values showed an increase of 21.76% at the 10th min compared with baseline values, and this increase continued until the 30th min. Completely failed block occurred in only four patients, while partially failed block occurred in five patients. The NIRS values of the successful block patients increased significantly 30 min after the block compared to both baseline NIRS values and those in the partial failure, complete failure patients, and contralateral hand. However, no significant increase occurred in either the NIRS or Ts values of the partial failure patients compared with the complete failure patients.

The other essential purpose of the present study was to define changes in Ts after a successful LIC block. The change in Ts values at 30th min was significantly higher in the successful block patients than in the complete failure patients and the contralateral hand, whereas no significant difference was found compared with partial failure patients.

Local anesthetic agents should be able to block both sensory and sympathetic nerve fibers for a successful block [13]. The clinical control of sensory fibers is evaluated using methods such as cold response and pinprick sensation [13–15]. The blockade of small non-myelinated sympathetic nerve fibers using local anesthetics causes vasodilatation, increased blood flow, and increased local temperature. It is known that sympathetic nerve fibers run peripherally along both major nerves and vessels [16]. In the present study, somatosensors were placed on the ventral aspect of the mid-forearm. We assumed that this region is the most intensive region for major vascular structures of the forearm and thereby would be the most appropriate site for the evaluation of tissue oxygen saturation.

![Fig. 4. Changes in Δ Ts values from baseline to 30th min of lateral infraclavicular block. Ts: skin temperature.](image-url)
Changes in Ts and thermography values after upper-extremity peripheral nerve blocks have been evaluated in many studies. Minville et al. [8] evaluated skin temperature after nerve stimulator-guided infraclavicular nerve block. They concluded that the block was successful only if nerve-distribution density increased in four major nerves (musculocutaneous, radial, median, and ulnar nerves). On the other hand, it has been stated in subsequent studies that peripheral blockade of the ulnar and median nerves leads to characteristic increases in hand-skin temperature, whereas peripheral blockade of the radial and musculocutaneous nerves caused no change in hand-skin temperature [12]. The palmar face of the fourth digit which represents a thermographically overlapping area between the median and ulnar nerves, appears to be an ideal area to rapidly and accurately assess the change in distal Ts value [17]. However, the intersection of the median and ulnar nerves makes this area diagnostically insignificant. Therefore, the first, second, and fifth digits are commonly preferred for the evaluation of distal Ts [12,17,18]. On the other hand, in the present study, skin temperature could not be measured at these sites because most of the patients would undergo hand surgery and their digits would be injured and bandaged or casted. Consequently, the skin temperature was measured at the bilateral wrist foldings, which is described in the literature as one of the sites used to evaluate skin temperature after upper extremity peripheral nerve blocks [18].

Asghar et al. [18] have preferred different anatomical regions to evaluate the efficacy of distal infrared thermography and skin temperature in predicting the success of US-guided interscalene brachial plexus in their study. The first, second, and fifth digits were used to evaluate the distal aspect of the hand. The wrist region of the hand was also used in a manner similar to that in our study. They found that skin temperature increased by 3.1°C in the wrists of successful block patients (from baseline to 30th min), whereas our study showed an increase of 2.69°C. Further, it has been noted in this study that the distal Ts of the thumb would be the most appropriate region for the prediction of block success.

Asghar et al. [17] evaluated the change in distal Ts from the second and fifth digits of patients who underwent infraclavicular block in another study and detected a significant elevation at 30th min compared with baseline values in successful block patients. Similar to our results, they stated that no significant change was observed in patients who received the failed block. However, we found no significant difference between patients with successful block and those with partially failed block in terms of the values at the 30th min. We believe that this may be due to the measurement site of Ts used in our study. Additionally, the distal skin temperature is exposed to great fluctuations due to changes in environmental temperature, sympathetic nerve activity (stress, anxiety), local inflammation, and previous trauma. We tried to cool both hands by putting them on cold packages to reduce the effects of these factors and standardize the measurements. However, fluctuations may have occurred because of the procedure itself, as well as the reasons mentioned above.

Thermography studies have become prominent in the successful evaluation of peripheral nerve blocks as well as the measurement of distal skin temperature. It is known that sympathetic nerve fibers run peripherally along both major nerves and vessels [16]. Hence, it may be difficult to predict thermographic patterns at various levels of brachial plexus block, such as axillary brachial plexus block, lateral infraclavicular block, and interscalene brachial plexus block.

Besides the present study, there is still insufficient data on evaluation of the changes in the tissue oxygen saturation based on NIRS responses and efficacy assessment of NIRS in the prediction of block success, whereas the number of studies on distal skin temperature and thermographic assessments to evaluate the success of peripheral nerve blocks have progressively increased. Nerve block was successfully evaluated using NIRS after blockade of the stellate ganglion [19], and it was stated that the use of NIRS would be appropriate to evaluate the success of the nerve block [19,20]. Tighe et al. [11] evaluated tissue oxygen saturation using NIRS after peripheral nerve blocks; however, they demonstrated no significant efficacy. However, these outcomes may be due to the use of a small number of patients, as they have stated, along with the application of various blocks in an identical methodology. In contrast with this outcome, NIRS appears to be an effective method for the prediction of successful block in our study compared with both completely and partially failed blocks beginning from the 10th min following the nerve block procedure. In addition, its practicality and clinical understanding are easier to comprehend than those of thermographic measurements.

In other studies, pulse oximetry and oxygen electrodes following a peripheral nerve block were used to detect changes in tissue oxygenation and perfusion [21–23]. However, none of these methods include non-invasive measurements of the subcutaneous oxygenation state following upper and lower peripheral nerve blocks.

Therefore, we conclude that the assessment of tissue oxy-
gen saturation by NIRS in the evaluation of peripheral nerve block is a rapid, efficient, and practical method. We believe that as the first study in this field, our results would shed light on future studies which will investigate the role of the assessment of tissue oxygen saturation by NIRS in predicting the success of various peripheral nerve blocks.

**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**


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Mehmet Selçuk Uluer, https://orcid.org/0000-0002-5699-8688

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INTRODUCTION

Establishing peripheral intravenous (IV) access is essential for surgical patients for the administration of medications, fluids, and blood products during the perioperative period. However, obtaining reliable peripheral IV access in some patients can be challenging such as those with obesity and a history of IV drug abuse, as well as those who have received chemotherapy via peripheral cannula, frequent IV cannulation, and dialysis [1,2]. Central venous catheterization...
tion (CVC) can provide reliable venous access; however, it is more difficult than peripheral IV cannulation and can have severe complications such as thrombosis, pneumothorax, and infection [3,4].

The external jugular vein (EJV) is a superficial central vein located away from major neurovascular structures with less anatomical variation than other central veins [5,6], possibly accounting for the lower risks of major complications after EJV cannulation relative to those noted with other central vein cannulations [7,8]. Additionally, the EJV is more visible than other central veins and located closer to the heart than peripheral veins [9]. Therefore, EJV cannulation has been used in patients with difficult IV access mainly in emergency medicine [1,10]. EJV cannulation can be also a good alternative for surgical patients in whom it is difficult to establish peripheral IV access. If it is difficult to access peripheral veins due to the surgical drape or proximity to surgical site, EJV can be relatively easily accessible intraoperatively except for head and neck surgeries. EJV was also proposed as an alternative to other central venous access in patients with severe coagulopathy or in cases where ultrasound is not available [5,11].

For these reasons, EJV cannulation has been commonly performed by anesthesiologists for surgical patients with difficult IV access in our institution. However, its feasibility and safety for surgical patients has been scarcely reported. Therefore, we aimed to retrospectively analyze its feasibility and safety using the data of surgical patients in our institution over the past 12 years.

METHODS

Study design

We performed a retrospective review of EJV cannulation in surgical patients at a tertiary care teaching hospital. The study was approved by the Institutional Review Board of our institution (no. 2201–106–1291) on January 26, 2022; the requirement for informed consent was waived. The paper also adheres to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) criteria for observational studies [12].

EJV cannulation procedure

In our institution, EJV cannulation has been mainly performed for surgical patients with difficult large-bore IV access or those who need additional large-bore IV access during surgery (Fig. 1). Patients are placed in the Trendelenburg position, with the head slightly tilted to the opposite side of the EJV cannula insertion site. The pillow is removed to facilitate visualization of the EJV during the procedure. Due to the possibility of anatomical variation in EJV [13], ultrasound may be used at the discretion of attending anesthesiologist when the EJV is not readily visualized or palpable. After cleaning the insertion site with an alcohol swab, a needle is inserted at a shallow angle (approximately 10 degrees) above the EJV. When blood appears in the flash chamber of the catheter, the needle is advanced 1–2 mm farther. After that, the catheter over the needle is smoothly inserted while the needle is fixed, after which the needle is removed. After the catheter is successfully placed, it is connected to IV fluid bags. The success of catheter insertion is confirmed by successful blood aspiration via the catheter and no visible or palpable swelling after the administration fluid. EJV cannulation is routinely removed immediately after completion of surgery in the operating room or after the post-anesthesia care unit (PACU) or intensive care unit (ICU) admission. However, depending on the attending anesthesiologist, EJV access may be maintained after surgery for the administration of medication, fluids, or blood products. After removal of the EJV cannulation, manual pressure with a sterile gauze pad at the insertion site is applied by the attending anesthesiologists or nurses for at least 5 min.

Study population and data collection

This study included only adult (≥ 18 years) patients who underwent anesthesia for surgery and received EJV cannulation, performed by the attending anesthesiologists, in the operating room between 2010 and 2021. We collected data from 2010 as EJV cannulation data had been recorded in the electronic medical records (EMRs) since 2010.

In our institution, anesthesiologists routinely record the type (arterial-, peripheral-, or central line) and site of any vascular cannulation performed during anesthesia in the anesthetic records. To maximize the sensitivity for the screening of EJV cannulation cases during anesthesia, we used a search algorithm with the following keywords and their potential errata: “EJV,” “ext. jugular,” and “external jugular.” The anesthetic records were manually reviewed by two independent researchers to confirm the EJV cannulation.

We reviewed the EMRs and recorded the following variables: age, sex, body mass index, surgery type, robotic sur-
gery, laparoscopic surgery, emergency, discharged to intensive care unit, type of anesthesia (general, neuraxial, or monitored anesthesia care), and the amount of infused crystalloid, colloid, and blood products. The following cannulation-related variables were also retrieved from the anesthetic records: insertion time (induction of anesthesia vs. during surgery), purpose (for fluid administration, central venous pressure monitoring, or both), insertion side (right, left, both, or not specified), insertion technique (blind technique vs. ultrasonographic guidance), type of catheter (16-, 18-, 20-, 22-gauge intravenous catheter, or central-line catheter), and connection to rapid infusion system. Information about the type and manufacturer of the catheter is provided in Table 1.

To evaluate the efficacy and safety of EJV cannulation, any cannulation-related complications (insertion site swelling, infection, thrombophlebitis, pneumothorax, and arterial cannulation) were evaluated using the records identified for the present study. In addition, postoperative medical records, including progress notes, consultant notes, nursing records, and discharge notes, were also screened in the same manner to identify any EJV cannulation-related complications within 7 days after surgery. This information was then manually reviewed by the researchers. Any disagreements between researchers were resolved through discussion. During the revision process, EJV cannulation-related death was investigated among the in-hospital death cases.

**Statistical analysis**

Descriptive statistical analyses was conducted using R software version 4.0.0 (R Core Team, 2020) (R: Language and
Table 1. Type and Manufacturer of the Catheter Used for External Jugular Vein Cannulation

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Country</th>
<th>Name</th>
<th>Size</th>
<th>Outer diameter (mm)</th>
<th>Length (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Togo Medikit Co.</td>
<td>Japan</td>
<td>Safety IV catheter</td>
<td>22-gauge</td>
<td>0.9</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20-gauge</td>
<td>1.1</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18-gauge</td>
<td>1.3</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16 gauge</td>
<td>1.7</td>
<td>3.1</td>
</tr>
<tr>
<td>ARROW®</td>
<td>USA</td>
<td>Three-Lumen CVC</td>
<td>7 French</td>
<td>2.5</td>
<td>16</td>
</tr>
</tbody>
</table>

IV: intravenous, CVC: central venous catheterization.

RESULTS

We obtained the data of 9,577 (9,100 patients) from 494,447 anesthesia cases (339,077 patients) at our institution between 2010 and 2021 using a search algorithm for EJV cannulation during anesthesia. Patients who were found not to receive EJV cannulation during anesthesia after the review of anesthetic records (94 cases) and those who did not undergo surgery (1 case) were excluded from the analysis. Finally, a total of 9482 anesthesia cases of 9,062 patients were analyzed.

Table 2 includes the demographic data, surgery, and anesthesia-related profile information of patient cases considered in the study. For the analyzed cases, the most commonly performed surgery type was general surgery (49.6%), followed by urologic surgery (17.5%) and obstetric and/or gynecologic surgery (15.7%). Most patients received general anesthesia (9,341 cases, 98.5%), but some patients received neuraxial anesthesia (136 cases, 1.4%) or monitored anesthesia care (5 cases, 0.1%).

Table 3 presents the EJV cannulation-related data. In most cases, EJV cannulation was performed during anesthetic induction (9,604 patients, 90.7%); however, for 878 (9.3%) cases, unplanned EJV cannulation was performed emergently during surgery. The majority of emergent EJV cannulation were performed during general surgery (558 cases, 63.6%), followed by obstetric and/or gynecologic surgery (143 cases, 16.3%) and urologic surgery (83 cases, 9.5%). The main purpose of EJV cannulation was fluid administration (98.8%); in rare cases, EJV cannulation was performed solely for central venous pressure monitoring (0.4%). The most commonly performed cannulation technique was Lt. EJV cannulation (68.6%) under blind technique (99.3%) with an intravenous catheter size of 18-gauge or larger (58.2%). When the 7-Fr central venous catheter was used, the median duration of catheter placement was 1 day, and its range was 0–11 days. The EJV cannulation was connected to the rapid infusion system for 212 (2.3%) cases. The only EJV cannulation-relat-
ed complication was swelling at the EJV-cannula insertion site (65 cases, 0.7%). Among them, 63 cases were recorded solely in the anesthetic record and resolved with manual compression during anesthesia without any requirement for further evaluation or treatment. Only two cases (0.02%), elaborated below, recorded in the postoperative medical records were determined to be related to EJV cannulation. Of the 160 in-hospital death cases included in the study, EJV cannulation-related death was not identified.

In the first of the two cases mentioned above, a 16-gauge IV catheter was placed at the right EJV during the anesthesia induction, and a total of 1,100 ml of crystalloid was infused over 145 min of anesthesia with an estimated surgical blood loss of 300 ml. During the PACU stay, a swelling on the right side of the patient’s neck was found by a nurse before the removal of EJV catheter. The patient did not present with any related symptoms such as neck pain or dyspnea. The right EJV was then evaluated by a radiologist using ultrasound on the day after surgery, and no significant abnormalities were found. The patient was discharged without any other complications on postoperative day 4. In the second case, a 16-gauge IV catheter was placed at the left EJV during the anesthesia induction. The duration of anesthesia was 330 min, and the estimated surgical blood loss was 950 ml. A total of 2,750 ml of crystalloid and 500 ml of hydroxyethyl starch was infused through IV routes. After surgery, the adhesive surgical drape used to secure the catheter was removed, and edema from the left chest to the left cheek was observed. The cause of the edema was suspected to be the extravasation of fluid through the left EJV route, and the estimated amount of leakage was 700 ml. Concerned about the possibility of airway compression, the patient was transferred to the ICU under intubated status. The edema subsided on postoperative day 1. An endotracheal cuff-leak test was then performed to confirm the absence of post-extubation stridor, after which the patient was extubated. The patient was transferred to a general ward on the same day and discharged on postoperative day 8 without any complications.

## DISCUSSION

This study investigated the feasibility and safety of EJV cannulation in surgical patients. During the 12 years of the study period, EJV cannulation was performed for 9,482 anesthesia cases from 9,062 patients, of which 878 (9.3%) cases were performed emergently during surgery. The only identified complication related to EJV cannulation in this study was swelling around the cannula insertion site, and no other complication was identified. Our results suggest the feasibility and safety of EJV cannulation for administering fluids in surgical patients.

EJV cannulation has been performed mainly for fluid administration in surgical patients in our institution. As a part of improving postoperative recovery, unnecessary CVCs have been gradually reduced to enhance early ambulation and recovery after surgery [14]. However, since unexpected intraoperative bleeding cannot be entirely avoided [15], the need for large-bore access IV remains for surgical patients.

Previous studies have debated the usefulness of EJV cannulation in surgical patients [1]. One randomized controlled trial (RCT) involving patients who underwent open-heart surgery reported that EJV cannulation required a longer procedure duration and had a higher failure rate than the ante-

### Table 3. External Jugular Vein Cannulation-related Profile

<table>
<thead>
<tr>
<th>Variables</th>
<th>Total (n = 9,482)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insertion time window</td>
<td></td>
</tr>
<tr>
<td>Induction of anesthesia</td>
<td>8,604 (90.7)</td>
</tr>
<tr>
<td>Emergently during surgery</td>
<td>878 (9.3)</td>
</tr>
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<td>Purpose</td>
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<tr>
<td>Fluid administration</td>
<td>9,367 (98.8)</td>
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<tr>
<td>Central venous pressure monitoring</td>
<td>40 (0.4)</td>
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<tr>
<td>Both</td>
<td>75 (0.8)</td>
</tr>
<tr>
<td>Insertion site</td>
<td></td>
</tr>
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<td>Right external jugular vein</td>
<td>2,893 (30.5)</td>
</tr>
<tr>
<td>Left external jugular vein</td>
<td>6,505 (68.6)</td>
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<tr>
<td>Both external jugular vein</td>
<td>67 (0.7)</td>
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<tr>
<td>Not specified</td>
<td>17 (0.2)</td>
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</tr>
<tr>
<td>22-gauge intravenous catheter</td>
<td>7 (0.1)</td>
</tr>
<tr>
<td>20-gauge intravenous catheter</td>
<td>88 (0.9)</td>
</tr>
<tr>
<td>18-gauge intravenous catheter</td>
<td>3,196 (33.7)</td>
</tr>
<tr>
<td>16-gauge intravenous catheter</td>
<td>2,254 (23.8)</td>
</tr>
<tr>
<td>7-Fr central venous catheter</td>
<td>66 (0.7)</td>
</tr>
<tr>
<td>Not specified</td>
<td>3,871 (40.8)</td>
</tr>
<tr>
<td>Connected to rapid infusion system</td>
<td>212 (2.2)</td>
</tr>
<tr>
<td>Catheter-related complications</td>
<td></td>
</tr>
<tr>
<td>Insertion site swelling</td>
<td>65 (0.7)</td>
</tr>
<tr>
<td>Infection</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Arterial cannulation</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

Values are expressed number (%).
cubital venous cannulation [16]. Another RCT reported that the success rate of EJV cannulation was lower than that of ultrasound-guided peripheral IV cannulation for patients with difficult vascular access [1]. However, these two studies involved trainees inexperienced with EJV cannulation. We could not obtain information on the practitioners of EJV cannulation due to our retrospective study design; however, it is usually performed by an anesthesiologist experienced with EJV cannulation in our institution. Another RCT reported the low success rate of CVC via the EJV using the blind technique (10/30, 33%) and ultrasound-guided technique (6/30, 20%) [17]. However, this low success rate may have been due to their study participants (inexperienced trainees) and guidewire-guided CVC insertion. The anatomical variation in the EJV-SCV junction can contribute to the difficulty in inserting CVC via EJV [7]. We mainly used an IV catheter for EJV cannulation without using a guidewire, which could have contributed to the simpler implementation of EJV compared to CVC.

As EJV is directly connected to the central compartment, complications related to central venous catheterization, including bloodstream infection, arterial puncture, hematoma, pneumothorax, thrombosis, and air embolism, can theoretically occur after EJV cannulation [18]. However, in our study, no significant complications related to EJV cannulation were identified. Some previous studies reported that the only complication associated with EJV cannulation was a small subcutaneous hematoma at the failed insertion site, and there was no related arterial complication [19]. There have also been previous case reports of very rare but severe complications of EJV cannulation. One report was of a case of pulmonary air embolism through the open hub of an EJV cannula that was accidentally disconnected from the IV set in a patient who underwent bilateral humerus fracture surgery [20]. Another report was of a case of fracture and distal migration of the IV cannula placed in the EJV in the ICU patient [21]. Although we did not identify these complications in our patients, anesthesiologists should be careful of severe complications associated with EJV cannulation during cannula insertion, maintenance, and removal.

In our study, the only identified complication was swelling around the insertion site, which may have been due to extravasation caused by catheter tip malposition during surgery. There was only one case of an unplanned ICU admission due to swelling related to EJV cannulation. Since the extravasation of a large volume of fluids in the cervical area may cause airway obstruction [22,23], it may be helpful to assess the patency of the EJV cannula by inspection and palpation of the insertion site to minimize this complication. The unexpected extravasation of vasoactive drugs, hypertonic solution, and concentrated electrolyte solution may occur during anesthesia, which may lead to the necrosis of skin and subcutaneous tissue, even requiring surgery in rare cases [24]. In our study, skin necrosis was not identified during the review of medical records, probably because EJV access was mainly used for the administration of crystalloid or blood products in this study.

EJV cannulation was performed emergently during surgery for 9.3% of our cases, and most of them were for abdominal surgeries. These results may be attributed to the easier access to the EJV than peripheral veins at extremities during the abdominal surgery, as well as the ease with which EJV cannulation can be performed with blind techniques relative to internal jugular vein cannulation. Further, EJV cannulation may have a low risk of major complications due to anatomical characteristics. Therefore, EJV cannulation can provide safe and reliable IV access, especially when additional rescue IV access is emergently required during abdominal surgeries. However, anesthesiologists should pay attention to its high malposition rate due to the relatively common anatomical variation of EJV [25,26].

The results of our study should be interpreted with caution. First, this was a retrospective cohort study, and the complication rate may have been underestimated. We thoroughly screened the anesthetic and postoperative medical records using the search algorithm for any clinically significant complications. However, subclinical complications, such as mild insertion site swelling or extravasation, may have occurred without being documented in the medical records. Although the EJV catheters were removed immediately after surgery, unidentified EJV catheter-related bloodstream infections may have also occurred. In addition, only the amount of fluid or blood, or vasopressors administered through the entire IV routes, and not the EJV cannula, could be measured. Second, we could not investigate the success rate of EJV cannulation. EJVs in obese patients may be less visualized or palpable than those in non-obese patients. Further studies are warranted to examine the potential factors affecting the success rate of EJV cannulation, such as obesity and ultrasound guidance. Third, since most cases of EJV cannulation were performed by experienced anesthesiologists, the extent to which the results may be generalized to other institutions with less EJV cannulation experience is uncertain. Fourth, we did not include EJV cannulation cases...
in pediatric patients. Although there is evidence on the central venous access via EJV in pediatric patients [27,28], the feasibility of EJV cannulation with intravenous catheter in this population warrants further investigation. Lastly, we could not directly compare the feasibility and safety of EJV cannulation with that of other IV access.

In conclusion, our study showed the feasibility and safety of EJV cannulation for surgical patients. EJV cannulation was also useful for securing emergent IV access during surgery. No serious complications, except swelling around the insertion site, could be found in our study. EJV cannulation can be useful for safe and reliable IV access in surgical patients.

**FUNDING**

None.

**CONFLICTS OF INTEREST**

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

**DATA AVAILABILITY STATEMENT**

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request and with permission of the Institutional Review Board of the Seoul National University Hospital.

**AUTHOR CONTRIBUTIONS**


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**REFERENCES**

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The purpose of a pre-anesthetic evaluation is to establish an optimal perioperative anesthesia plan by identifying risk factors, including unrecognized diseases or disorders, that may affect perioperative anesthesia management and assessing already known diseases. Pre-anesthetic evaluations should be considered for their potential benefits and adverse effects. While they may improve the safety and effectiveness of anesthesia management, their potential adverse effects include injuries, discomfort, inconvenience, delay in surgery, and additional costs [1]. Pre-anesthetic evaluations include reviews of medical records, patient interviews, physical examination, and preoperative tests, including electrocardiography, chest radiography, and laboratory tests, when indicated. However, preoperative tests may increase risks and costs, and test results often do not significantly alter anesthesia management in relatively healthy patients. Therefore, the guidelines for pre-anesthetic or preoperative evaluations by the American Society of Anesthesiologists, European Society of Anesthesiology, and National Institute for Health and Clinical Excellence (NICE) recommend that pre-
operative tests are performed based on the grade of surgery, physical status of the patient, and underlying diseases [1-3].

Despite the pre-anesthetic evaluations, anesthesiologists often encounter serious situations during anesthesia due to diseases or conditions that are not identified before anesthesia. Massive bleeding and subsequent complications may occur during surgery when a bleeding tendency is not detected during the pre-anesthetic evaluation. In addition, the patients can be life-threatened without adequate patient monitoring, intravenous access, and preparation for transfusion. We report two cases of severe pancytopenia and acquired coagulation factor deficiency that were not detected during pre-anesthetic evaluations.

**CASE REPORT**

This report was approved by the Institutional Review Board (IRB) of our hospital, and the requirement for informed consent was waived (IRB no. E2022-15).

**Case 1**

A 74-year-old female patient was scheduled to undergo cranioplasty and removal of a meningioma under general anesthesia. The patient was diagnosed with subarachnoid hemorrhage and meningioma, and underwent emergency craniectomy and cerebral aneurysm clipping 3 weeks ago. The subarachnoid hemorrhage was caused by an aneurysmal rupture of the left posterior communicating artery. In addition, meningioma of the right frontal lobe revealed by computed tomography in the emergency room. She had no history except for hypertension, and the complete blood count (CBC) conducted five days before surgery showed a hemoglobin (Hb) of 8.9 g/dl, hematocrit (Hct) of 26.7%, platelet count (PLT) of 314,000/μl, and white blood cell count (WBC) of 7,000/μl. Noninvasive blood pressure, electrocardiography, and pulse oximetry were monitored after the patient was admitted to the operating room. Propofol and remifentanil were used for the induction and maintenance of anesthesia. After endotracheal intubation, an arterial cannula was inserted into the left radial artery for continuous invasive blood pressure measurements. Additionally, a central venous catheter was placed in the right subclavian vein. Arterial blood gas analysis (ABGA) and CBC were performed to establish the initial baseline status of the patient during surgery after a skin incision in the scalp for cranioplasty. Pancytopenia was confirmed based on the severe decrease in the Hb to 6.5 g/dl, Hct to 19%, PLT to 13,000/μl, and WBC to 2,000/μl. We immediately notified the surgeon of the pancytopenia and repeated the CBC to rule out errors. Hb and PLT had further reduced: Hb, 5.7 g/dl; Hct, 17.2%; PLT, 10,000/μl; and WBC, 2,100/μl. Blood pressure and heart rate were stable at 110/50 mmHg and 65 beats/min, respectively, at the time of laboratory tests. No abnormal bleeding was observed at the surgical site. In addition, there were no signs of unexpected acute bleeding, such as abdominal distension or hematuria. We decided to proceed with cranioplasty because the operation proceeded after the skin incision, and there was no abnormal bleeding at the surgical site. However, craniotomy was required to remove the brain tumor because the meningioma was located on the right side, and the risk of bleeding and postoperative infection increased. Therefore, the meningioma removal was canceled. The estimated blood loss during surgery was 700 ml. Five units of packed red blood cells (PRBC) were transfused. A crystalloid solution (1,500 ml) and colloid solution (500 ml) were administered during surgery. The patient’s vital signs were intraoperatively stable. The postoperative laboratory test finding in the intensive care unit showed Hb at 9.9 g/dl, Hct at 29.3%, PLT at 11,000/μl, and WBC at 6,300/μl. Sepsis, disseminated intravascular coagulation, and drug-induced pancytopenia were evaluated in consultation with the hematologist. Normocytic normochromic anemia, normal WBC, and thrombocytopenia were observed on a peripheral blood smear. This was bicytopenia with a restored WBC count. Schistocytes were not observed. The coagulation tests showed activated partial thromboplastin time (aPTT; normal range 23.5–32.5 s) of 35.4 s, prothrombin time (PT; normal range 8.3–10.4 s) of 10.4 s, and an international normalized ratio (INR; normal range 0.93–1.16) of 1.14. The fibrinogen was 255 mg/dl (normal range 193-412 mg/dl) and the D-dimer was 1.44 μg/ml (normal range 0–0.5 μg/ml). The vital signs were stable during the perioperative period, and there were no symptoms or signs of bleeding or infection. Considering the results of the laboratory tests and the condition of the patient, drug-induced pancytopenia was suspected. Levetiracetam and ceftriaxone were presumed to be the causes. Levetiracetam was administered after cerebral aneurysmal clipping to prevent epileptic seizures, and ceftriaxone was used five days before surgery to treat urinary tract infection. Ceftriaxone was discontinued, and levetiracetam was replaced with valproate. Periodic laboratory tests were performed intermittently with the transfusions of PRBC and platelet concentrates (PC) (Table 1). The bicytopenia recov-
ered 14 days after the surgery, and the patient was discharged without meningioma removal.

**Case 2**

A 71-year-old male patient was scheduled for the excision of a choledochal cyst under general anesthesia. He was hospitalized with abdominal pain and evaluated for disease. He was taking medications, including aspirin, for hypertension and diabetes. The laboratory tests performed 7 days before surgery showed that only the aPTT increased to 43.3 s; the PT was 9.5 s and the INR was 1.04. The CBC and serum chemistry results were normal. There were no specific findings from the pre-anesthetic patient interview or physical examination a day before surgery. Bruises in the intravenous access site and a large ecchymosis involving the back, waist, and buttocks were observed while verifying the identity of the patient and attaching the patient monitoring device after admission to the operating room. After discussing the condition of the patient with the surgeon, we decided to examine and treat the bleeding tendency before surgery. The CBC results were normal. The coagulation test showed aPTT of 75.7 s, PT of 10.7 s, and INR of 1.17. In addition, the plasma mixing test showed transient normalization of aPTT, coagulation factor VIII level of 3% (normal range: 50–150%), and coagulation factor IX level of 92% (normal range: 50–150%). The coagulation factor VIII antibody was positive. The patient was diagnosed with acquired coagulation factor VIII deficiency and transferred to the Department of Hemato-Oncology. The coagulation test results and coagulation factors were normalized approximately four weeks after treatment with steroids, and the patient was discharged after surgery. Table 2 summarizes the results of the coagulation and coagulation factor VIII tests.

**DISCUSSION**

Pancytopenia and acquired coagulation factor deficiency are uncommon but they can cause severe bleeding when surgery is performed without detecting them. Laboratory tests, such as CBC and coagulation tests, are essential for their diagnoses. However, laboratory tests are recommend-

---

**Table 1. Complete Blood Count for Case 1**

<table>
<thead>
<tr>
<th>Timing</th>
<th>Hemoglobin (mg/dl)</th>
<th>White blood cell count (cells × 10^3/μl)</th>
<th>Platelet count (cells × 10^3/μl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st operation (pre)</td>
<td>11.3</td>
<td>8.1</td>
<td>279</td>
</tr>
<tr>
<td>1st operation (post)</td>
<td>7.9</td>
<td>15.9</td>
<td>149</td>
</tr>
<tr>
<td>2nd operation (pre)</td>
<td>8.9</td>
<td>7.0</td>
<td>314</td>
</tr>
<tr>
<td>Intraoperation 1</td>
<td>6.5</td>
<td>2.0</td>
<td>13</td>
</tr>
<tr>
<td>Intraoperation 2</td>
<td>5.7</td>
<td>2.1</td>
<td>10</td>
</tr>
<tr>
<td>2nd operation (post)</td>
<td>9.9</td>
<td>6.3</td>
<td>11</td>
</tr>
<tr>
<td>POD 1</td>
<td>9.7</td>
<td>4.1</td>
<td>18</td>
</tr>
<tr>
<td>POD 3</td>
<td>9.7</td>
<td>4.2</td>
<td>12</td>
</tr>
<tr>
<td>POD 5</td>
<td>9.9</td>
<td>4.4</td>
<td>20</td>
</tr>
<tr>
<td>POD 7</td>
<td>9.2</td>
<td>4.5</td>
<td>43</td>
</tr>
<tr>
<td>POD 9</td>
<td>8.8</td>
<td>6.6</td>
<td>91</td>
</tr>
<tr>
<td>POD 14</td>
<td>8.6</td>
<td>6.1</td>
<td>295</td>
</tr>
</tbody>
</table>

The first operation is cerebral aneurysmal clipping, and the second operation is cranioplasty. POD: postoperative day.

**Table 2. Coagulation Test and Factor VIII for Case 2**

<table>
<thead>
<tr>
<th>Variable</th>
<th>aPTT (s)</th>
<th>PT (s)</th>
<th>PT (%)</th>
<th>INR</th>
<th>Factor VIII (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal range</td>
<td>23.5–32.5</td>
<td>8.3–10.4</td>
<td>70–127</td>
<td>0.93–1.16</td>
<td>50–150</td>
</tr>
<tr>
<td>Preoperation</td>
<td>43.3</td>
<td>9.5</td>
<td>90</td>
<td>1.04</td>
<td></td>
</tr>
<tr>
<td>Postoperation</td>
<td>75.7</td>
<td>10.7</td>
<td>72</td>
<td>1.17</td>
<td>3</td>
</tr>
<tr>
<td>POD 1</td>
<td>54.5</td>
<td>10.1</td>
<td>80</td>
<td>1.11</td>
<td>5</td>
</tr>
<tr>
<td>8 days after steroid treatment</td>
<td>36.9</td>
<td>9.5</td>
<td>87</td>
<td>1.05</td>
<td>60</td>
</tr>
<tr>
<td>15 days after steroid treatment</td>
<td>26.4</td>
<td>9.0</td>
<td>99</td>
<td>1.00</td>
<td>&gt; 100</td>
</tr>
</tbody>
</table>

aPTT: activated partial thromboplastin time, PT: prothrombin time, INR: international normalized ratio, POD: postoperative day.
ed “selectively” rather than “routinely” during pre-anesthetic evaluation because they can lead to adverse effects and additional costs, and abnormal results often do not significantly change the anesthetic management. According to the guidelines of the American Society of Anesthesiologists, Hb and Hct are measured for old age or a history of liver disease, anemia, hemorrhage, or other hematologic diseases. Coagulation tests should be performed for patients with bleeding disorders, renal impairment, and hepatic impairment and those who use anticoagulants [1]. The NICE guidelines recommend that preoperative tests should be guided by the American Society of Anesthesiologists physical status (ASA) of the patient and surgical grade (minor, intermediate, or major surgery). CBC is recommended for all patients with ASA I–IV before major surgery, and it should be considered before intermediate surgery when patients with ASA III–IV have underlying diseases. Coagulation tests are recommended as needed for patients with ASA III–IV for both intermediate and major surgeries [3].

In our hospital, pre-anesthetic evaluation includes the review of pertinent medical records, patient interviews, and physical examinations. It is conducted a day before elective surgery. In contrast with the recommendations of the American Society of Anesthesiologists and NICE, electrocardiography, chest radiography, and laboratory tests are performed routinely; the laboratory tests include CBC, serum chemistry, and coagulation tests. In general, when elective surgery is scheduled, preoperative tests are performed at the outpatient clinic, and further consultation or examination depends on their results.

Therefore, the duration between the preoperative tests and surgery may differ from weeks to months. Both patients were evaluated after hospitalization. The most recent laboratory tests were performed on the fifth and seventh days before surgery. Nevertheless, we did not detect pancytopenia or acquired coagulation factor deficiency during the pre-anesthetic evaluation.

For case 1, the patient had normal CBC results except for anemia preoperatively. No symptoms or signs suggestive of pancytopenia, such as fever, palpitation, or bleeding, were observed. In this patient, it can be inferred that pancytopenia developed after the preoperative tests. Levetiracetam and ceftriaxone are presumed to be causes [4-6]. Drug-induced pancytopenia is a rare condition; however, various drugs, including nonsteroidal anti-inflammatory drugs, anti-epileptics, anti-thyroid drugs, rheumatologic drugs, and antimicrobials, have been implicated. Myelosuppression and consumption or destruction of peripheral blood may underlie drug-induced pancytopenia [7]. Levetiracetam induces pancytopenia via bone marrow suppression. Most cytopenia cases occur within 24 hours to a few days after using levetiracetam, but it may be first detected several months after drug use [8]. Ceftriaxone-induced cytopenia is a rare condition. It is known to induce drug-induced immune thrombocytopenia rather than pancytopenia [9]. A drug-dependent antibody binds to the glycoprotein of the PLT membrane and activates PLT consumption in drug-induced immune thrombocytopenia. Anesthesiologists recognize that various drugs can cause hematologic disorders, but it is difficult to consider these during pre-anesthetic evaluations. As with case 1, it may be impossible to diagnose cytopenia that develops after laboratory tests during the pre-anesthetic evaluation because tests are not repeated without significant changes in the condition of a patient. In this case, pancytopenia was confirmed in patient evaluation during anesthesia. We place the arterial cannula for invasive blood pressure monitoring and laboratory tests, such as ABGA, during the surgery when a significant amount of bleeding is expected, and intraoperative tests are conducted early to establish a baseline for the laboratory tests. In case 1, CBC was performed along with ABGA because the Hb reduced to 8.9 g/dl in the preoperative test. These early examinations during anesthesia can help detect unpredictable changes in the condition of the patient.

The acquired coagulation factor VIII deficiency detected in Case 2 is predominantly idiopathic, but it may be caused by autoimmune or cancerous diseases [10]. It is classified as severe (< 1%), moderate (1–5%), or mild (> 5%), depending on the activity of coagulation factor VIII. The aPTT was prolonged 2–3 times during the coagulation test. The degree and frequency of bleeding vary with the coagulation factor activity. Spontaneous hemorrhage within the muscle or joint and life-threatening hemorrhage may occur in severe. Spontaneous bleeding is uncommon, but bleeding after trauma often occurs in moderate. The coagulation factor activity in this patient was 3%, which was moderate. In addition to the extensive ecchymosis, bruises were also found at the site where intravenous cannulation was attempted or failed. If bleeding tendencies, such as bruising and ecchymosis, were more carefully investigated without ignoring the increased aPTT detected by the coagulation test, acquired coagulation factor deficiency may have been confirmed during the pre-anesthetic evaluation via additional examinations.

Pancytopenia and acquired coagulation factor deficiency
can cause severe intraoperative bleeding, which can seriously compromise patient safety. When an unexpected bleeding tendency that is not detected during the pre-anesthetic evaluation occurs during surgery, the anesthesiologist should perform CBC and coagulation tests to confirm cytopenia or coagulopathy. If significant cytopenia or impairment of coagulation is present, the surgeon should be immediately notified and the continuation of the surgery should be discussed. The surgical plan may be changed or the surgery may be discontinued when these disorders are detected before anesthesia induction or at an early stage of the surgery. However, treatment is mandatory for cases requiring surgery. PRBC and PC are transfused in pancytopenia, and the transfusion of fresh frozen plasma or cryoprecipitates and PRBC is required to correct coagulation impairment. Coagulation factor deficiency is treated by supplementing the deficient coagulation factor.

Pancytopenia or aggravation of coagulopathy may occur after preoperative tests for pre-anesthetic evaluation. These findings may not be confirmed during pre-anesthetic patient interviews and physical examinations. Performing pre-anesthetic evaluations continuously until the induction of anesthesia and conducting intraoperative tests early may help to detect these diseases and prevent risks during anesthesia. Therefore, anesthesiologists should be aware that unexpected changes in patient conditions may occur during perioperative period, and the safety of patients should be ensured by conducting continuous patient evaluations.

FUNDING

None.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

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REFERENCES

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.

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

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APM publishes articles in English. The 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.

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

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 a draft of 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 upon reasonable request.
- Data sharing is 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 included in this published article [and its supplementary infor-
mation 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].

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APM allows authors to submit the preprint to the journal. It is not treated as duplicate submission or duplicate publication. APM recommends authors to disclose it with DOI at the time of submission process. Otherwise, it may be screened from the plagiarism check program — iThenticate. Preprint submission will be processed through the same peer-review process with a usual submission. If the preprint is accepted for publication, authors are recommended to update the info at the preprint with a link to the published article in APM, including DOI at APM. It is strongly recommended that authors cite the article in APM instead of the preprint at their next submission to journals.

6. 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 the 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 of 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 with 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/.

7. Article processing charge and publication fee

There is no submission-related fee. An 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.

8. Copyrights and secondary publication

The APM owns copyrights of all published materials. On behalf of the co-author(s), the 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

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

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

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

2. Statement of informed consent

Copies of written informed consents and Institutional Review Board (IRB) approval for clinical research are recommended to be kept. The editor or reviewers may request copies of these documents to clarify potential ethical issues.

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 the 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 assure 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 that a submitted manuscript 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 to be 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, and 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, and 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 a duplicate publication is detected, the APM editorial office will notify the counterpart journal of this violation. Additionally, it will be notified of the authors’ affiliation, and penalties will be imposed on the authors. It is possible to republish manuscripts if they 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 (https://www.equator-network.org).

CONSORT for reporting of randomized controlled trials (http://www.consort-statement.org)

STARD for reporting of diagnostic accuracy studies (http://www.stard-statement.org)

STROBE for reporting of observational studies in epidemiology (http://www.strobe-statement.org)

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

MOOSE for reporting of observational studies (http://www.emgo.nl/kc/reporting-your-study-results-in-a-scientific-article)

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

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, a full expression of the abbreviated words should be provided at the first use, with the abbreviation following in parentheses.

Ex) target controlled infusion (TCI)

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

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

3. Word spacing

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

Leave no space when using a 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, methods, results, discussion, acknowledgments, references, tables, figures, and figure legends. Figures should be uploaded as separate files. The title of each new section should begin on a new page. The conclusion should be included in the discussion section. Number pages consecutively, beginning with the first page of the manuscript. Page numbers should be placed in the middle of the bottom of the page. For survey-based clinical studies, the original survey document does not need to be included in the body of the manuscript but may be included as a supplement in an appendix.

6. Organization of manuscript

1) Clinical or experimental research
(1) Cover page (upload separately)

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 should be provided with no more than 40 characters, including letters and spaces in Korean, or 10 words in English. 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 at 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, is mandatory.

6. Conflicts of interest
   Any conflicts of interest for any or all authors within the 36 months of submission. If there are 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 article’s purpose concisely and include background information relevant to the paper’s purpose.

4. Methods
   The 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 others can further replicate it. Institute and author names should be avoided.
   When reporting experiments with human or animal subjects, the authors should indicate whether the Institutional Board supervised the handling of the animals 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. [ × ], 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 TM as a superscript and the manufacturer’s name and country.

• Ions
  Ex) Na⁺[O], Mg²⁺[O], Mg⁺²[×], Mg⁺⁺[×]
  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 the data provided in the tables or figures in the text; emphasize or summarize only the most important observations. Results can be sectioned by subsection titles but should not be numbered. The citation of tables and figures should be provided as Table 1 and Fig. 1. 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 (1Q, 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 in enough detail so 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, an exact test or asymptotic method with appropriate adjustments should be used if the number of events and sample is small. The standard chi-squared test or difference-in-proportions test may be performed only when the sample size and the number of events are sufficiently large.

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

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

G. A priori sample size calculation should be described in detail. Sample size calculation must aim at preventing false negative results pertaining to the primary, instead of secondary, endpoint. Usually, the mean difference and standard deviation (SD) are typical parameters in estimating the effect size. The power must be equal to or greater than 80 percent. In the case of multiple 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 to reflect the original degree of precision. Calculated or estimated numbers (such as mean and SD) should be expressed in no more than one significant digit beyond the measured accuracy. Therefore, the mean (SD) of cardiac indices in patients measured on a scale that is accurate to 0.1 L/min/m² should be expressed as 2.42 (0.31) L/min/m².
J. Except when otherwise stated herein, authors should conform to the most recent edition of the American Medical Association Manual of Style.

Discussion
The discussion should be described to emphasize the new and important aspects of the study, including the conclusions. Do not repeat in detail the results or other information that is provided in the introduction or the results section. Describe the conclusions according to the purpose of the study but avoid unqualified statements that are not adequately supported by the data. Conclusions may be stated briefly in the last paragraph of the discussion section.

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

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

References
- References should be obviously related to documents and should not exceed 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.
  Ex) Blitt C. Monitoring the anesthetized patient. In: Clinical Anesthesia. 3rd ed. Edited by Barash PG, Cullen BF, Stoelting RK: Philadelphia, Lip-
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 (IQR, 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 *p < .05, †p < .01, ‡p < .001 and written as superscripts.

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 for online reading. However, since it will be charged upon the publication, authors may choose to use colors only for online reading.
2. Standard colors should be used (black, red, green, blue, cyan, magenta, orange, and gray). Avoid colors that are difficult to see on the printed page (e.g., yellow) or are visually distracting (e.g., pink). Figure backgrounds and plot areas should be white, not gray. Axis lines and ticks should be black and thick enough to frame the image clearly. 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. The width of figure should be 84 mm (one column). The contrast of photos or graphs should be at least 600 dpi. The 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 computer not used for their creation, to check for compatibility issues.

7) Individual video files should be a minimum of 480 x 320 pixels (smaller clips will not be accepted) and a maximum of 2 GB. Files of < 15 MB will be rejected outright unless special arrangements have been made with the editorial board prior to submission. Approval of > 2 GB files 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. The 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, the 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.

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

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8. Should be fewer than 250 words.

Contents: (Introduction-Discussion)

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8. A maximum of five authors is allowable.
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