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Aims and Scope

Anesthesia and Pain Medicine (APM) is the official journal of the following ten subsocieties of the Korean Society of Anesthesiologists: Korean Society of Neuroscience in Anesthesiology and Critical Care, the Korean Society for Anesthetic Pharmacology, the Korean Society of Obstetric Anesthesiologists, the Korean Society of Pediatric Anesthesiologists, the Korean Neuromuscular Research Society, the Korean Society of Cardiothoracic and Vascular Anesthesiologists, the Korean Society of Transplantation Anesthesiologists, the Korean Spinal Pain Society, the Korean Society of Regional Anesthesia, and the Korean Society for Airway Management. Its abbreviated title is “Anesth Pain Med.” It is published four times a year in English, on the last days of January, April, July, and October.

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- Anesthesia for cardiothoracic and vascular surgery and the management of patients undergoing surgery for cardiac, pulmonary, and vascular diseases
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- Pathophysiology, pharmacology, and all aspects of spine-related pain
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INTRODUCTION

Remimazolam besylate (Byfavo injection in South Korea, Anerem® in Japan, Aptimyda™ in EU, ByFavo™ in the USA, and Ruima® in China) is a water-soluble, ultra-short-acting intravenous (IV) benzodiazepine (BDZ). It has recently been approved as a general anesthetic (in January 2020 in Japan and January 2021 in South Korea) and for use in procedural sedation (in July 2020 in the USA and China, March 2021 in Europe, and August 2021 in South Korea) in adults [1].

Similar to midazolam, remimazolam enhances γ-amino-butyric acid A (GABA_A) receptor activity to induce cell membrane hyperpolarization, thereby inhibiting neural activity via an increase in chloride influx [2]. In addition, it is a soft drug designed to incorporate a carboxylic ester moiety into the BDZ core (Fig. 1) [3]. With such structural modifications similar to remifentanil, remimazolam is rapidly hydrolyzed to a pharmacologically inactive metabolite (CNS 7054) via non-specific tissue esterase activity (Fig. 2) [4,5], which leads to the fast onset and offset of sedation and predictable dura-
tion of action. Similar to other BDZs, flumazenil can be used to reverse the sedation effect of remimazolam [6]. Owing to its favorable properties, including rapid onset, organ-independent metabolism, short duration of action, predictable recovery, availability of a reversal agent, and a superior safety profile similar to other BDZs in terms of hemodynamic stability, remimazolam appears to have several advantages over currently available short-acting sedative drugs [1,7].

In this review, the pharmacokinetic and pharmacodynamic characteristics and clinical applications of remimazolam have been discussed along with the currently available literature evidence.

**PHARMACOLOGICAL CHARACTERISTICS**

**Pharmacokinetics**

The pharmacokinetic properties of IV remimazolam have been investigated in previous phase I studies involving healthy volunteers administered single bolus injection [8,9] and continuous infusion [10,11], and it was found that remimazolam exhibits a relatively high clearance, a small steady-state volume of distribution ($V_{ss}$), a short elimination half-life, a short context-sensitive half-life (CSHT), first-order, and linear pharmacokinetics. The major pharmacokinetic properties of remimazolam are summarized in Table 1.

The initial phase I dose-finding study, the first human trial of remimazolam, was conducted to compare the pharmacokinetics of remimazolam (0.01–0.30 mg/kg administered over 1 min) with that of midazolam (0.075 mg/kg administered over 1 min) [8]. The mean $V_{ss}$ of remimazolam was 34.8 L, whereas that of midazolam was 81.8 L. In addition, the elimination clearance of remimazolam was approximately three times that of midazolam (70.3 vs. 23.0 L/h) and independent of body weight. The mean residence times of remimazolam and midazolam were 0.51 h and 3.62 h, respectively; the terminal half-life values were 0.75 h and 4.29 h, respectively. A subsequent pharmacokinetic analysis that included data from 20 healthy male volunteers receiving continuous remimazolam infusion (5 mg/min for 5 min, followed by 3 mg/min for 15 min and 1 mg/min for 15 min) showed similar profiles to those of an earlier phase I study involving IV bolus injection of remimazolam [10]. The analysis revealed a small $V_{ss}$ (35.4 L/h), high elimination clearance (1.15 L/min), short half-life (70 min), and first-order linear pharmacokinetics.

Remimazolam is rapidly and extensively metabolized by tissue esterase (chiefly, liver carboxylesterase) to a pharmacologically inactive carboxy acid metabolite (CNS 7054), which has approximately 300 times lower affinity than that of its parent compound [5,12,13]. Simultaneous pharmacokinetic analysis of CNS 7054 and remimazolam revealed that CNS 7054 has a pharmacokinetic profile with smaller volume of distribution, slower clearance rate, and longer mean residence time than those of remimazolam [10]. In addition, a recent trial using a 3D bioreactor system to investigate the long-term stability of remimazolam metabolism in human liver cells demonstrated that continuous infusion of remimazolam over 5 days exhibited a stable metabolism and had
After 3 h of constant rate infusion, the area under the concentration-time curve value from zero to infinity (AUC0–∞) was higher and clearance was lower in patients with severe hepatic impairment than those in normal healthy volunteers (38.1%, both). Consequently, remimazolam exposure may be increased, and elimination may be prolonged in patients with severe hepatic impairment; therefore, careful dosage adjustment is recommended for these patients [19]. However, these pharmacokinetic analyses were performed using sparse data from small populations; hence, large-scale randomized controlled studies are needed to clarify the safety profile of remimazolam in the aforementioned populations.

**Pharmacodynamics**

IV administration of remimazolam enhances the activity of γ-subunit-containing GABA<sub>A</sub> receptors, and consequently initiates cell membrane hyperpolarization and subsequent neural activity inhibition via an increase in chloride influx [20]. Similar to midazolam, remimazolam enhances GABA<sub>A</sub> currents in cells stably transfected with GABA<sub>A</sub> receptor subtypes (α1, α2, α3, or α5); it does not have clear selectivity for...
different subtypes [5]. Pharmacodynamic analyses of sedative effect of remimazolam based on various parameters such as the electroencephalogram (EEG) beta ratio, bispectral index (BIS), Narcotrend index, and Modified Observer’s Assessment of Alertness/Sedation (MOAA/S) scores [21] showed a rapid onset and offset and dose-related depth and duration of sedation (Table 2) [8–11,17,22]. In a single ascending-dose study of healthy volunteers, fast onset and dose-dependent sedation assessed by MOAA/S scores were observed after IV injection of remimazolam at a concentration of 0.5 mg or higher. In addition, 0.075–0.20 mg/kg of IV remimazolam induced more rapid peak sedation (within 1–4 min after injection) and deeper sedation than 0.075 mg/kg of IV midazolam (MOAA/S score < 2 vs. 3–4, respectively) as well as faster median recovery time (5–20 min vs. 40 min, respectively) [8]. Later, a phase I study found that a continuous remimazolam infusion (induction with 0.2 mg/kg of remimazolam over 1 min and subsequent maintenance with 1.0 mg/kg/h for 2 h) resulted in deeper sedation and more rapid recovery than those of midazolam (0.15 mg/kg over 1 min and subsequent 2-h maintenance with 0.05 mg/kg/h) [11]. Furthermore, a pharmacodynamic study involving healthy male volunteers found that the MOAA/S score quickly decreased from 5 to < 2 (i.e., full alertness to loss of consciousness) within 5 min of commencing a 35-min remimazolam infusion, and full alertness was achieved after 19 min of cessation of the infusion [10]. A recent time-to-event modeling analysis using various clinical trial data demonstrated that the non-cumulative sedative effect of remimazolam was observed for approximately 9 h even when administered during general anesthesia [23]. These results could be explained by the rapid offset and short CSHT of remimazolam [10].

1. Effects on EEG-derived hypnotic index

In modern anesthesia practice, processed EEG-based hypnotic depth indicators have been widely used to assess the sedative effect of anesthetic drugs, particularly for IV anesthetics because of greater interindividual variability than inhalation anesthetics [24]. Thus, assessment of the effects of remimazolam on EEG-derived hypnotic indices during anesthesia is a crucial practical issue.

A previous study revealed that the EEG changes after IV bolus of midazolam (0.2 or 0.3 mg/kg) were predominantly beta activation, particularly in the frontal lobe, and these resulted in BIS values remaining around 60 [25]. At present, the EEG changes produced by remimazolam have not been fully clarified. In a phase I study of 20 healthy volunteers, the EEG changes during remimazolam infusion were characterized by an initial transient power increase in the beta frequency band and a subsequent power increase in the delta frequency band; isoelectric EEG patterns or burst suppression were not evident [22].

Table 2. Summary of the Major Pharmacodynamic Parameters of Remimazolam in Healthy Volunteers

<table>
<thead>
<tr>
<th>Study (yr)</th>
<th>Study population</th>
<th>Treatment group</th>
<th>Remimazolam dose and duration</th>
<th>PD measure</th>
<th>Time to onset (min)</th>
<th>Time to peak sedation (min)</th>
<th>Mean recovery time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antonik et al.</td>
<td>Healthy volunteers (n = 72)</td>
<td>Remimazolam Midazolam Placebo</td>
<td>0.01–0.3 mg/kg 1 min</td>
<td>MOAA/S, BIS</td>
<td>≤ 1</td>
<td>1–4</td>
<td>5.5–31.5</td>
</tr>
<tr>
<td>Wiltshire et al.</td>
<td>Healthy volunteers (n = 65)</td>
<td>Remimazolam* Midazolam</td>
<td>0.01–0.45 mg/kg 1 min</td>
<td>MOAA/S, BIS</td>
<td>≤ 2</td>
<td>≤ 4</td>
<td>21.5</td>
</tr>
<tr>
<td>Zhou et al.</td>
<td>Healthy volunteers (n = 20)</td>
<td>Remimazolam Midazolam</td>
<td>5 mg/min for 5 min, followed by 3 mg/min for 15 min and 1 mg/min for 15 min</td>
<td>MOAA/S, BIS, EEG beta ratio, Narcotrend index</td>
<td>≤ 5</td>
<td>5.0 ± 1.0</td>
<td>19 ± 7</td>
</tr>
<tr>
<td>Eisenried et al.</td>
<td>Healthy volunteers (n = 62)</td>
<td>Remimazolam Midazolam Placebo</td>
<td>0.025–0.4 mg/kg (SAD study) 0.2 mg/kg/min, then 1–2 mg/kg/h (Infusion study)</td>
<td>MOAA/S, BIS</td>
<td>≤ 1</td>
<td>1–2</td>
<td>12.3–25.0</td>
</tr>
</tbody>
</table>

Data are presented as the mean ± SD or range. SAD: single ascending dose, PD: pharmacodynamics, MOAA/S: Modified Observer’s Assessment of Alertness/Sedation, BIS: bispectral index, EEG: electroencephalogram. *Remimazolam tosylate, a slightly different salt form of remimazolam, was used.
The BIS algorithm was optimized to yield an approximately linear and monotonic response to increasing doses of propofol. In contrast, the depth of sedation and the BIS index were weakly correlated for midazolam than for propofol [26]. Moreover, the databases used to develop the BIS index did not include EEG data from patients under remimazolam anesthesia. To date, the proper range of the EEG-derived hypnotic index for remimazolam anesthesia have not been clearly demonstrated [2]. Furthermore, the Narcotrend index, one of the EEG-derived hypnotic indices, exhibited a relatively weak relationship with the MOAA/S score in volunteers receiving remimazolam [22]. Consequently, further studies investigating the characteristics of EEG induced by remimazolam and the effects of remimazolam on EEG-derived hypnotic indices are required to determine appropriate levels of hypnosis during anesthesia and sedation with remimazolam.

Target-controlled infusion (TCI)

Target-controlled infusion is a method of infusing IV drugs while maintaining a user-defined predicted drug concentration. It has been used for more than two decades in clinical anesthesia practice to administer hypnotics and opioids [27]. In particular, TCI is a well-established technique for propofol sedation and anesthesia. The TCI system is also available for administration of remifentanil, an ultra-short-acting drug, even if the benefit of TCI is less obvious compared to that of manual infusion [28]. There is also a controversy about TCI application to remimazolam, another ultra-short-acting drug with a short half-life, high clearance, and $V_{\text{ss}}$ which would usually be titrated by adjusting the infusion rate [22,29].

However, a previous trial revealed that in simulations of TCI with several anesthetics, steady-state concentration after remimazolam infusion and propofol infusion was achieved after approximately 60 min and more than 60 min, respectively, whereas it took approximately 10 min after remifentanil infusion [22]. These findings indicate that the clinical application of TCI for the administration of remimazolam would be reasonable and beneficial [22,29]. In principle, pharmacokinetic/pharmacodynamic (PK/PD) parameters estimated using a multi-compartment mammillary model are required to administer drugs via the TCI method using the currently available equipment [29]. A PK/PD model for remimazolam using a multi-compartment mammary model has been introduced. However, this model has been developed in 20 healthy male volunteers only [10,22]. The PK/PD model only applies when the clinical conditions and patient characteristics match those of the subjects in the model development group. Consequently, the above-mentioned model is also not suitable for administration of remimazolam via the TCI method in various surgical populations [10,22]. Even though a population PK/PD model using a multi-compartment mammillary model was constructed in surgical patients, this model is not suitable for the currently available TCI system because the clearance parameter was estimated to change over time [30]. Therefore, new compartmental PK/PD models should be developed in diverse populations and clinical settings for wide applications of TCI to administer remimazolam.


**CLINICAL APPLICATIONS OF REMIMAZOLAM**

**Remimazolam for procedural sedation**

Procedural sedation is used to allow effective completion of diagnostic or therapeutic procedures that may be uncomfortable for patients or painful [31]. It is thought that ideal characteristics of the hypnotic agents used for procedural sedation include fast onset of action and recovery, minimal residual sedation, ease of use, and few adverse effects [7]. The major characteristics of three widely used sedatives in modern anesthesia practice are summarized in Table 3. BDZ sedatives, including midazolam that is considered to be the gold standard, have been frequently used because of their faster onset and high amnestic potential. However, active metabolite of midazolam is a potent sedative [7] that may prolong the sedation time. In contrast, remimazolam has a rapidly hydrolyzed ester linkage that produces an inactive metabolite; therefore, it seems to be an ideal sedative in terms of minimal residual sedation and organ-independent metabolism.

In comparison to midazolam, remimazolam as a sedative for procedural sedation (typically supplemented by an opioid) produces rapid-onset sedation and clear-headed recovery with low liability for blood pressure perturbation and respiratory depression [7,32–34]. In a phase III study comparing the efficacy and safety of remimazolam with those of midazolam, a total of 461 patients who underwent colonoscopy were randomly assigned to one of the three study arms (5 mg remimazolam with supplementary doses of 2.5 mg remimazolam, midazolam, or placebo plus midazolam res-
Procedural success was defined as the completion of colonoscopy without a rescue sedative; it was achieved in 91.3, 25.2, and 1.7% of patients receiving remimazolam, midazolam, and placebo plus midazolam rescue, respectively. In addition, compared with those who received midazolam, fewer patients who received remimazolam experienced hypotension and showed faster recovery. These findings indicate that remimazolam can be administered safely for procedural sedation, and it permits fast recovery of neuropsychiatric function compared with midazolam.

Propofol is another sedative frequently used for procedural sedation. Although it has a rapid onset of action and a very short half-life, it precipitates more adverse events, notably possible hypotension, respiratory depression, bradycardia, and pain upon injection. Therefore, there is a need for safer sedatives while ensuring their efficacy [35]. Clinical studies comparing efficacy and safety of remimazolam vs. propofol for procedural sedation suggested that remimazolam was non-inferior in terms of sedative efficacy and exhibited better safety profile than that of propofol [32,34,36]. Chen et al. [32] demonstrated that the procedure success rate in the remimazolam group was similar to that in the propofol group (96.91% vs. 100%, respectively) in 384 patients who underwent colonoscopy [32]. The safety assessment revealed that the total number of adverse events was lower in the remimazolam group than in the propofol group; in particular, injection site pain, increased bilirubin, decreased respiratory rate, and hypoxia were less frequent in patients receiving remimazolam. Similar findings were reported in another non-inferior study performed on patients who underwent upper gastrointestinal endoscopy [34]. In summary, remimazolam and propofol had similar success rates for sedation, but remimazolam had a more favorable safety profile than that of propofol.

In addition, a patient’s physical status affects safety and recovery from procedural sedation; a higher American Society of Anesthesiologists (ASA) physical status classification is associated with a higher risk of adverse periprocedural events [37]. A randomized trial involving patients who underwent high-risk colonoscopy found that the efficacy and safety data of remimazolam for procedural sedation of high-risk ASA patients were comparable to those with low-risk ASA [38]. These results indicate remimazolam to be equally efficient and safe for procedural sedation in patients with low- and high-risk ASA.

Taken together, remimazolam can be used as a safe and effective alternative to other widely-used sedatives, such as midazolam and propofol, for IV sedation in patients undergoing various procedures. Further clinical studies with respect to the quality of patient experience, new formulations (for example, intranasal or inhalation), and post-market cost-benefit analyses are important factors in acquiring the widespread use of remimazolam in procedural sedation.

### 1. Dosage and administration

To induce and maintain procedural sedation in adults, remimazolam dosage should be titrated and individualized to achieve the desired clinical response. IV remimazolam was used at a dose of 5 mg over 1 min for induction. Supplemental IV doses of remimazolam (2.5 mg) over 15 s with ≥ 2 min between doses can be given, if required. The recommended dosage should be reduced in patients with ASA class III/IV as follows: an induction dose of 2.5–5 mg remimazolam and top-up doses of 1.25–2.5 mg on the basis of patient’s general condition and at the physician’s discretion [39,40].

### Table 3. Major Characteristics of Propofol, Midazolam, and Remimazolam as Intravenous Hypnotics for Anesthesia and Sedation

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Propofol</th>
<th>Midazolam</th>
<th>Remimazolam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ready-to-use injectable formulation</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Free from pain on injection</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Free from liability for cardiovascular and respiratory depression</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Active metabolite</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Availability of a reversal agent</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Short context-sensitive half-time</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Onset (min)</td>
<td>&lt; 1</td>
<td>3–5</td>
<td>1–2</td>
</tr>
<tr>
<td>Recovery (min)</td>
<td>10</td>
<td>20–80</td>
<td>10–40</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic/extrahepatic</td>
<td>Hepatic</td>
<td>Hydrolysis by tissue esterase</td>
</tr>
<tr>
<td>Protein binding (%)</td>
<td>98</td>
<td>97</td>
<td>92</td>
</tr>
</tbody>
</table>

+ and – represent the presence and absence of the relevant characteristics, respectively.
The prescribing information for remimazolam specifies cautions related to sedation, such as hypoxia, bradycardia, and hypotension [40]. Accordingly, remimazolam should typically be administered by personnel trained in the administration of procedural sedation. Before administration of remimazolam, drugs, personnel, and equipment for monitoring and resuscitation should be prepared. Continuous monitoring of vital signs must be performed during procedural sedation and during the entire recovery period.

**Remimazolam for general anesthesia**

The introduction of remimazolam in clinical practice provides a chance to reappraise BDZ as a principal anesthetic for general anesthesia. IV remimazolam, which was used as the hypnotic component of total intravenous anesthesia (TIVA), was as effective as propofol and showed superior safety profile for the induction and maintenance of general anesthesia in surgical patients with ASA class I/II [41]. Remimazolam (6 or 12 mg/kg/h IV infusion, n = 150 or 150, respectively) was administered for induction followed by 1 mg/kg/h of initial maintenance dose. A third group of patients received a standard dose regimen of IV propofol (2.0–2.5 mg/kg/h, followed by 4–10 mg/kg/h) (n = 75). All patients were administered 0.25–0.5 µg/kg/min of remifentanil during the entire study period. The primary efficacy endpoint, defined as no rescue sedative requirement, absence of intraoperative awakening or recall, and no body movement, was accomplished in all three groups of patients, thereby achieving noninferiority. The mean time to loss of consciousness and time to extubation were significantly longer for patients treated with remimazolam than in patients treated with propofol (102.0 s for 6 mg/kg/h remimazolam and 88.7 s for 12 mg/kg/h remimazolam vs. 78.7 s for propofol, and 19.2 and 19.2 min vs. 13.1 min, respectively) [41]. In contrast, compared with propofol, remimazolam regimens exhibited excellent safety profile. The patients in the remimazolam groups (35.3% and 34.7%, respectively) experienced fewer hypotensive-specific events than those in the propofol group (60.0%). Fewer patients in the remimazolam groups needed vasopressors (40.0% and 42.7%, respectively) or treatment for bradycardia (6.0% and 6.7%, respectively) than in the propofol group (64.0% required vasopressors and 9.3% required treatment for bradycardia).

Subsequent randomized comparative trials confirmed that remimazolam would be a more useful agent as the hypnotic component of TIVA, particularly when used for clinically vulnerable patients. Interestingly, both induction regimens (6 and 12 mg/kg/h) were equally efficient and safe in 67 high-risk surgical patients [42]. In addition, an unpublished clinical study comparing remimazolam with propofol suggested that remimazolam had better hemodynamic stability and similar hypnotic efficacy in 90 high-risk patients undergoing major cardiac surgery [43]. The induction dosages were 6 or 12 mg/kg/h of IV remimazolam (n = 34 and 28, respectively), followed by maintenance dose of 1–3 mg/kg/h. Another group received an induction dosage of 2–2.5 mg/kg IV propofol, and was maintained using inhaled sevoflurane (until the start of extracorporeal circulation) and propofol (during extracorporeal circulation) (n = 28). The primary endpoint (no requirement for an additional sedative) was achieved in 98% of patients administered remimazolam and 96% of those administered propofol. Onset (time to loss of consciousness) and offset (time to extubation) of action were similar in all study groups. Patients who received remimazolam required significantly less dose of noradrenaline than those who were anesthetized using propofol-sevoflurane.

Taken together, early reported clinical data suggest that remimazolam has excellent efficacy and safety profile as a hypnotic component of balanced anesthesia. Notably, at present, a principal reason for considering remimazolam as a hypnotic underpinning of general anesthesia may be its superior hemodynamic stability. However, to gain widespread use, additional clinical studies investigating postoperative delirium and postoperative nausea and vomiting (PONV) and pharmacological interaction with opioid analgesics are required. These clinical data would further help to clarify remimazolam characteristics as an IV anesthetic.

1. **Dosage and administration**

The licensed prescribing information of remimazolam for use in general anesthesia specifies an initial dose of 6 or 12 mg/kg/h for induction, followed by 1 mg/kg/h (2 mg/kg/h of maximal infusion rate) for maintenance. The maintenance infusion rate should be adjusted based on the patient’s general condition and sedation level.

To date, there have been no published clinical trials of bolus administration of remimazolam to induce anesthesia; thus, bolus administration is not currently recommended for general anesthesia. Therefore, future trials on bolus remimazolam injection for induction of general anesthesia are warranted to establish more practical administration methods [44].
Remimazolam for intensive care unit (ICU) sedation

Because ICU patients are critically ill with essential organ failure (hepatic or renal), the ideal drug of choice in such a scenario would be a short-acting agent with metabolism independent of the liver or kidney. In this respect, remimazolam could theoretically be a promising drug for long-term sedation in ICU patients due to its favorable properties of organ-independent metabolism, minimal accumulation, and availability of a reversal drug [1].

Currently, there is no published clinical evidence on the potential utility of remimazolam in ICU sedation. Several trials are ongoing to investigate the feasibility of long-term sedation with remimazolam in critically ill patients (NCT04611425 and NCT04815265).

Flumazenil reversal

The hypnotic effect of remimazolam can be reversed using flumazenil, which is an antagonist of the positive allosteric modulator effects of BDZs. However, reversal is not possible for several other hypnotics, including propofol [1]. Reversal of the sedative effect of remimazolam by flumazenil has been well described in several previous studies [6,41]. For instance, after successive sedation (MOAA/S ≤ 3) with 0.25 mg/kg of IV remimazolam in healthy volunteers who underwent colonoscopy, the median (range) time until the subjects were fully alert (3 consecutive MOAA/S scores of 5) was shorter for patients receiving flumazenil (0.5 mg) than for patients in the placebo group (1.0 [1–5] vs. 10.5 [5–52] min, respectively).

To reverse the hypnotic effect of BDZs, 0.2 mg flumazenil is recommended as an initial dose; it should be slowly injected over a 15-s period to avoid possible adverse events (hypertension, tachycardia, and anxiety). If the desired level of consciousness is not achieved after 60 s of the initial dose, a second dose of 0.2 mg can be injected and repeated at 60-s intervals up to a maximum of four additional times and a maximum total dose of 1 mg. Subsequently, the dosage should be administered according to the patient’s response. If re-sedation occurs, repeated doses may be administered at 20-min intervals. For repeated treatment, no more than 1 mg should be administered at any one time, and no more than 3 mg should be injected during any 1-h period [45,46].

Clinicians should keep in mind that unlike the relationship between rocuronium and sugammadex, the mechanism of action of flumazenil against BDZs is merely based on competitive antagonism and that flumazenil has a short terminal half-life of 40–80 min [47,48]. As the plasma flumazenil concentration decreased, the hypnotic effect of remimazolam could re-emerge. Accordingly, after administration of flumazenil, patients should be monitored for re-sedation, respiratory depression, and other persistent or recurrent hypnotic effects for a sufficient time period. In practice, routine administration of flumazenil to reverse remimazolam-induced sedation is not recommended because of the likelihood of rebound sedation [49,50].

Safety concerns and future directions

Adverse reactions associated with remimazolam during procedural sedation and anesthesia settings are well documented in various clinical studies, which are in accordance with those observed with other classical BDZs. The most common beings are blood pressure and heart rate changes, nausea, and vomiting [33,41]. Additional adverse events include headache, somnolence, and hypoxia [8]. In addition, results of a cardiac electrophysiology study showed that cardiac repolarization is not prolonged by remimazolam, even if a transient heart rate increase may result from a small increase in the QTc interval [51].

When compared with propofol in both sedation and general anesthesia, remimazolam exhibited better safety profile, including a lower incidence of hypotension, less bradycardia treatment requirement, and no pain on injection [34,36,41]. However, propofol was less likely to develop PONV.

Another safety issue related to the administration of hypnotics is drug abuse or potential misuse [52]. One study investigating the abuse potential of remimazolam demonstrated that it has a comparable or lower abuse potential than that of midazolam, which is known to be a drug with a low potential for IV abuse [53].

The solubility of remimazolam decreases at pH > 4.0; therefore, the package insert instructions specify that it should not be dissolved in an alkaline solution. Accordingly, Ringer’s lactate should not be used as a solvent because the drug does not dissolve completely in solution and forms a precipitate [40]. Sasaki et al. [54] reported the formation of white precipitates related to the combined use of remimazolam and Ringer’s solution, and examined the effect of remimazolam concentration on precipitate formation. In this experimental study, both types of Ringer’s solution (Ringer’s lactate [pH 5.9–6.2] and Ringer’s acetate [pH 6.0–
formed precipitates with remimazolam. In addition, the authors suggested that if combined use is unavoidable, lower remimazolam concentrations and higher Ringer’s solution infusion rates are recommended to prevent precipitate formation.

Although there are several ongoing trials for the potential use of remimazolam in various clinical settings in pediatric patients (NCT04720963, NCT04851717, and NCT04601350), their safety and effectiveness have not yet been established. Therefore, to date, remimazolam for both general anesthesia and sedation is not available in pediatric population.

At present, limited data are available to characterize remimazolam comprehensively as a hypnotic, even though several volunteer studies and clinical trials suggest that remimazolam is well tolerated and effective for procedural sedation and induction and maintenance of general anesthesia. So yet, to ensure patient safety, the careful introduction of this novel hypnotic agent is needed in clinical practice. Future trials with regard to pharmacological interaction with concomitant anesthetics, new formulations, safety profiles in the special population, characteristics of the EEG changes, bolus administration for the induction of anesthesia, PONV, postoperative cognitive impairment, and post-market cost-benefit analyses would be essential for the comprehension of the complete profile of remimazolam.

CONCLUSION

Remimazolam is a novel ultra-short-acting hypnotic agent invented out of ‘a soft drug’ development. Its primary benefits include rapid onset/offset, predictable duration of action, metabolism almost unaffected by organ function, availability of a reversal drug, and maintenance of stable hemodynamics, making it a potential drug for use in various clinical practices. However, further clinical studies are essential to comprehensively evaluate the efficacy and safety profile of this drug before its extended application in various clinical settings.

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CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

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INTRODUCTION

Epidural blood patch (EBP) is the injection of autologous blood into the epidural space with the intent of sealing off a dural tear and stopping the leakage of cerebrospinal fluid (CSF) [1]. EBP may cause an increase in intracranial pressure due to the mass effect of the injected blood volume, causing CSF from the spinal compartment to enter the intracranial compartment [2].

The first EBP, performed with 2–3 ml of blood, was reported by Gormley [3] in 1960 after the observation that bloody taps were associated with reduced post-dural puncture headache (PDPH) [4,5]. Since then, the technique of EBP has undergone substantial modifications. In 1980, Crawford reported [6] a success rate of 70% using 6–15 ml of blood, compared with 96% when a larger volume of 20 ml was used [4].

Conservative treatment for the first 24–48 h is considered the initial management strategy for headache (HA) attributed to low CSF pressure because more than 85% of such HAs resolve with conservative treatment [7]. Conservative treatment measures include bed rest, intravenous hydration, caffeine supplementation, and analgesics [7,8]. EBP is usually considered in the treatment of moderate to severe HA attributed to low CSF pressure that does not respond to conservative management [8]. According to the International Classification of Headache Disorders, 3rd edition (ICHD-3), HA attributed to low CSF pressure is described as orthostatic...
HA caused by low CSF pressure (either spontaneous or secondary) or CSF leakage, usually accompanied by neck pain, tinnitus, changes in hearing, photophobia, and/or nausea. It remits after normalization of CSF pressure or successful sealing of the CSF leak. Diagnostic criteria are described in Table 1. PDPH, CSF fistula HA, and HA attributed to spontaneous intracranial hypotension (SIH) are subcategories of HA attributed to low CSF pressure.

As pain management is his sub-specialty, the author encounters numerous patients with intractable PDPH and SIH in his practice. Dramatic improvement in such cases is observed with EBP. Although many studies on PDPH and SIH have been conducted until recently, only few reviews have summarized the effectiveness of EBP from the perspective of a pain physician.

Therefore, in this review, the author will summarize the current concepts regarding the indications, mechanisms, technical considerations, outcomes, adverse effects, contraindications, and alternatives to EBP and the peculiarities of EBP during the coronavirus disease 2019 (COVID-19) pandemic.

PATHOPHYSIOLOGY OF HEADACHE ATTRIBUTED TO LOW CSF PRESSURE

The dura mater is a dense, connective tissue layer made up of collagen and elastic fibers. The classical description of the spinal dura mater is that it is made up of collagen fibers running in a longitudinal direction. However, recent light and electron microscopic studies of human dura mater have contested this classical description [9]. These recent studies describe the dura mater as consisting of collagen fibers arranged in several layers parallel to the surface. Each layer consists of both collagen and elastic fibers that do not demonstrate specific orientation. The outer or epidural surface may indeed have dural fibers arranged in a longitudinal direction, but this pattern is not repeated through successive dural layers. Recent measurements of dural thickness have also demonstrated that the posterior dura varies in thickness and that the thickness of the dura at a particular spinal level is not predictable within an individual or among individuals. Perforation in a thick area of dura may be less likely to lead to CSF leak than perforation in a thin area, and this may explain the unpredictable consequences of dural perforation [9].

The choroid plexus secretes more than 75% of the CSF; the rest is secreted by the brain capillaries entering the ventricles via the ependyma [5]. The rate of CSF formation, in contrast to its volume, is fairly constant (0.35 ml per minute or approximately 500 ml per 24 h in adults) [5,8–10]. CSF is absorbed by arachnoid villi into the cerebral venous sinuses and veins via a valve-like mechanism called bulk flow [5,10]. A minor portion of the CSF is absorbed into the cerebral vessels by simple diffusion, and another small portion is likely absorbed via the lymphatics of the cribriform plate region into the nasal submucosa [10]. Old autopsy data estimated the total volume of CSF as approximately 150 ml [10]. In the horizontal position, CSF pressures at the lumbar, cisternal, and presumably intracranial or vertex levels are equal, measuring approximately 65–195 mmH$_2$O [10,11]. On assuming the erect position, the vertex pressure becomes negative, while the lumbar pressure increases to over 400 mmH$_2$O [9,11]. The relationship between CSF pressure and volume is exponential. Withdrawal of approximately 10% of CSF will decrease the already negative vertex pressure in the upright position by more than 40% [5,10]. If a lumbar duraplasty is so large that CSF leak is greater than CSF production, the CSF pressure will drop. Orthostatic HA is thought to occur if more than 10% of the total CSF volume is lost [5,9].

<table>
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<tr>
<th>Table 1. Diagnostic Criteria for 7.2 Headache Attributed to Low Cerebrospinal Fluid Pressure</th>
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<tr>
<td>A. Any headache* fulfilling criterion C</td>
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<tr>
<td>B. Either or both of the following:</td>
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<td>1. Low CSF pressure (&lt; 60 mmH$_2$O CSF)</td>
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<td>2. Evidence of CSF leakage on imaging$^1$</td>
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<tr>
<td>C. Headache has developed in temporal relation to the low CSF pressure or CSF leakage, or led to its discovery$^2$</td>
</tr>
<tr>
<td>D. Not better accounted for by another ICHD-3 diagnosis</td>
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CSF: cerebrospinal fluid, ICHD-3: International Classification of Headache Disorders, 3rd edition, MRI: magnetic resonance imaging, CT: computed tomography, *7.2 Headache attributed to low cerebrospinal fluid pressure is usually but not invariably orthostatic. Headache that significantly worsens soon after sitting upright or standing and/or improves after lying horizontally is likely to be caused by low CSF pressure, although this cannot be relied upon as a diagnostic criterion. $^1$Brain imaging showing brain sagging or pachymeningeal enhancement, or spine imaging (spine MRI, or MRI, CT or digital subtraction myelography) showing extradural CSF. $^2$Evidence of causation may depend upon onset in temporal relation to the presumed cause, together with exclusion of other diagnoses.
Two possible explanations for the mechanism of HA due to CSF leak are brain sagging and compensatory dilatation of intracranial veins. First, the lowering of CSF pressure causes traction on the intracranial structures in the upright position. The pain-sensitive nature of these structures leads to the characteristic HA [5]. Second, the loss of CSF produces compensatory venodilatation vis-à-vis the Monro-Kellie doctrine [1,5,9,11,12]. The Monro-Kellie doctrine states that the sum of the volumes of the brain, CSF, and intracranial blood is constant. A decrease in CSF volume results in a compensatory increase in blood volume under conditions of unchanged intracranial volume [1,5]. Dilation of the intracranial arteries and veins is a key pathogenetic link in the occurrence and development of HA [9,12]. The beneficial effects of vasoconstrictor drugs, such as caffeine and theophylline, support this mechanism [7].

INDICATIONS

Indications for EBP are PDPH, CSF fistula, SIH, chronic daily HA with postural component, and CSF leak after spinal or thoracic surgery.

Post-dural puncture headache

PDPH occurs occasionally after spinal anesthesia, myelography, diagnostic lumbar puncture, and accidental dural puncture (ADP) during epidural anesthesia [8,13]. The overall incidence of PDPH after neuraxial procedures varies from 6% to 36% [8]. Studies have found that 90% of these HAs occur within 3 days of the procedure, and 66% start within the first 48 h [5,9,14]. A postural component may not be present in up to 5% of cases of PDPH [4,5]. Furthermore, in one-third of cases, dural puncture may not have been recognized [4]. Although more than 90% of PDPHs are self-limiting and resolve spontaneously in 7 to 10 days [1,14], long-term complications of PDPH may include chronic HA, hypoacusis, diplopia, sinus thrombosis, and subdural hematoma [8,15]. Moreover, in severe cases, it can cause cerebral herniation and even death if not treated promptly [1,4,5,16,17].

According to the ICHD-3, PDPH was previously called post-lumbar puncture HA and is described as HA occurring within 5 days of a lumbar puncture, caused by CSF leakage through the dural puncture [4,5,18]. The diagnostic criteria for PDPH are listed in Table 2. It is usually accompanied by neck stiffness and/or subjective hearing symptoms [18]. However, recent studies indicate that PDPH mostly occurs within 3 days after dural puncture [6-8], and up to 29% of patients have HA as the only symptom [7]. It remits spontaneously or after sealing of the leak with autologous epidural lumbar patch [4,5]. Rarely, the HA may last for months or even years [7,18]. HA is the predominant, but not ubiquitous, presenting complaint. It is described as severe, “searing and spreading like hot metal.” The common distribution is over the frontal and occipital areas, radiating to the neck and shoulders [5,18]. The pain is exacerbated by head movement and adoption of the upright posture and relieved by lying down [8]. An increase in severity of the HA on standing is the sine qua non of PDPH [9]. Cranial nerve (CN) involvement (vestibulocochlear nerve [CN8] involvement [manifesting as isolated tinnitus, hearing loss, and others] and abducens nerve [CN6] palsy [presenting as diplopia]) can also occur [1,18]. Early administration of an EBP within 24 h of the onset of abducens nerve palsy may be associated with better outcome.

Independent risk factors for PDPH have recently been demonstrated, namely female sex, young age, pregnancy, vaginal delivery, previous history of PDPH, and previous history of chronic HA [1,5,7,8,14,18]. Obesity does not increase the risk of PDPH after ADP [7,13,18]. Reintroducing the stylet before removing the spinal needle has been recommended to reduce the risk of an arachnoid strand being pulled out through the puncture site and thus reduce the risk of PDPH [5].

The incidence of PDPH has been reported to be associated with needle size, needle orientation, needle design, surgeon skill level, and fatigue. Large spinal needles will clearly produce large dural perforations, with high likelihood of PDPH. Conversely, smaller needles produce smaller dural perforations with a lower incidence of HA [8,9,14]. However, fine-gauge spinal needles (29 G or smaller) are technically more difficult to use and, for spinal anesthesia at least, are associated with a high failure rate [9]. A balance must therefore be struck between the risks of PDPH and technical failure; hence, 25 G, 26 G, and 27 G needles probably represent the optimal needle size for spinal anesthesia [9]. There are

Table 2. Diagnostic Criteria for 7.2.1 Post-dural Puncture Headache
| A. Headache fulfilling criteria for 7.2 Headache attributed to low cerebrospinal fluid pressure, and criterion C below |
| B. Dural puncture has been performed |
| C. Headache has developed within 5 days of the dural puncture |
| D. Not better accounted for by another ICHD-3 diagnosis |

many clinical and laboratory studies that lend credence to the hypothesis that perpendicular orientation of the bevel of a spinal or epidural needle leads to reduction in the incidence of PDPH. The Quincke type spinal needle is reported to be more associated with PDPH than the Whitacre, Sprotte, and Atraucan types [8,9]. Nevertheless, Cochrane Database of Systematic Reviews about the needle tip gauge and tip designs for preventing PDPH reported that the use of traumatic needles was associated with a higher risk of PDPH than the use of atraumatic needles, although large and small gauges showed no significant difference in terms of the risk of PDPH regardless of whether a traumatic or atraumatic needle was used [8,19]. ADP during epidural anesthesia is a more common cause of PDPH. During epidural needle placement, ADP occurs at a rate of 1.5%, and around 50% of these patients develop PDPH [5,7]. It has been suggested that the incidence of ADP during epidural anesthesia is inversely related to surgeon experience [5]. However, sleep deprivation, surgeon fatigue, and the effect of night work may be the confounding variables producing the higher incidence of ADP in association with junior personnel performing epidural anesthesia [9].

Imaging techniques for detecting CSF leak, such as brain/spinal magnetic resonance imaging (MRI), computed tomography (CT) myelography, magnetic resonance (MR) myelography, and radioisotope cisternography, may be helpful. Brain MRI with contrast enhancement may reveal pachymeningeal enhancement, subdural fluid collection, brain sagging, and pituitary hyperemia [4,9]. Diagnostic lumbar puncture may demonstrate low CSF opening pressure or a “dry tap,” slightly elevated CSF protein, and elevated CSF lymphocyte count [9].

PDPH should be differentially diagnosed with serious pathology, such as infection, pre-eclampsia, cerebral venous thrombosis, intracranial tumor, intracranial hemorrhage, pituitary apoplexy, uncal herniation, migraine, non-specific HA, and pneumocephalus [1,5,8,9]. In case of a HA persisting for a month after a lumbar puncture, despite the use of all therapeutic options, another etiology of HA must be considered [1]. Moreover, PDPH may worsen the clinical course of a previous chronic HA [1].

In the management of PDPH, hydration and bed rest are commonly used for conservative treatment. However, no evidence has been found to suggest that routine bed rest after ADP is beneficial for preventing PDPH. Furthermore, bed rest has been found to likely increase the risk of PDPH compared with early ambulation [5]. There is also no evidence to support the benefit of prophylactic fluid supplementation [1,5,7]. Intravenous and parenteral caffeine can however reduce the pain temporarily [5]. Moderate to severe PDPH that has been refractory to conservative measure is a main indication for EBP. Factors that influence the decision to perform EBP are the severity of HA, response to medical treatment, degree of incapacitation by the HA, and nature of the patient’s activity. Therapeutic EBP after epidural anesthesia should be delayed until after 24 h of trying conservative treatment because the high failure rate associated with early administration of EBP has been attributed to interference due to clot formation resulting from the use of local anesthetics [5]. If EBP is to be performed early, it would be better to delay it until the neuraxial blockade has regressed completely, to avoid unpredictable cephalad spread of the local anesthetics due to epidural pressure surge transmitted to the CSF compartment. EBP still remains the gold standard for treatment of PDPH, with complete relief of symptoms in 32% of cases and partial relief in 73% [5].

An updated Cochrane review has concluded that there is insufficient evidence to support the performance of prophylactic epidural blood patching (PEBP) [5,9,14,18]. Studies in vitro have shown that both lidocaine and CSF have a detrimental effect on coagulation. High concentration of lidocaine causes hypocoagulability and fibrinolysis, whilst CSF has both procoagulant and clot-destabilizing effects [4]. Moreover, PEBP should be performed after full recovery of sensation to prevent accidental total spinal anesthesia [7].

Cerebrospinal fluid fistula headache

According to the ICHD-3, CSF fistula HA is described as orthostatic HA occurring after a procedure or trauma that causes persistent CSF leakage, resulting in low ICP [1]. It re-emits after successful sealing of the CSF leak. Diagnostic criteria for CSF fistula HA are listed in Table 3. Evidence of low CSF pressure (< 60 mmH2O) and evidence of CSF leakage on CT or MR myelography or radionuclide cisternography are needed to make the diagnosis [1]. EBP may be used to manage CSF fistula that complicates long-term intrathecal catheters inserted for the drainage of CSF after neurosurgical procedures or for the administration of intrathecal medications [20–22].

Spontaneous intracranial hypotension

SIH is actually a misnomer, as the majority of patients with
the condition have opening CSF pressures within the normal range. SIH results from non-iatrogenic CSF hypovolemia due to CSF leakage from the spinal canal, rather than CSF hypotension [23–26]. The incidence has been estimated to be around 5/100,000 per year, peaking around the fourth or fifth decade of life and being slightly more common in women (female to male ratio, 3:2) [11,23,25–30]. However, mis- and under-diagnosis of the condition are common, and its actual incidence would be considerably greater [26,27,29]. Spontaneous CSF leak is considered a disorder with a variety of clinical manifestations and imaging features, sometimes quite different from what may be seen after dural puncture [10].

According to the ICHD-3, HA attributed to SIH was previously called HA attributed to spontaneous low CSF pressure or primary intracranial hypotension, low CSF-volume HA, and hypoliquorrhoeic HA. It is described as orthostatic HA caused by low CSF pressure of spontaneous origin [24]. It is usually accompanied by neck stiffness, subjective hearing symptoms, nausea, and vomiting [23]. The diagnostic criteria for SIH are listed in Table 4. The diagnosis of SIH cannot be made in a patient who has undergone lumbar puncture in the past month [1].

The most common causes of spontaneous spinal CSF leaks include fragile meningeal diverticula usually associated with nerve root sleeves (42%), ventral dural tears often caused by calcified disk protrusions or osteophytes (27%), and CSF-venous fistulas (3%) [24,27]. Heritable connective tissue disorders, such as Marfan syndrome or Ehlers-Danlos syndrome, may predispose patients to the formation of meningeal diverticula [24,28]. Therefore, patients with CSF leaks should be screened for connective tissue and vascular abnormalities. Skull-base leaks are rare in SIH [10,11,24].

SIH patients can present with orthostatic HA (92%), nausea and vomiting (54%), posterior neck pain (43%), dizziness (27%), hypoacusis (28%), tinnitus (20%), vertigo (17%), diminished vision (14%), photophobia (11%), and, sometimes, decreased level of consciousness (15%) [10,11,25,26,28]. Often, the onset of HAs is sudden, and some patients can recall the specific day or even moment when the HAs started [27]. HA is frequently occipital, frontal, or diffuse [26]. On physical examination of SIH patients, maneuvers that increase intra-abdominal pressure will improve their HA or other symptoms. In one study, 8% of patients had non-orthostatic HA and 3% did not experience HA [26]. Therefore, not all orthostatic HAs are due to CSF leaks, and not all HAs in people with CSF leaks are orthostatic [25,26]. Moreover, with chronicity, the orthostatic nature of the HA may diminish [10].

The differential diagnosis of SIH may include a primary HA disorder, such as new daily persistent HA, or secondary causes of SIH, including subarachnoid hemorrhage, carotid or vertebral artery dissection, cerebral venous thrombosis, benign intracranial hypertension, post-traumatic HA, and meningitis [25,28]. Postural tachycardia syndrome and cervicogenic HA with postural changes in the neck can be confused with SIH [25,28].

Imaging techniques for detecting the CSF leak are brain/spinal MRI, CT myelography, MR myelography, and radioisotope cisternography [1]. The best tool for diagnosing SIH is brain MRI with contrast enhancement [23]. MRI may reveal diffuse pachymeningeal enhancement (73%), venous engorgement (57%), brain sagging (43%), subdural fluid collection (35%), and pituitary hyperemia (38%) in SIH [1,10,11,23,24,26,27]. Pachymeningeal enhancement is a diffuse meningeal enhancement with gadolinium and a hall-

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<th>Table 3. Diagnostic Criteria for 7.2.2 Cerebrospinal Fluid Fistula Headache</th>
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<tbody>
<tr>
<td>A. Headache fulfilling criteria for 7.2 Headache attributed to low cerebrospinal fluid pressure, and criterion C below</td>
</tr>
<tr>
<td>B. A procedure has been performed, or trauma has occurred, known sometimes to cause persistent CSF leakage (CSF fistula)</td>
</tr>
<tr>
<td>C. Headache has developed in temporal relation to the procedure or trauma</td>
</tr>
<tr>
<td>D. Not better accounted for by any other ICHD-3 diagnosis</td>
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<th>Table 4. Diagnostic Criteria for 7.2.3 Headache Attributed to Spontaneous Intracranial Hypotension</th>
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<tbody>
<tr>
<td>A. Headache fulfilling criteria for 7.2 Headache attributed to low cerebrospinal fluid pressure, and criterion C below</td>
</tr>
<tr>
<td>B. Absence of a procedure or trauma known to be able to cause CSF leakage*</td>
</tr>
<tr>
<td>C. Headache has developed in temporal relation to occurrence of low CSF pressure or CSF leakage, or has led to its discovery†</td>
</tr>
<tr>
<td>D. Not better accounted for by any other ICHD-3 diagnosis</td>
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</table>

CSF: cerebrospinal fluid, ICHD-3: International Classification of Headache Disorders, 3rd edition, MRI: magnetic resonance imaging. *7.2.3 Headache attributed to spontaneous intracranial hypotension cannot be diagnosed in a patient who has had a dural puncture within the prior month. †Dural puncture to measure CSF pressure directly is not necessary in patients with positive MRI signs of leakage, such as dural enhancement with contrast.
mark of SIH. The meningeal enhancement involves the pachymeninges but spares the leptomeninges [9,10,23]. Approximately 10% of patients with SIH have normal brain imaging [24–26]. As the symptoms of SIH persist, there is a notable reduction in MRI findings: dural enhancement and HA symptoms were observed on an average for 15 weeks in one study [28]. Spinal imaging, such as MRI and CT or MR myelography, is an important part of the evaluation of SIH because demonstration of epidural leakage of CSF confirms the diagnosis, and may also direct treatment efforts. In studies for the definitive location of CSF leak on CT or MR myelography, the most common leak location was the thoracic spine (41%), followed by the cervicothoracic junction (25%), the cervical spine (14%), and the lumbar spine (12%) [26,28]. Leaks were reported to be multiple in 24% of cases [26]. Radionuclide cisternography is less commonly used currently due to its relative invasiveness, poor spatial resolution, and limited sensitivity and specificity and advances in cross-sectional imaging techniques [24]. The definitive location of the leak may not be established in a significant number of cases investigated with the imaging techniques mentioned above [10]. CT myelography is considered to be the gold standard for the detection of spinal CSF leaks [24,27]. However, because of its risk and invasiveness, brain and spine MRI with enhancement could be performed as first-line investigations in patients with clinical suspicion of SIH [26]. Brain MRI provides a view of the sequelae of a CSF leak and is helpful for initial diagnosis, whereas spinal MRI is used primarily to locate the source of the leak [29].

A CSF opening pressure < 6 cmH$_2$O during lumbar puncture is considered to be clear evidence of abnormally low CSF pressure and can be used to establish the diagnosis of SIH [27,28]. However, it should not be used to exclude SIH. Many patients with SIH have CSF pressures that are in the normal range (6–20 cmH$_2$O), and some may even have symptomatic spinal fluid leaks with CSF pressures in excess of 20 cmH$_2$O [26–28].

The triad of orthostatic HA, diffuse pachymeningeal enhancement on MRI, and low CSF opening pressure is considered the hallmark for the diagnosis of SIH [10].

Optic nerve sheath diameter measured with transorbital sonography in supine and upright positions in patients with orthostatic HA was found to be significantly decreased, providing a novel non-invasive technique for evaluation of SIH [28,29].

In an evaluation for potential biomarkers, the CSF composition of patients diagnosed with SIH using MRI was compared with that of non-SIH patients. Two proteins, lipo-calci-n-type prostaglandin D synthase and brain-type trans-ferrin, had high sensitivity for detecting SIH [28].

Conservative treatment, which includes bed rest, hydration, and caffeine, is often advocated as first-line therapy for patients with SIH [11,27]. In 15–30% of cases, SIH resolves spontaneously or with only conservative treatment measures within 1–2 weeks from the symptom onset [11,27,28]. Medications, such as analgesics, corticosteroids, and theophylline, play only an adjunctive role in the management of SIH [27]. Moderate to severe HA associated with SIH syndrome that has been refractory to conservative measure is the main indication for EBP [10,30]. In SIH, the success rate with each EBP varies from 30% to 90% [24,28,30]. The success rate in one report was 87.1% after the first targeted EBP and 52% after the first blind EBP [24,27,28]. Many patients require more than one EBP [28,30]. A second or even third blood patch may be required at times but should alert the physician to review the differential diagnosis. The success rate of EBP for SIH is significantly less impressive than that seen in PDPH [10,31]. This difference is a consequence of several factors, including the clarity of the level and site of the leak in PDPH and the often more complex anatomy of the leak in SIH.

Complications of SIH are subdural hematoma, rebound intracranial hypertension, cerebral venous sinus thrombosis, superficial siderosis, brachial amyotrophy, and syringomyelia. CSF leaks can recur at variable intervals from previous leaks and with variable frequency; they are not uncommon, although their incidence is not well established [10].

**MECHANISM**

Mass effect and epidural plug formation have been suggested as the main mechanisms of action of EBP.

Mass effect theory posits that injection of blood into the epidural space pressurizes the spinal compartment of the subarachnoid space and causes the CSF to be displaced to the more cephalad cranial compartment [23]. Compression of the thecal space for the first 3 h and presumed elevation of subarachnoid pressure may explain the rapid resolution of the HA [9]. Pressure surge brought about by injection of blood has been demonstrated to be maintained for longer time compared with that caused by injection of crystalloids in experimental models and clinical MRI scans.

Epidural plug theory supposes that the formation of a gelatinous plug, induced by interactions between the injected...
blood and procoagulant components in leaking CSF, seals off the dural tear until the natural healing process restores the integrity of the torn dura. MRI studies have found that epidural blood adheres to the thecal sac, resulting in clot formation for 18–24 h [7]. At 7–13 h, there is clot resolution, leaving a thick layer of mature clot over the dorsal part of the thecal sac. Animal studies have demonstrated that 7 days after the administration of an EBP, there is widespread fibroblastic activity and collagen formation [9]. That is consistent with the time course of PDPH observed in clinical practice but fails to account for the rapid and often immediate relief upon receiving an EBP.

**PROCEDURAL CONSIDERATION**

Before performing an EBP, written informed consent should be obtained from the patient. Information about the EBP, including risks, benefits, and alternative treatment, must be discussed and documented [4]. The patient is positioned prone with a pillow under the chest (for cervicothoracic EBP) or abdomen (for lumbar EBP) [17]. Strict asepsis should be ensured for both collecting blood and accessing the epidural space. Double asepsis with povidone iodine and chlorhexidine-alcohol is usually recommended [17]. The epidural space is first localized with fluoroscopy, and blood is drawn from the patient by an assistant. The use of fluoroscopy promotes localization of the epidural space and is thought to reduce complications [17]. Tuohy needles of 18–20 G are usually used for epidural access.

The needle entry site for epidural access is usually determined by the known or expected location of the dural tear. Studies have shown the mean spread of 15 ml of blood to be six spinal segments cephalad and three segments caudad with a mean volume per segment of 1.6 ml [4,9]. Therefore, blood injected during an EBP preferentially spreads in the cephalad direction. For PDPH, the same interspace or one space lower is usually selected [4,14].

EBP should be performed by an experienced pain physician with the administration of contrast agent under real-time fluoroscopy to monitor the spread of the injectate. The reasons for the injection of contrast under real-time fluoroscopy are to confirm that the needle tip is in the epidural space, to detect any intravascular injection, and to therefore predict the spread of the injectate (Fig. 1). Fluoroscopy-guided targeted EBP should be employed if the primary origin of CSF leak has been determined [11,23,25,27]. EBP via an upper thoracic route should be employed if the diagnostic imaging techniques could not identify the primary origin of CSF leak in cases of SIH because the CSF leaks usually involve the cervicothoracic area. The technique for needle placement in targeted EBP is similar to that used for other epidural injections and most commonly involves either a transfornaminal or an interlaminar approach [25]. Needle placement into target dorsal or ventral epidural space and potential spread of EBP are confirmed by contrast epidurogram [25]. Fluoroscopy- or CT-guided targeted transforaminal EBP would be helpful for sealing the ventral surface of the thecal sac, where dural tears caused by disk herniations usually occur in SIH [27].

A blood volume of 20 ml is recommended for EBP via interlaminar approach [8]. Injection should stop before 20 ml has been injected if the procedure is not tolerated by the patient (evidenced by intolerable pain or neurologic deficit) [5,7,18]. Volumes of blood larger than 20 ml have been used but appear to offer no additional benefit and may increase the risk of side effects [4,18]. EBP volume was a strong predictor of EBP efficacy in both univariate and multivariate analyses, with a volume of 20 ml being most associated with an effective EBP [14,23]. Approximately 5 ml is recommended for EBP via the transfornaminal approach [25]. The recommended rate of injection is approximately 5 ml/min [23]. When the first EBP does not result in clinical benefit, a minimum interval of 5 days is recommended before another EBP to limit the risk of spinal cord compression due to excessive EBP volume [11].

**POST-PROCEDURAL MANAGEMENT**

There is insufficient evidence to recommend routine blood culture or administration of antibiotics after performing EBP. Nevertheless, EBP should not be performed if there is systemic infection.

Patients should be positioned in the supine position for 2 h after an EBP to promote clot formation at the supposed site of dural tear [1,4,23,29]. Post-procedurally, patients should avoid intense exercise, Valsalva maneuvers, and long journey for approximately 7 days. They should also avoid constipation by using laxatives. These precautions may reduce the risk of dislodgement of the blood clot covering the dural tear. In addition, patients should be told to avoid twisting and bending, and to keep their backs straight, as these measures are thought to reduce the risk of HA recurrence [4].
OUTCOME

Estimates for success rates of non-targeted EBP vary widely, with success rates of 30–70% reported for the initial epidural patch [27]. Targeted EBP may be more effective than blind EBP, with 87% of targeted EBPs achieving treatment success, compared with 56% of blind EBPs [27,29,30]. In one study, a smaller proportion of patients initially treated with targeted EBP required repeat EBP compared with those initially treated with blind EBP (21% and 61%, respectively) [30]. EBP is considered ineffective or inadequately performed if symptoms do not subside within 2 days of its administration [1]. The initial EBP is reported to be associated with a success rate of approximately 93% for inducing partial or complete relief of HA [5]. With complete relief as the target, the success rate drops to around 75% only. The success rates of the first EBP are 95% for ADP with spinal needle and 30–75% for ADP with epidural needle in PDPH. A second EBP may be considered after other causes of HA have been excluded. If the first EBP produced some improvement in symptoms but the HA recurs, a second EBP can be considered. However, in cases where the first EBP has no effect or fails to relieve the symptoms, other causes of HA must be considered, and involvement of other specialties is recommended [4]. Approximately 30% of patients require a second EBP, following which 50% experience complete relief, 36–38% experience partial relief, and 12–14% experience no relief [4,5,18].

Previous studies reported some factors associated with better outcome after EBP—older age, absence of tinnitus,
pachymeningeal enhancement, subdural fluid collection, iter > 2 mm below the incisural line (the iter being defined as the opening of the Sylvian aqueduct and incisural line along the plane extending from the anterior tuberculum sellae through the confluence of the great cerebral vein, inferior sagittal sinus, and straight sinus) on MRI, larger volume of blood ( > 20 ml), and longer time interval between dural puncture and EBP (more than 48 h) [4,23]. Sex and body mass index were found to have no correlation with response to EBP [23].

**COMPLICATIONS OF EBP**

Common adverse effects of EBP are HA, backache, neck pain, radicular irritation by blood by-products, and mild pyretic reaction [11,18]. These are usually mild and transient. The incidence of backache after EBP is reported as approximately 80%, with resolution by 4 weeks in most cases [4,18]. It is thought to be a consequence of increased pressure within the spinal canal resulting from the injection of blood [4]. Delayed radicular symptoms have also been described and may be related to irritation of the nerve roots by hemolytic by-products of the injected blood [4,18].

An important complication experienced by many patients after successful closure of a CSF leak is rebound intracranial hypertension (RIH) [27,30]. Caused by an increase in CSF pressure, this phenomenon is characterized by the development of a new HA phenotype shortly after closure of the leak site by EBP or surgery. Most commonly, HAs associated with RIH are worse when lying down and may change in location, compared with SIH. They often occur in the frontal or periorbital region, while occipital HAs are typical for SIH. Symptoms may develop rapidly after EBP or over the course of days to weeks. Treatment is typically with acetazolamide or topiramate [27]. If symptoms are severe, therapeutic lumbar puncture may help relieve them immediately. RIH is very common, although it is not usually severe and may resolve within several days in many cases [27].

Reported rare adverse effects of EBP are chronic adhesive arachnoiditis, subdural or spinal hematoma, seizure, cerebral venous sinus thrombosis, transient bradycardia, infection, intracerebral hemorrhage, facial nerve palsy, visual disturbance, incontinence, monoplegia, cerebral ischemia, cauda equina syndrome, pneumocephalus, formation of a calcific epidural mass, and scarring of the epidural space with distortion of epidural anatomy [11,18,29,30].

The failure rate of EBP is 15–20%. The incidence of dural puncture during an EBP may be less than 1% but may worsen PDPH by inadvertently creating additional dural rent(s) [4,14]. If dural puncture occurs during an EBP, it may increase the risk of intrathecal blood injection, which can lead to an intrathecal or subdural hematoma [4,32,33].

**COMPLICATIONS RELATED TO NOT PERFORMING EBP**

Complications related to continued CSF leak if EBP is not performed are chronic HA, chronic back pain, cranial subdural hematoma, cerebral venous sinus thrombosis, cranial nerve palsy (CN 6 and 7), seizures, and, more rarely, death [4].

In one study among parturients, 18 months after delivery, significantly more women in the dural puncture group (28%) reported HAs, compared with controls (5%). In the dural puncture group, the HA rate among women who received EBP was 20%, compared with 40% among those who did not. CSF leak causes caudal shift of the brain, which may lead to rupture of the fragile subdural bridging veins and bleeding into the subdural space. Minimizing CSF leak with an EBP may therefore reduce the incidence of cranial subdural hematoma [24]. Hypercoagulability in pregnancy increases the risk of thrombotic complications. Dural puncture may further increase the risk of cerebral venous sinus thrombosis due to both damage to the cerebral venous endothelium caused by a negative spinal-cranial pressure gradient and stasis from cerebral vasodilation [1].

ADP itself could be associated with reduced quality of future epidural blocks and higher incidence of complications, although EBP administered after ADP does not appear to further increase the risk of future adverse effects [4].

**CONTRAINDICATIONS**

Absolute contraindications to EBP are coagulation disorders, infection at the puncture site, febrile illness, bacteremia or septicemia, and patient refusal [15]. Relative contraindications are gross anatomic deformity, acquired immune deficiency syndrome, and leukemia. In several studies, EBP was found safe if the platelet count was more than 75,000/mm². However, the author does not recommend EBP when the platelet count is less than 100,000/mm².

**ALTERNATIVES TO EBP**

Initial conservative treatment regimens center on non-in-
vasive modalities to counteract the proposed mechanisms of HA attributed to low CSF pressure, namely CSF loss and cerebral vasodilation. For example, hydration therapy has been proposed to increase CSF production. Although this modality has remained popular, till date, there is no evidence to support its use [15]. In addition to hydration therapy, other conservative options include bed rest, supine/prone positioning, and abdominal binders, although these are also not supported by evidence [15].

First-line medications are non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids, or combination medications commonly prescribed for tension and migraine HAs (in which barbiturates, acetaminophen, and caffeine are added in one formulation) [15]. Caffeine and theophylline are some of the most studied medications for relief of HA attributed to low CSF pressure. These medications act by two mechanisms. First, they interfere with calcium uptake by the sarcoplasmic reticulum, block phosphodiesterase, and antagonize adenosine, which all result in cerebral vasoconstriction. Second, they increase CSF production by stimulating sodium-potassium pumps [15]. Adrenocorticotrophic hormone (ACTH), cosyntropin (an ACTH analogue), and hydrocortisone (which interacts with the ACTH axis) have also been proposed as a therapeutic option. The mechanism by which these medications treat HA attributed to low CSF pressure is unclear, although several theories exist, including expansion of blood volume by releasing aldosterone, dural edema causing overlap of dural hole, increase in CSF production through active sodium transport, and increase in brain β-endorphins [15]. Pharmacologic therapy with medications that are effective in treating other HA and pain syndromes has also been trialed. Sumatriptan, a serotonin type 1-d receptor agonist, commonly used in treating migraines, showed promise in early case series studies. Methylergonovine, a commonly used uterotonic agent, has also been used to treat migraines because of its alpha activity. Gabapentin and pregabalin have analgesic properties and can inhibit the sympathetic pathway of pain, which may contribute to the pain of HA attributed to low CSF pressure [15].

Pain intervention, such as greater occipital nerve block (GONB) or sphenopalatine ganglion block (SPGB) for the treatment of HA attributed to low CSF pressure showed beneficial effects in reducing pain severity, although the evidence is limited [7,15,17,18]. Dural stretching may activate the trigeminal nucleus caudalis, causing some of the pain from HA attributed to low CSF pressure, and this pathway may be blocked by GONB. SPGB is believed to work by blocking parasympathetic outflow to cerebral vasculature, which halts vasodilation [15].

No evidence has been found to support the use of intrathecal catheterization, epidural saline, epidural dextran, epidural hydroxyethyl starch, and epidural/intrathecal/pa- enteral opioids to treat or prevent PDPH [1,5,8,13,15,16].

Fibrin glue and allogeneic EBP can be other alternatives to EBP. Injection of fibrin glue may be used in cases of persistent HA attributed to low CSF pressure with the identified CSF leak site when repeated EBPs have failed [16,28,34]. Allogeneic EBP may be considered if there is concern over the use of autologous blood, as in febrile, HIV-positive, or COVID-19 patients. In such cases, it is appropriate to use crossmatched and tested blood, and the procedure should be conducted under aseptic conditions [17]. Nonetheless, allogeneic EBP has been criticized in view of the risk of transmitting prion diseases, such as Creutzfeldt-Jakob disease [35,36]. For patients with CSF leaks that are confidently localized by imaging but in whom epidural patching has failed, surgical closure of the dural perforation may be considered [4,27]. Procedures include clipping of the leaking root sleeve, epidural packing, and primary dural repair [7,23]. If the site of CSF leak cannot be identified and confidently localized, surgical treatment options are limited [27].

EBP IN PATIENTS WITH COVID-19

There have been recommendations from several medical societies to maximize the use of regional and neuraxial anesthesia for COVID-19 patients in the perioperative period. This is hypothesized to reduce the risk of aerosolization of viral particles, which is associated with the airway manipulation that occurs with general anesthesia. As a result, the use of neuraxial anesthesia for COVID-19 patients has increased over the past few months. Inevitably, a percentage of these patients may develop complications such as PDPH, requiring an EBP to manage their symptoms. A primary concern regarding the use of EBPs in COVID-19 patients is the possibility of seeding the virus in the central nervous system (CNS). In general, an extremely low risk of transferring a blood-borne pathogen into the CNS has been reported when performing EBP with autologous blood for a patient with an ongoing infection. Another important concern is related to the known hypercoagulable state in COVID-19 patients and associated organ dysfunction that may alter the metabolism of anticoagulants [17]. These patients will often be treated with anticoagulants, such as unfractionated hep-
arin, low-molecular weight heparin, or direct oral anticoagulants. Before performing EBP in this population, laboratory studies and the last dose of anticoagulant must be reviewed. The risks of suspending anticoagulation for an EBP should be carefully weighed against the risks associated with a hypercoagulable state, and it should be discussed with a hematologist [17].

In COVID-19 patients with PDPH, it is important to employ conservative treatments (hydration; bed rest; caffeine; analgesics, such as acetaminophen and NSAIDs; theophylline; and cosyntropin [an ACTH analogue]) and to wait till the resolution of active infection [5,17]. If these fail, interventions other than EBP, including bilateral GONB or SPGB, could also be considered [17]. If severe and disabling PDPH persists despite conservative treatments and nerve blocks, EBP should be considered. A fluoroscopic approach may be preferable as it has been shown to be more precise and associated with a higher success rate than a blind technique [17]. The prone position may also offer greater distance for the care team from the patient’s face and may be more comfortable for patients with COVID-19 and improve their respiratory mechanics. Complete personal protection for care personnel, including an N95 mask, a face shield, a gown, a head cover, and sterile gloves, must be utilized. The patient should remain masked throughout the procedure [17].

CONCLUSION

The main indications for EBP are PDPH and SIH. EBP may be considered in cases of moderate to severe PDPH and SIH that are refractory to conservative measures. Prophylactic administration of EBP after ADP can hardly be substantiated at present. Before EBP, diagnostic testing, such as brain and spine MRI with enhancement, is essential for both establishing the diagnosis and localizing CSF leaks. EBP is generally safe but may rarely be associated with serious complications. Therefore, strict asepsis should be employed for both blood collection and epidural puncture. Moreover, EBP should be performed in the prone position under C-arm fluoroscopic guidance. Complete personal protection for care personnel, including an N95 mask, a face shield, a gown, a head cover, and sterile gloves, must be utilized when performing EBP in COVID-19 patients. Further investment, including a large qualified trial on EBP, is warranted, and careful attention should be paid to the timing, prophylactic use, and injection volume and speed of EBP until substantial evidence is available.

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CONFLICTS OF INTEREST

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DATA AVAILABILITY STATEMENT

Data generated or analyzed during this study are included in this published article listed in references.

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INTRODUCTION

Oxygen metabolism is essential for living tissue function, and without oxygen, human cells cannot survive. For successful oxygen transport, sufficient oxygenated blood should first be generated, usually from the cardiopulmonary system, and this oxygenated blood should be transported to the tissues and, finally, cells. Microcirculation is the circulation within the microvessels (diameter, < 20 μm) and the final step of oxygen transport to the cell level [1].

Inappropriate oxygen delivery and tissue ischemia are frequent in critically ill patients, including surgical patients [2–4]. Tissues may recover from ischemia or progress to localized necrosis. However, tissue ischemia or cell death itself may aggravate inflammatory reactions and result in necrosis, thus entering a vicious cycle. Therefore, appropriate oxygen transport to tissues is the primary goal for the hemodynamic management of surgical patients.

Traditionally, hemodynamic monitoring and interventions have focused on macrocirculatory parameters, such as cardiac output and blood pressure [5]. However, even with appropriate macrocirculatory parameters, such as sufficient cardiac output and blood pressure, a sufficient amount of oxygen may not reach the tissue and cells with microcirculatory dysfunction [6]. Thus, even if appropriate macrocirculatory parameters are achieved, some patients may experience...
various ischemic complications, including mortality [7,8].

Considering the lack of monitoring tools and understanding of microcirculation during routine clinical practice, our intervention to augment macrocirculatory parameters may not be helpful for microcirculation but rather may impair microcirculation and aggravate tissue ischemia [9].

EVALUATION OF MICROCIRCULATION

As the hemodynamic measurement of macrocirculatory parameters, such as blood pressure and cardiac output, is significant during traditional hemodynamic management, it is of particular importance to establish validated, reliable, and practical measurement methods for microcirculation. While abundant knowledge and experience have been collated regarding the measurement of macrocirculatory parameters (e.g., cardiac output and blood pressure) [5], the microcirculatory assessment has not yet been standardized sufficiently to be incorporated into routine clinical practice [10]. Despite this limitation, several noninvasive or minimally invasive tools for microcirculatory evaluation have been developed and are readily available.

Sublingual microscopy

Microcirculation is generally defined as a complex network of microvessels (usually with a diameter of < 20 μm) consisting of capillaries, arterioles, and venules [11]. Sublingual microscopy enables direct inspection and evaluation of the microvascular network at the bedside [12]. Another notable strength of sublingual microscopy is its noninvasiveness [12]. Since the introduction of handheld vital microscopes (HVMs) in the late 1990s [13], three techniques for sublingual microscopy have been established [14]. First-generation HVMs use an orthogonal polarized spectral imaging technique where cross-polarized green light is emitted to visualize microvasculature and not transilluminate the tissue surface [15]. However, there are several weaknesses in orthogonal polarized spectral imaging HVMs, such as bulkiness and the requirement for high-powered light sources, which limit their application [13]. Second-generation HVMs have been developed to overcome these limitations. These devices adopted a sidestream dark-field imaging technique [16]. The most recently developed devices, third-generation HVMs, use an incident dark-field imaging technique and further improve the image quality of microcirculation [17]. Currently, second- and third-generation HVMs are commercially available.

HVMs usually contain a ring of stroboscopic light-emitting diodes. Light with a wavelength of 530 nm is absorbed by hemoglobin, thereby helping visualize the microvascular flow of red blood cells (Fig. 1). Microcirculatory images can be obtained by directly applying an HVM to the mucosal membrane in various regions. Several previous studies on microcirculation have predominantly focused on the sublingual mucosa, which is the most commonly selected region for HVMs (Fig. 1) [18]. Studies have also evaluated microcirculation in various organs, such as the lungs [19], liver [20], and brain [21]. However, contrary to the sublingual mucosa, such organs are not always accessible for measurement in most clinical scenarios, except in the surgical setting.

Images obtained using an HVM can be analyzed with (a)

Fig. 1. Direct inspection of microcirculation and video acquisition from the sublingual mucosa (A); images are stored in a computer, which is connected to a handheld vital microscope (B).
bedside visual assessment [22], (b) the aid of offline software [23], or (c) online automatic software [24,25]. From images obtained using a HVM, two physiological components can be analyzed: convective and diffusive oxygen transport [18]. While the convective property of microcirculation describes the flow of red blood cells in microvessels, the diffusive property refers to the density of perfused microvessels. For the qualification or quantification of these two microcirculatory components, several microcirculatory parameters were recommended in an expert consensus meeting [26]. An update of the expert consensus meeting was published recently [18]. The microcirculatory parameters recommended by the expert consensus are listed and described in Table 1.

However, the application of sublingual microscopy in daily clinical settings outside the research area is currently not recommended [18,27], although it has provided a better understanding of microcirculation to researchers and clinicians.

**Vascular occlusion test**

During the vascular occlusion test (VOT), a pneumatic cuff applied on the upper arm is inflated, and after transient ischemia to the arm, it is released [28]. During this procedure, the tissue oxygen saturation sensor on the thenar muscle measures the changes in tissue oxygenation (Fig. 2). Thus, microvascular reactivity can be evaluated by analyzing changes in tissue saturation [29–31]. Among the VOT pa-

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<tr>
<td>Total vessel density (TVD, mm/mm²)</td>
<td>Total vessel area per surface area</td>
<td>Surrogate for capillary distance (diffusive property)</td>
</tr>
<tr>
<td>De Backer score (n/mm)</td>
<td>The number of vessels crossing a grid (three horizontal and vertical equidistance lines drawn on the screen) divided by the total length of the gridlines</td>
<td>Surrogate for TVD applicable to different vessel types</td>
</tr>
<tr>
<td>Proportion of perfused vessels (PPV, %)</td>
<td>Percentage of perfused vessels per total vessels</td>
<td>Based on binomial determinant of perfusion: “flow” or “no-flow” (convective property)</td>
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<td>Perfused vessel density (PVD, mm/mm²)</td>
<td>TVD × PPV</td>
<td>Determinant of capillary distance (diffusive property) and red blood cell velocity (convective property)</td>
</tr>
<tr>
<td>Microvascular flow index (MFI, arbitrary unit)</td>
<td>Grid-based score per quadrant: 0, stop flow; 1, intermittent flow; 2, sluggish flow; and 3, normal flow</td>
<td>Quick, semiquantitative assessment of the red blood cell velocity by “eyeballing”</td>
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<tr>
<td>Space–time diagram (STD, mm/s)</td>
<td>Measurement of exact red blood cell velocity</td>
<td>Determinant of red blood cell velocity (convective capacity)</td>
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<tr>
<td>Heterogeneity index (HI, arbitrary unit)</td>
<td>Coefficient of variation, expressed as (maximum − minimum value) / average</td>
<td>Determinant of heterogeneity of blood flow</td>
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![Fig. 2. Vascular occlusion test (A) and a schematic plot of the change in tissue oxygenation (B).](image-url)
rameters, the recovery slope has been widely used. The recovery slope of the VOT measures the velocity of tissue oxygen saturation change from the nadir value to its baseline values and has been reported to be related to clinical outcomes in patients with severe sepsis and cardiac surgery [32]. Previously, we reported that the recovery slope decreased during cardiac surgery, and this decrease in recovery slope recovered on the first postoperative day in patients without postoperative complications but not in patients with postoperative complications [33].

Laser Doppler flowmetry

Microvascular perfusion can be measured not only by HVMs but also by laser Doppler flowmetry (LDF; Fig. 3) at the bedside [34]. As with HVMs, LDF can be applied to all organ surfaces, particularly the skin. The LDF technique quantifies backscattered Doppler-shifted light from the tissue during motion [35]. The backscattered light from each point of the skin was detected separately, thus generating a color-coded two-dimensional image [36,37]. LDF imaging has long been used in both clinical and experimental settings [38–41].

Unfortunately, LDF does not provide absolute microvascular blood flow values in individual vessels or vascular heterogeneity [7,35]. Furthermore, the ability to reflect actual microcirculatory alterations, not just changes in regional blood flow, is questionable [42].

Other methods for microcirculatory evaluation

The evaluation of microcirculation is also possible using near-infrared spectroscopy [31] or with assessment based on the tissue partial pressure of carbon dioxide [43,44], gastric pH [45], indocyanine green plasma disappearance rate [46], or gastric mucosal-arterial pressure gradient of carbon dioxide [46].

MICROCIRCULATION IN SEPSIS

Sepsis may be the case in which microcirculation is the most widely studied. In patients with sepsis, microcirculatory dysfunction is observed ahead of the macrocirculatory abnormality [47–49], which is one of the strongest predictors of clinical outcomes. Microcirculatory dysfunction is more severe in nonsurvivors [47,50], and there are also differences in the recovery of microcirculatory dysfunction based on therapeutic interventions between survivors and nonsurvivors [51–53].

Twenty years earlier, goal-directed therapy using macrocirculatory parameters showed strong clinical benefits in patients with sepsis [54] and was subsequently recommended in the guidelines [55]. However, in recent large clinical trials using similar protocols with macrocirculatory parameters, clinical benefits have not been observed [56–59]. If the optimization of macrocirculation reaches certain target values, further clinical benefit may not be possible with usual goal-directed therapy using macrocirculatory parameters without microcirculatory improvement.

MICROCIRCULATION IN NONCARDIAC SURGERY

In the meta-analysis, microcirculation via sublingual microscopy was impaired during both cardiac and noncardiac surgeries [60]. Several clinical trials have evaluated microcirculation without sublingual microscopy using the gastric pH [45], LDF technique [61], indocyanine green plasma disappearance rate, and gastric mucosal-arterial pressure gradient of carbon dioxide [46].

Among 25 patients undergoing major abdominal surgery, those with postoperative complications showed higher microvascular dysfunction with impaired sublingual microscopy parameters [62]. However, there were no differences in macrocirculatory parameters, such as cardiac output, blood pressure, oxygen delivery, and lactate levels [62]. Among 31
general or thoracic surgery patients, postoperative microcirculation dysfunction 1 h postoperatively via sublingual microscopy was correlated with blood lactate level elevation 24 h postoperatively [63].

**MICROCIRCULATION IN CARDIAC SURGERY**

Cardiac surgery is one of the most invasive surgeries that induce a strong inflammatory reaction [64–68]. Moreover, several cardiopulmonary bypass-related factors may affect microcirculation. These include hypothermia [69], non-pulsatile blood flow [70], vasoactive drugs [71], and hemodilution [72]. In addition, heart failure and cardiogenic shock are related to microcirculation dysfunction [73–75]. Although most previous clinical trials enrolled a small number of patients, a certain degree of microcirculatory dysfunction was observed [76–81]. It was also shown that anesthesia itself may induce microcirculatory alterations [77–79,81]. In one study, which included on-pump and off-pump cardiac surgery and thyroid surgery, perfused small vessel density decreased most severely and for the longest duration in on-pump cardiac surgery and decreased the least and was transient in thyroid surgery [76]. In another study of cardiac surgery patients, microcirculation was preserved only in those undergoing off-pump cardiac surgery [80].

**RELATIONSHIP BETWEEN MICROCIRCULATION AND MACROCIRCULATION**

If there is no cardiac output, microcirculation is not observed. Therefore, a 100% dissociation between macrocirculation and microcirculation may not be possible. However, in several clinical studies performed under various critical clinical situations, microcirculation parameters showed an independent pattern from macrocirculatory parameters [6,51,82–84].

We also previously showed that among cardiac surgery patients, those with complications showed lower microcirculation function on VOT, but there were no differences in the macrocirculatory parameters [33].

**MICROCIRCULATION AND INTERVENTION**

Microcirculation has been observed during various hemodynamic and non-hemodynamic interventions.

**Vasopressor**

Increasing arterial pressure with the use of conventional vasopressors is not effective in restoring microcirculation but rather may aggravate microcirculation in patients with sepsis or animal models [85–87]. Similarly, for cardiac surgery patients undergoing cardiopulmonary bypass, increasing blood pressure from 47 to 68 mmHg with phenylephrine resulted in a decrease in small vessel blood flow measured using sublingual microscopy [78]. Thus, increasing perfusion pressure with vasopressor use may not improve microcirculation but rather impair it; however, at the same time, it should be considered that increasing perfusion pressure was reported to be beneficial for perfusion of other organs, such as the kidney [88].

**Vasodilator**

Interestingly, in patients with septic shock, local acetylcholine application in the sublingual area completely recovered microcirculation dysfunction when examined using sublingual microscopy [47]. However, in a randomized trial of 70 patients with sepsis, intravenous nitroglycerin did not promote microcirculation when examined using sublingual microscopy [89].

In a study by De Backer et al. [90], the intravenous administration of dobutamine (5 μg/kg/min) improved sublingual microcirculation in patients with septic shock. Interestingly, this microcirculatory improvement was independent of changes in cardiac output and blood pressure and was closely related to the decrease in lactate concentration. Thus, the microcirculatory effect of dobutamine could not be detected using conventional macrocirculatory parameters.

**Fluid administration**

In several previous clinical trials with patients with sepsis, fluid infusion improved the microvascular flow index when measured using sublingual microscopy. In one study, this improvement in microcirculation was similar to the effect of passive leg raising [91]. In another study, fluid resuscitation improved the clinical signs of impaired organ perfusion and microvascular flow index when measured using sublingual microscopy for patients with a microvascular flow index of < 2.6. However, in patients with baseline microvascular flow index
values of > 2.6, there was no improvement in the clinical signs of impaired organ perfusion and microvascular flow index [92]. In another study on patients with sepsis, fluid administration improved microcirculation examined using sublingual microscopy only in the early phase of sepsis [93].

In a prospective randomized trial with 20 patients with sepsis, goal-directed therapy using 6% hydroxyethyl starch 130/04 showed better microcirculation when examined on sublingual microscopy than when using isotonic saline [94].

**Transfusion**

In several previous studies, red blood cell transfusion improved sublingual microvascular density in patients undergoing cardiac surgery [95,96].

Meanwhile, in another study performed in 35 patients with sepsis, although sublingual microcirculation remained unchanged after transfusion, transfusion improved sublingual microcirculation in a subgroup of patients who had impaired microvascular perfusion at baseline [97]. This finding indicates that the effect of transfusion varies significantly according to the microcirculatory status of each individual patient; microcirculatory evaluation may help identify patients who would benefit from transfusion.

**Hydrocortisone**

In a previous study, intravenous hydrocortisone improved microcirculation, as evaluated using sublingual microscopy [98]: microcirculatory parameters, such as small vessel density and proportion of perfused vessels, increased after the administration of “stress dose” hydrocortisone (50 mg per 6 h) in 20 patients with septic shock.

**THE PRESENT AND FUTURE OF MICROCIRCULATION**

Until now, there has been no reliable and practical intervention that can improve or prevent microcirculatory dysfunction. Most previous studies on interventions to improve microcirculation were small, single-center studies showing inconsistent results [99–105]. Traditional hemodynamic interventions to improve macrocirculation may not improve and may even impair microcirculation. It is possible that some interventions can improve microcirculation.

Even if we establish an intervention that may improve microcirculation, there is one more point to consider. Although the relationship between microcirculatory dysfunction and poor clinical outcome has been well proven in various clinical situations [106–108], it does not necessarily mean that the recovery of microcirculatory dysfunction will improve the clinical outcome.

It could be said that there is a long way to go in this research field. However, considering that a substantial number of patients with microvascular dysfunction experience morbidity and mortality even after the optimization of macro-hemodynamic parameters, establishing an intervention to improve microcirculation will have great clinical impact on critical and perioperative medicine.

**CONCLUSIONS**

Traditionally, the hemodynamic management of surgical patients has mainly focused on macrocirculatory parameters, such as cardiac output and blood pressure. However, microcirculatory dysfunction occurs frequently in surgical patients, and both macrocirculation and microcirculation are essential for successful oxygen transport to tissues. Thus, even after achieving sufficient adequate macrocirculatory parameters does not necessarily guarantee for sufficient microcirculatory dysfunction, which is also important to optimize postoperative outcomes. This is still related to postoperative complications. However, unlike traditional macrocirculatory hemodynamic management, there is a lack of research on microcirculatory hemodynamic management, and little is known about how to improve microcirculation. Therefore, future research should focus on effective interventions to recover microcirculation. To determine these interventions, we require a more standardized and practical monitoring tool to evaluate microcirculation in the clinical field.

**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 in the current study.

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Microcirculation during surgery


INTRODUCTION

Arterial tourniquets are widely used in the operative field to prevent bleeding during surgery \[1,2\]. However, tourniquets are likely to result in the development of tourniquet-induced hypertension (TIH), defined as an increase in systolic blood pressure (SBP) or diastolic blood pressure (DBP) of at least 30% within 1 h of tourniquet inflation \[3,4\]. Among patients under general anesthesia with a tourniquet, the incidence of TIH can be as high as 67% \[4\]. TIH can oc-
cur even at an appropriate depth of anesthesia and may be dangerous for patients with cardiovascular diseases [1,5]. Although the mechanism of TIH development remains unclear, its onset is considered to be associated with the activation of C fibers that cause N-methyl-D-aspartate (NMDA) receptor activation associated with the central sensitization mechanism [6-8]. TIH is also associated with sympathetic nervous system activation [9]. Various methods have been used to prevent TIH during surgery [10-13]. Several studies have assessed ketamine, a pain-regulating drug, as an NMDA receptor antagonist, which effectively reduced the development of TIH when pre-administered at small doses or more [11,14,15].

Lidocaine is a local anesthetic with well-known anti-inflammatory and analgesic properties [16]. The administration of a bolus dose of lidocaine with/without continuous intravenous (IV) infusion effectively prevents intraoperative pain and an increase in blood pressure and reduces the use of other anesthetics and postoperative pain [10,17]. A bolus administration of lidocaine (1 mg/kg) followed by continuous infusion (2 mg/kg/h) reduced the incidence of TIH in patients undergoing lower limb surgery using a tourniquet [16].

However, whether a bolus administration of lidocaine without a continuous infusion can prevent TIH development in patients undergoing lower limb surgery remains unknown. Accordingly, we hypothesized that a bolus administration of lidocaine would also be effective in preventing TIH. To confirm this hypothesis, we investigated whether a bolus administration of lidocaine before tourniquet inflation could reduce the incidence of TIH in patients undergoing lower limb surgery under general anesthesia. Additionally, we compared the effect of bolus lidocaine on TIH prevention to that of bolus ketamine.

**MATERIALS AND METHODS**

**Study design**

The protocol for this randomized, double-blind, prospective study was reviewed and approved by the Institutional Review Board (no. UUHIRB-2019-01-015) and written informed consent was obtained from all study participants.

**Study population and intervention**

The study included 75 patients aged 18-75 years, with American Society of Anesthesiologists physical status grade I or II who underwent lower limb surgery using a tourniquet under general anesthesia. Patients with a medical history of ischemic heart disease, peripheral vascular disease, deep vein thrombosis, or a history of allergic reactions or seizures triggered by local anesthetics were excluded from this study.

Patients were randomly assigned to one of three groups (lidocaine, ketamine, and control; allocation ratio 1:1:1) using a random number table generated by online randomization software (https://www.randomizer.org). Patients in the lidocaine and ketamine groups were intravenously administered lidocaine 1.5 mg/kg and ketamine 0.2 mg/kg, respectively, which were diluted with 10 ml of normal saline 10 min before tourniquet inflation. The control group was intravenously administered 10 ml of normal saline. Each syringe was assigned according to the allocation. The medical staff participating in the anesthesia did not know the contents of each syringe.

**Anesthesia regimen and measurement**

No preoperative medications were administered to any patient. After entering the operating room, the patients were administered 5 ml/kg lactated Ringer’s solution before anesthesia induction, and patient monitoring was initiated by attaching a basic monitor (electrocardiogram, pulse oximeter, noninvasive blood pressure [NIBP]). Invasive blood pressure monitoring was applied for patients aged ≥ 65 years, and the bispectral index (BIS; BIS VISTA™ monitor, Aspect Medical Systems, USA) was monitored to assess the adequacy of anesthetic depth during surgery. Tracheal intubation was performed with propofol (2 mg/kg), rocuronium (0.8 mg/kg), or remifentanil (1 μg/kg). The patients were ventilated in volume control mode with a tidal volume of 7 ml/kg, positive end-expiratory pressure of 6 cmH2O, and fraction of inspired oxygen of 0.5. The respiratory rate was controlled to maintain an end-tidal CO₂ pressure of 35–40 mmHg. After inducing anesthesia, remifentanil was continuously administered, along with 1.5–2.5% sevoflurane. The sevoflurane concentration was adjusted to maintain a BIS value between 40 and 60. After tracheal intubation, the dose of remifentanil was maintained at 0.05 μg/kg/min. When the SBP changed by more than 10% from that measured before anesthesia induction, the dose of remifentanil was increased or decreased by 0.03 μg/kg/min. If the SBP increased to > 180 mmHg, 300 μg nicardipine was administered intravenously. A tourniquet (20 cm wide) was placed on the upper thigh of the surgical side and inflated to 300 mmHg after the lower limb was...
lifted to an angle of 45° for 5 min.

The anesthesiologists who participated in anesthesia management, the orthopedic surgeons, and the patients were all blinded to patient allocation. Another anesthesiologist, who did not participate in the patient’s anesthesia, was given a group of randomly assigned patients through sealed opaque envelopes and prepared the “study drug”. All syringes used in the study were the same and were labeled as “study drug”. The anesthesiologist who participated in each patient’s anesthesia management recorded the following values: the incidence of TIH, defined as an SBP or DBP increase ≥ 30% of the baseline value; SBP, DBP, and heart rate (HR) measured before tourniquet inflation (baseline value), after tourniquet inflation for 60 min at 10-min intervals, and immediately after tourniquet deflation; duration of anesthesia, surgery, tourniquet inflation; total dose of remifentanil administered during anesthesia; number of patients nicardipine administration during anesthesia; number of patients receiving fentanyl administration in the post-anesthesia care unit (PACU). The numerical rating scale (NRS, 0–10) score was measured immediately after transfer to the PACU and after 20 min, and again 24 h after surgery.

The administration of all anesthetics was discontinued at the conclusion of surgery. For neuromuscular block reversal, glycopyrrolate (0.008 mg/kg) and pyridostigmine (0.1 mg/kg) were administrated. After confirming proper neuromuscular recovery, the patients were extubated and transferred to the PACU.

Sample size

This study aimed to determine whether a single IV dose of lidocaine (1.5 mg/kg) could prevent an increase in blood pressure caused by tourniquet inflation and to compare the single IV dose of lidocaine to that of ketamine, which is already known for its preventive effects. Satsumae et al. [14] reported TIH incidence rates of approximately 60% and < 20% in the control and ketamine groups, respectively. Thus, we calculated the sample size in the present study assuming a 40% difference in the incidence of TIH between the control and lidocaine groups. Assuming an attrition rate of 10%, 25 patients per group were determined to be an adequate sample size to achieve 80% power and 5% type-1 error.

Data analysis and statistical methods

IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., USA) was used to perform all the statistical analyses. For continuous variables, we used Kolmogorov-Smirnov tests to evaluate the distributions for normality. Normally distributed variables are expressed as means and standard deviations. Continuous variables with normal distribution were compared between the three groups using one-way Analyses of variance (ANOVA) with Tukey’s post-hoc tests. Continuous variables including SBP, DBP, and HR were analyzed using repeated-measures ANOVA with Bonferroni’s post-tests to determine intra-group comparisons over time. For repeated measures ANOVA models, sphericity was assessed by Mauchly test and Greenhouse-Geisser correction was applied when required. Categorical variables (such as the incidence of TIH, nicardipine administration during anesthesia, and fentanyl administration in the PACU) were analyzed by chi-square or Fisher’s exact tests, as applicable. Categorical data were expressed as numbers or percentages.

Statistical significance was set at P < 0.05, except for pairwise between-group comparisons. For the problem of multiple comparisons (each group versus each other group = 3 comparisons), a Bonferroni-corrected significance level of 0.05/3 = 0.017 was used. We have showed Bonferroni-corrected P values.

RESULTS

While 82 patients were considered eligible, seven patients declined to participate in this study. Thus, a total of 75 patients were randomized, with each group including 25 patients (Fig. 1). As shown in Table 1, there were no significant differences among the three groups in the demographic profile, including sex, age, years, height, and weight. The duration of surgery, anesthesia, tourniquet inflation time, and type of surgery also did not differ significantly between the three groups.

TIH was observed in 14 of 25 patients (56%) in the control group, occurring significantly more often compared to the lidocaine (four patients, 16%) and ketamine (three patients, 12%) groups (P = 0.001) (Table 2).

There was a significant interaction between the three groups over time in SBP and DBP (all P < 0.001) (Fig. 2A, B). Pairwise comparison showed a significantly higher SBP in the control group than that of the ketamine group at 50 min after tourniquet inflation (P = 0.001). However, the difference was not statistically significant between the control and lidocaine groups (P = 0.105) and between the ketamine and lidocaine groups (P = 0.363). Sixty min after tourniquet infla-
Assessed for eligibility (n = 82)
  Excluded (n = 7)
    • Not meeting inclusion criteria (n = 0)
    • Declined to participate (n = 7)
    • Other reasons (n = 0)
Randomized (n = 75)
  Allocated to lidocaine (n = 25)
    • Received allocated intervention (n = 25)
    • Did not receive allocated intervention (n = 0)
  Allocated to ketamine (n = 25)
    • Received allocated intervention (n = 25)
    • Did not receive allocated intervention (n = 0)
  Allocated to normal saline (n = 25)
    • Received allocated intervention (n = 25)
    • Did not receive allocated intervention (n = 0)
Lost to follow-up (n = 0)
  Discontinued intervention (n = 0)
Analysed (n = 25)
  • Excluded from analysis (n = 0)

Fig. 1. Flowchart of the study participants.

Table 1. Patient and Operation Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lidocaine group (n = 25)</th>
<th>Ketamine group (n = 25)</th>
<th>Control group (n = 25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>9/16</td>
<td>6/19</td>
<td>8/17</td>
<td>0.654</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>55.2 ± 23.2</td>
<td>57.9 ± 20.0</td>
<td>56.9 ± 22.1</td>
<td>0.905</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>159.9 ± 13.4</td>
<td>158.0 ± 11.0</td>
<td>157.7 ± 12.6</td>
<td>0.789</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.2 ± 11.4</td>
<td>65.5 ± 11.9</td>
<td>64.1 ± 9.2</td>
<td>0.245</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>83.0 ± 10.4</td>
<td>82.2 ± 10.0</td>
<td>87.4 ± 14.5</td>
<td>0.253</td>
</tr>
<tr>
<td>Duration of anesthesia (min)</td>
<td>143.6 ± 22.0</td>
<td>142.0 ± 2.5</td>
<td>146.0 ± 20.9</td>
<td>0.809</td>
</tr>
<tr>
<td>Duration of tourniquet inflation (min)</td>
<td>67.8 ± 4.6</td>
<td>66.8 ± 4.5</td>
<td>67.8 ± 4.1</td>
<td>0.653</td>
</tr>
<tr>
<td>Types of surgery</td>
<td></td>
<td></td>
<td></td>
<td>0.607</td>
</tr>
<tr>
<td>TKRA</td>
<td>15</td>
<td>15</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Arthroscopy evaluation</td>
<td>1</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>ACL reconstruction</td>
<td>5</td>
<td>2</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number or mean ± SD. TKRA: total knee replacement arthroplasty, ACL: anterior cruciate ligament.

flation, the SBP of the control group was significantly higher than that of the ketamine and lidocaine groups (all P < 0.001). The DBP of the control group was higher than that of the ketamine and lidocaine groups at 60 min after tourniquet inflation (P = 0.005, P = 0.022, respectively).

During tourniquet inflation, changes in HR between the three groups also showed a significant interaction with time (P = 0.007) (Fig. 3). Pairwise comparisons showed a higher HR in the control group compared to that in the ketamine group at 60 min after tourniquet inflation (P = 0.022).

As shown in Table 2, the total doses of remifentanil used during anesthesia in the lidocaine and ketamine groups were significantly lower than that in the control group (P < 0.001). The numbers of patients administered nicardipine due to increased SBP to ≥ 180 mmHg during surgery (5 [20%] in the control group, 1 [4%] in the lidocaine group, and 0 [none] in the ketamine group) did not differ significantly (P = 0.315). The number of patients receiving fentanyl in the
Table 2. Intraoperative and Postoperative Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lidocaine group (n = 25)</th>
<th>Ketamine group (n = 25)</th>
<th>Control group (n = 25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of TIH</td>
<td>4 (16)</td>
<td>3 (12)</td>
<td>14 (56)*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total dose of remifentanil (μg)</td>
<td>365.2 ± 92.4</td>
<td>347.3 ± 129.1</td>
<td>622.2 ± 109.0*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Nicardipine administration</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>4 (16)</td>
<td>0.119</td>
</tr>
<tr>
<td>Fentanyl administration in the PACU</td>
<td>18 (72)</td>
<td>19 (76)</td>
<td>16 (64)</td>
<td>0.734</td>
</tr>
<tr>
<td>NRS immediately after entering the PACU</td>
<td>6.1 ± 1.5</td>
<td>6.2 ± 1.3</td>
<td>6.1 ± 1.1</td>
<td>0.970</td>
</tr>
<tr>
<td>NRS after 20 min in the PACU</td>
<td>3.9 ± 1.0</td>
<td>3.6 ± 0.8</td>
<td>5.0 ± 0.6*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>NRS 24 hours after the operation</td>
<td>4.0 ± 0.8</td>
<td>4.1 ± 0.9</td>
<td>5.8 ± 1.1*</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are expressed as number (%) or mean ± SD. TIH: tourniquet-induced hypertension, NRS: numerical rating scale, PACU: post-anesthesia care unit. *Compared with lidocaine and ketamine groups.

Fig. 2. Changes in blood pressure in the three groups during anesthesia. (A) Systolic blood pressure (SBP), (B) diastolic blood pressure (DBP). There was a significant interaction between the three groups over time in SBP and DBP by repeated-measures analysis of variance and Bonferroni post-hoc test (all P < 0.001). T0: immediately before tourniquet inflation, T10–T60: every 10 min after tourniquet inflation, respectively, Toff: after tourniquet deflation. †P < 0.05 compared to the ketamine group. *P < 0.05 compared to the ketamine and lidocaine groups.
PACU did not differ significantly among the three groups. There were also no significant differences among the three groups in NRS scores immediately after entering the PACU (P = 0.970). However, the NRS scores measured 20 min after entering the PACU and 24 h after surgery differed significantly among the three groups (all P < 0.001).

**DISCUSSION**

The results of this study demonstrated that the bolus administration of 1.5 mg/kg lidocaine 10 min before tourniquet inflation prevented an increase in blood pressure caused by tourniquet inflation in patients undergoing general anesthesia, an effect similar to that for single 0.2 mg/kg dose of ketamine.

After 30–60 min of tourniquet inflation, patients may develop an increase in SBP and HR that persists until tourniquet deflation, a phenomenon known as ‘tourniquet pain.’ An increase in blood pressure due to tourniquet application may occur despite an adequate depth of anesthesia [1]. In this study, the blood pressure and HR of patients who did not receive treatment also showed a steadily increasing pattern after tourniquet inflation, whereas the patients treated with lidocaine and ketamine before tourniquet inflation showed constant blood pressure and HR up to 60 min after tourniquet application. This preventive effect of lidocaine and ketamine on rising blood pressure was also effective in reducing the incidence of TIH, which is defined as an increase of 30% or more in blood pressure. El-Sayed and Hasanein [10] reported that the incidence of TIH decreased from 53% to 26% with the bolus administration of 1 mg/kg lidocaine followed by a continuous infusion of 2 mg/kg/h lidocaine 10 min before tourniquet inflation in patients undergoing anterior cruciate ligament reconstruction under general anesthesia. The present study observed a significantly reduced incidence of TIH following the administration of a 1.5 mg/kg bolus dose of lidocaine 10 min before tourniquet inflation without a continuous infusion of lidocaine. Perioperative IV lidocaine may have preventive analgesic activity, likely by preventing the induction of central hyperalgesia [18]. In this study, we confirmed that the bolus administration of lidocaine prevented blood pressure increase without continuous infusion in patients in whom a tourniquet is used.

The present study compared a single bolus of lidocaine to that of ketamine, which is known for its TIH-preventing effect. Several studies have assessed the effect of preventing TIH using ketamine, an NHDA receptor antagonist. Satsuae et al. reported that preoperative IV ketamine (0.25 mg/kg or more) significantly prevented tourniquet-induced systemic arterial pressure increase in patients under general anesthesia [14]. Another study demonstrated that the preadministration of low-dose ketamine (0.1 mg/kg) attenuated tourniquet pain and arterial pressure increase using a high tourniquet pressure of 400 mmHg and prolonged tourniquet time in healthy awake volunteers [19]. In the present study, the incidence of TIH in patients administered 0.2 mg/kg ket-
amine was 44% lower than that in patients receiving normal saline. Moreover, we found that this dose of ketamine had a similar effect to the 1.5 mg/kg doses of lidocaine administered to patients.

Patients treated with lidocaine and ketamine had a lower NRS score 24 h after surgery compared to the score in patients receiving normal saline. Several studies have suggested that lidocaine and ketamine have beneficial preemptive analgesic effects in patients undergoing surgery [20,21]. Ketamine reduced postoperative morphine consumption and significantly increased the time to first analgesic request [22]. Lidocaine also has preventive effects against postoperative pain and morphine consumption after abdominal surgery [18,23]. Gholipour Baradari et al. [17] measured the visual analog scale (VAS) scores for 24 h after surgery following the administration of a small bolus dose of lidocaine (1.5 mg/kg) during anesthesia induction in patients undergoing cesarean section. They reported lower VAS scores among patients in the lidocaine group at the 24-hour time point compared to that in patients in the placebo group (mean VAS scores: 2.4 vs. 3.6) [17]. The results of the present study also showed lower NRS scores at 24 h after surgery in patients administered lidocaine or ketamine compared to the score in those administered normal saline. However, there was no difference in NRS score immediately after entering the PACU and the number of patients administered fentanyl with an NRS score of 5 or more did not differ among the three groups. However, there was a difference in NRS scores evaluated 20 min after entering the PACU. This study was unable to assess whether fentanyl used in the PACU affected these differences in NRS scores. It also did not record the total amount of analgesics used in 24 h. Hence, further research is needed to evaluate the effect of a single bolus of lidocaine on postoperative analgesia in patients with lower extremity surgery.

In our study, anesthesia was maintained using sevoflurane, an inhalation anesthetic, and remifentanil, a synthetic opioid. Remifentanil is believed to contribute to hemodynamic stabilization by preventing the release of stress hormones when patients are exposed to stressful situations during surgery [24,25]. The administration of remifentanil in the maintenance of anesthesia prevents the increases in blood pressure due to tourniquet application compared to when it is not used [12,26]. In the present study, the use of lidocaine and ketamine effectively prevented the increase in blood pressure over time after tourniquet inflation, even when remifentanil was used, and also reduced the amount of remifentanil used during anesthesia. The results of this study are considered to be beneficial for patients with an increased risk of complications due to tourniquet inflation.

This study has several limitations. First, as mentioned before, the amount of analgesic, including patient-controlled analgesia (PCA), used for 24 h after surgery was not measured; therefore, it was not possible to assess the difference in NRS scores between the three groups 24 h after surgery. Second, the infusion rate of remifentanil was adjusted by increasing or decreasing according to the changes in the patient blood pressure after the induction of anesthesia. During the design process of this study, we thought that the adjustment of the infusion rate of remifentanil according to changes in patient blood pressure was commonly performed in actual clinical practice, and this was reflected in this study. However, considering the pure effect of lidocaine or ketamine on SBP, which we wanted to evaluate in this study, this could be a limitation of this study. Since this study aimed to evaluate the changes in blood pressure during surgery, it is important to measure blood pressure in the same way for all patients regardless of age. However, we measured blood pressure with NIBP if a patient’s age was under 65 and conducted invasive blood pressure measurement if a patient’s age was over 65 in this study. The use of different BP measurement methods depending on the patient’s age may be another limitation of this study.

In conclusion, the bolus administration of lidocaine (1.5 mg/kg) 10 min before tourniquet inflation reduced the incidence of TIH and postoperative pain, with a reduction comparable to that of bolus ketamine in patients undergoing lower limb surgery under general anesthesia.

**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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REFERENCES


Verification of the performance of the Bispectral Index as a hypnotic depth indicator during dexmedetomidine sedation

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Background: Differences in the effects of propofol and dexmedetomidine sedation on electroencephalogram patterns have been reported previously. However, the reliability of the Bispectral Index (BIS) value for assessing the sedation caused by dexmedetomidine remains debatable. The purpose of this study is to evaluate the correlation between the BIS value and the Modified Observer’s Assessment of Alertness/Sedation (MOAA/S) scale in patients sedated with dexmedetomidine.

Methods: Forty-two patients aged 20–80 years, who were scheduled for surgery under spinal anesthesia were enrolled. Spinal anesthesia was performed using 0.5% bupivacaine, which was followed by dexmedetomidine infusion (loading dose, 0.5–1 μg/kg for 10 min; maintenance dose, 0.3–0.6 μg/kg/h). The MOAA/S score was used to evaluate the level of sedation.

Results: A total of 215082 MOAA/S scores and BIS data pairs were analyzed. The baseline variability of the BIS value was 7.024%, and BIS value decreased, as the MOAA/S scored decreased. The correlation coefficient and prediction probability between the two measurements were 0.566 (P < 0.0001) and 0.636, respectively. The mean ± standard deviation values of the BIS were 87.22 ± 7.06, 75.85 ± 9.81, and 68.29 ± 12.65 when the MOAA/S scores were 5, 3, and 1, respectively. Furthermore, the cut-off BIS values in the receiver operating characteristic analysis at MOAA/S scores of 5, 3, and 1 were 82, 79, and 73, respectively.

Conclusions: The BIS values were significantly correlated with the MOAA/S scores. Thus, the BIS along with the clinical sedation scale might prove useful in assessing the hypnotic depth of a patient during sedation with dexmedetomidine.

Keywords: Anesthesia, spinal; Consciousness monitors; Dexmedetomidine; Hypnotics and sedatives.
INTRODUCTION

Patients undergoing surgery under spinal anesthesia must be sedated to reduce anxiety and increase treatment satisfaction. Dexmedetomidine, a highly selective α2 adrenoceptor agonist, is a novel sedative that is widely used as an adjuvant during spinal anesthesia. It induces a unique sedative response due to its analgesic, anxiolytic, sympatholytic, and opioid-sparing properties, which results in an easy transition from sleep to wakefulness, thus allowing the patient to be cooperative and communicative when stimulated. Moreover, it rarely causes respiratory depression, and the sympatholytic effect of the drug enables the hemodynamics to remain stable during the perioperative period [1,2].

It is not easy to accurately predict the patient’s response to a sedative. The pharmacokinetics and pharmacodynamics of the drugs are affected by several factors, such as race, age, and the presence of comorbidities. Therefore, an identical dosage of the same drug could induce different levels of sedation among patients. Elderly patients are more sensitive to sedatives and present with greater variations in response to the drug. Several studies have shown that the level of sedation during surgery can affect the incidence of delirium, cognitive impairment, and mortality after surgery [3-6]. Furthermore, inadequate deep sedation can increase the time it takes to recover from the sedation and can disrupt the planned schedule of the surgery. Therefore, it is very important to maintain an adequate level of sedation using reliable monitoring devices and by observing the clinical signs.

The Bispectral Index (BIS) is a noninvasive monitoring measure used to assess the depth of sedation via an algorithmic analysis of the electroencephalogram (EEG). Its use in general anesthesia is considered essential to minimize the possibility of intraoperative awareness. Additionally, the BIS have been proven reliable for assessing the hypnotic effects of various anesthetic drugs and sedatives such as propofol, inhaled anesthetics, and midazolam [6-9]. However, the reliability of the BIS value in assessing the sedation effects of dexmedetomidine remains questionable. Xi et al. [10] reported differences in the EEG dynamics between dexmedetomidine and propofol at the same level of sedation and suggested that these differences might account for the alterations in the BIS value.

The aim of the present study is to evaluate the correlation between the BIS and the commonly used Modified Observer’s Assessment of Alertness/Sedation (MOAA/S) scale in patients sedated with dexmedetomidine. Furthermore, we intended to verify the clinical validity, reliability, and applicability of BIS as an objective assessment tool for monitoring the depth of sedation.

MATERIALS AND METHODS

Study design

This prospective observational study was approved by the Institutional Review Board at our hospital (BP IRB 2019-01-137), and informed consent was obtained from each patient. Clinical research was conducted by following the ethical principles for medical research involving human subjects in accordance with the Helsinki Declaration 2013. Forty-two patients aged between 20 and 80 years (American Society of Anesthesiologists physical status, class I–III) who were scheduled for elective surgery under spinal anesthesia were enrolled in this study. Patients with a history of cerebral nervous system diseases (such as epilepsy), uncontrolled hypertension or heart disease, chronic kidney disease (stage 4 or higher), and neuropsychiatric disorders; those who had difficulty in communicating; and those taking neuropsychiatric drugs were excluded.

The noninvasive blood pressure, heart rate, ECG, and pulse oximetry readings of the patients were monitored throughout the surgery. Spinal anesthesia was performed based on the site of the procedure using 0.5% bupivacaine (Marcaine® Spinal Heavy; 5 mg/ml, AstraZeneca, Sweden) 8–11 mg. The peak sensory block level was evaluated every 2 min until the block heights of the spinal anesthesia were no longer changed. End-tidal CO2 was monitored, and oxygen (2–3 L/min) was administered using a nasal prong.

Prior to dexmedetomidine administration, a BIS monitor (Bispectral Index™, Covidien, USA) was attached to the patient’s forehead as recommended by the manufacturer, and the baseline BIS values were recorded for 2 min and automatically stored in a computer. The Vital Recorder program was used to collect the patient’s data (vital signs and BIS values) [11]. The drug injection method was determined based on the prescription of dexmedetomidine, and a loading dose (1.0 μg/kg for those ≤65 years old and 0.5–0.75 μg/kg for those ≥65 years old) was given intravenously for over 10 min, followed by a continuous infusion of a maintenance dose (0.3–0.6 μg/kg/h). One investigator, who was blinded to the study, conducted the assessment of the depth of sedation using the MOAA/S scale. If the MOAA/S score was ≤2 during the infusion of the loading dose, the maintenance
dose was initiated before the planned loading dose was fully administered. The maintenance dose was adjusted within a range of 0.3–0.6 μg/kg/h to maintain the MOAA/S score at 3–4. In the event of bradycardia (heart rate below 40 beats/ min), atropine (0.5 mg) or ephedrine (5 mg) was injected intravenously. The MOAA/S score was recorded every 3–5 min during the loading dose infusion period and every 5–10 min during the maintenance dose infusion period. The infusion of dexmedetomidine was stopped approximately 10 min before the surgery was completed, and the MOAA/S score was evaluated every 2–3 min postoperatively to confirm the recovery from sedation.

Data preparation

The MOAA/S score was manually recorded every 3–6 min, and the BIS score was automatically stored in a computer every second. Consequently, the two data were merged based on the time to create data pairs (MOAA/S score–BIS value data pair) that were used for the analysis (Fig. 1A). If the MOAA/S score was 5 at both 12:10:00 and 12:13:00, the MOAA/S score for 3 min was assigned as 5 (Fig. 1B). Thus, the bias due to the waking up of the patient as a result of the physical stimulus while assessing the MOAA/S score was reduced by including the BIS values before, during, and after checking the MOAA/S scores. BIS values that were not stored properly or those with low signal quality index (SQI) values were excluded from the analysis.

Furthermore, if the interval between MOAA/S measurements was longer than 5 min, the BIS values 2.5 min before and after measuring the score were included in the analysis.

Statistical analysis

The primary outcome of the study was to assess the correlation between the MOAA/S score and the BIS value. MedCalc (version 18, MedCalc Software Bvba, Belgium) and GraphPad Prism (version 9, GraphPad Software, USA) were used to perform the statistical analyses. The coefficient of variation (relative standard deviation) of the BIS values obtained 2 min prior to the administration of dexmedetomidine was calculated as the baseline variability. The Spearman’s correlation coefficient and prediction probability (P_k) were determined to evaluate the correlation between the MOAA/S score and the BIS value. The P_k was calculated using the Somers’d statistic and fit4NM 4.6.0 (Eun-Kyung Lee and Gyu-Jeong Noh; http://www.fit4nm.org/download/246; last accessed: 24 June 2014) as follows: $P_k = (\text{Somers’d} + 1) / 2$. A $P_k$ value of 1 indicated a perfect agreement, whereas a $P_k$ value of 0.5 indicated a random relationship. Receiver operating characteristic (ROC) analysis was used to assess the discriminating performance of BIS and to obtain the cut-off BIS value to estimate sedation depth (MOAA/S score). Quantitative data are expressed as mean ± standard deviation (SD). A P value of < 0.05 was considered statistically significant.

RESULTS

This study comprised 42 participants (19 males and 23 females) who were undergoing surgical procedures such as transurethral vapor section for prostate cancer, transurethral bladder surgery for bladder cancer, or knee surgery. A total of 215082 MOAA/S scores and BIS data pairs were analyzed.
(MOAA/S = 5: 57,219 data pairs; MOAA/S = 4: 65,489 data pairs; MOAA/S = 3: 44,966 data pairs; MOAA/S = 2: 30,934 data pairs; MOAA/S = 1: 6,357 data pairs; and MOAA/S = 0: 10,117 data pairs). The data for MOAA/S scores 0 and 1 were low because the dose of dexmedetomidine was adjusted to maintain conscious sedation with a MOAA/S score of ≥ 3. The demographic characteristics of the 42 patients are shown in Table 1. Nineteen patients were < 65 years old and 23 were ≥ 65 years old. The mean ± SD operation time was 81.9 ± 39.1 min. Fig. 2 shows the changes in the vital signs during dexmedetomidine infusion. Both blood pressure and heart rate tended to decrease as the drug was intravenously administered. During sedation, the oxygen saturation of the patient was well maintained without any respiratory depression.

The baseline variability of the BIS value was 7.024%. The Spearman’s coefficient of rank correlation (95% confidence interval [CI]) was 0.566 (0.563–0.568; P < 0.0001), and the Pk (95% CI) was 0.636 (0.635–0.637). The BIS values significantly decreased with the increase in the level of sedation as evaluated by the MOAA/S score. The mean BIS values when the MOAA/S scores were 5, 3, and 1 were 87.22 ± 7.06, 75.85 ± 9.81, and 68.29 ± 12.65, respectively (Fig. 3).

Fig. 4 shows the results of the ROC analysis of the relationship between the BIS values and the MOAA/S scores (5, 3, and 1). The cut-off BIS values (Youden index) when the MOAA/S scores were 5, 3, and 1 were 82 (sensitivity, 76.65; specificity, 68.74; area under the curve [AUC], 0.787), 79 (sensitivity, 72.89; specificity, 73.08; AUC, 0.794), and 73 (sensitivity, 72.89; specificity, 79.74; AUC, 0.842), respectively.

Table 1. Demographic Characteristics of the Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients (n = 42)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
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<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>162.4 ± 8.0</td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.2 ± 11.7</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD.

Fig. 2. Change in blood pressure (BP) and heart rate (HR) during the study periods, including the dexmedetomidine sedation period. (A) The period before dexmedetomidine administration (baseline). (B) During the loading dose infusion period. (C) During the maintenance dose infusion period. (D) The period after the end of the dexmedetomidine infusion. The red line represents the mean and standard deviation, and the gray point represents the value of each participant. SBP: systolic BP, DBP: diastolic BP, MBP: mean BP.
After the administration of dexmedetomidine, the average time for the fall in the MOAA/S score to < 5 was 10.40 ± 5.80 min. During the administration of the loading dose, the MOAA/S score dropped to 2 or less, and the planned loading dose was not fully administered; it was altered to the maintenance dose in two male patients aged 55 and 67 years. The MOAA/S scores were monitored to avoid them from falling below 2 while adjusting the maintenance dose of dexmedetomidine. However, 30 patients (14 who were < 65 years old and 16 who were ≥ 65 years old) presented with scores that were ≤ 2. After stopping the dexmedetomidine infusion, the average time for the restoration of consciousness and the MOAA/S score to reach 5 points was 28.29 ± 18.75 min, and the longest time it took to fully recover was 59.63 min. The older the patients are, the longer it took to recover from sedation (regression equation Y = 0.638X − 10.986).

**DISCUSSION**

The BIS monitoring algorithm was developed to combine the following four key EEG features that characterize the full spectrum of the anesthetic-induced changes: degree of high-frequency (14 to 30 Hz) activation, amount of low-frequency synchronization, presence of nearly suppressed periods within the EEG, and presence of fully suppressed (i.e., isoelectric, “flatline”) periods within the EEG. The algorithm

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**Fig. 3.** The Bispectral index (BIS) value and Modified Observer’s Assessment of Alert/Sedation (MOAA/S) score. The line in the center of the box represents the median value, the whiskers indicate the 5 to 95 percentiles, and the plus sign (“+”) represents the mean value. *P < 0.05 vs. an MOAA/S score of 5; independent t-test.

**Fig. 4.** Receiver operating characteristic (ROC) analysis, which was obtained from the association between the MOAA/S score and the BIS value. (A) The cut-off value (up) and ROC curve (down) when the MOAA/S score was 5. (B) The cut-off value (up) and ROC curve (down) when the score was 3. (C) The cut-off value (up) and ROC curve (down) when the MOAA/S score was 1. BIS: Bispectral index, MOAA/S: Modified Observer’s Assessment of Alert/Sedation scale.
enables the optimum combination of these EEG features to provide a reliable processed EEG parameter of the effects of the anesthetic and sedative [12]. However, if the changes in EEG induced by a specific drug are different from those of other sedatives or anesthetics, the reliability and cut-off BIS values should be re-evaluated. Dexmedetomidine, which is widely used in recent years, is a highly selective α2-adrenergic receptor agonist that acts on the locus coeruleus of the brain stem and exerts a sedative effect [13–15]. A study published in 2018 demonstrated that dexmedetomidine and propofol had different effects on the EEG, wherein both dexmedetomidine and propofol induced increased spindle power during moderate sedation. However, dexmedetomidine increased the theta power and decreased the alpha/beta/gamma power across the whole cortex, whereas propofol decreased the alpha power in the occipital area and increased the global beta/gamma power. During deep sedation, dexmedetomidine was associated with increased global theta power and frontocentral spindle power and decreased alpha/beta/gamma power across the whole cortex, whereas propofol was associated with increased theta/alpha/spindle/beta power, which was maximized in the frontal area [10]. Therefore, the reliability of the BIS value during dexmedetomidine sedation and the application of a cut-off value similar to that applied for propofol are debatable. Several studies have evaluated the performance of BIS and its correlations with clinical sedation scales (Richmond agitation-sedation scale, Ramsay sedation scale, and OAA/S) under dexmedetomidine sedation and reported that the performance of the BIS was reliable during dexmedetomidine sedation. However, most of these studies were conducted in ICU patients who were on mechanical ventilation, and one study was conducted in patients undergoing spinal anesthesia with dexmedetomidine sedation using target-controlled infusion, a method not often used in clinical practice because it requires a special infusion pump [16–19]. In the current study, we targeted patients who were undergoing surgery under spinal anesthesia and were treated with dexmedetomidine, which was administered as described in the pharmacopeia (a popular method).

A significant correlation between the BIS value and MOAA/S score was observed, as reported in previous studies [16–21]. However, the average value of the BIS for specific sedation level showed difference. In one study, where a manual infusion of dexmedetomidine was used, the BIS values for moderate sedation (OAA/S score = 3) and deep sedation (OAA/S score = 1–2) were 69.3 and 62.6, respectively [21]. In another study, which used the TCI of dexmedetomidine, a BIS value of 66.12 was reported for moderate sedation (MOAA/S score = 3) [17]. In the current study, the BIS value for an MOAA/S score of 3 was 75.85, and the BIS values for MOAA/S scores of 1 and 0 were 68.3 and 63.6, respectively. In 2009, Kasuya et al. [20] reported lower BIS values with dexmedetomidine sedation than with propofol sedation among healthy volunteers. Additionally, the suggested cut-off values during deep sedation (OAA/S score, ≤ 2) for propofol and dexmedetomidine were 67 and 46, respectively. In the present study, the cut-off value during deep sedation (MOAA/S score, ≤ 1) for dexmedetomidine was 73. These discrepancies in the BIS mean value might be attributed to the age of the patients, method of drug administration, type of surgery (noise and atmosphere of the operating room), and type of sedation scale used.

This study has few limitations. Additional studies involving a larger sample size, a wider age group, and an analysis of the EEG can further provide more meaningful results. Furthermore, a control group comprising patients who undergo surgery in a quiet environment is required. The disadvantage of using the MOAA/S, OAA/S, and RSS methods is that the external stimuli can interfere with the sedation. According to a previous study, 78% of healthy volunteers sedated by dexmedetomidine were awakened by verbal or physical stimulation [22,23]. Therefore, when analyzing the paired BIS and MOAA/S data, the BIS values immediately before and after the MOAA/S measurements might be different. To reduce the bias that may be caused by this phenomenon, the BIS data were examined starting from a maximum of 2.5 min before examining the MOAA/S scale until after checking the scale. Nevertheless, the results of our study showed that the BIS values were relatively high at MOAA/S scores of 5, 3, and 1 when compared to those reported in previous studies [24,25]. This is because that the observational sedation scale, the MOAA/S scale is subjective and the score may vary depending on the examiner. Clinical scoring systems indicate the status of the patient at a single moment in time. Therefore, it is necessary to apply a continuous, objective, and reliable monitoring method, such as the BIS monitoring system, to maintain the appropriate hypnotic depth.

In conclusion, we confirmed that BIS, a monitoring device with an algorithm based on changes in the EEG according to the level of consciousness, along with the clinical signs can be used to assess the hypnotic depth of a patient under dexmedetomidine sedation. However, the BIS value was close to 70 in some patients who were maintained at a deep sedation.
level with dexmedetomidine, which indicates that patients need to be closely monitored using methods that are different from those used for general anesthesia with propofol.

**FUNDING**

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**CONFLICTS OF INTEREST**

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

**DATA AVAILABILITY STATEMENT**

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

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The use of sugammadex in an infant with prolonged neuromuscular blockade - A case report -

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Background: Residual neuromuscular blockade (RNMB) is a frequent event after general anesthesia, which can lead to serious complications, such as upper airway obstruction. Sugammadex is useful in reversing RNMB. However, its use in infants has not yet been approved by the Food and Drug Administration. Therefore, anesthesiologists can be hesitant to use it, even in situations where no other choice is available.

Case: A two-month-old baby presented to the hospital for umbilical polypectomy. At the end of the surgery, neostigmine was administered. Even after waiting for 30 min and injecting an additional dose of neostigmine, neuromuscular blockade was not adequately reversed. Eventually, sugammadex was administered, and spontaneous breathing returned.

Conclusions: If there were no particular causes of delayed return to spontaneous breathing in infants, RNMB should be considered and reversal with sugammadex would be useful.

Keywords: Delayed emergence from anesthesia; Infant; Residual neuromuscular block; Rocuronium; Sugammadex.
a lack of research on establishing safety and effectiveness. Cases of safe use in children abroad and in Korea have been reported continuously [6,7], but very less research data exist regarding its use in infants than that of children.

Herein, we report a case of reversal of neuromuscular blockade using sugammadex in a two-month-old infant with a review of the related literature.

**CASE REPORT**

Prior to the publication of this case, a written informed consent was obtained from the patient’s parents.

A two-month-old infant presented to the hospital for umbilical polypectomy. He was born at a gestational age of 38\(^{+1}\) weeks, weighing 2.99 kg, and had no particular features other than a mass protruding from the navel. Under the diagnosis of umbilical granuloma, cautery using AgNO\(_3\) was performed twice in the clinic, but no improvement was observed.

After admission, vital signs were normal, and the weight was measured at 5.4 kg, and laboratory tests showed no abnormalities. When visited for preoperative evaluation before surgery, the patient was active and showed no signs of decreased muscle tone. As a premedication, intramuscular atropine 0.1 mg was administered. The patient was closely monitored using electrocardiography, pulse oximetry, and esophageal body temperature during surgery. The patient’s heart rate exceeded the normal range, probably due to dehydration or the effect of premedication with atropine. After intravenous administration of thiopental 25 mg, mask ventilation was performed out using sevoflurane, followed by intravenous injection of rocuronium 3 mg. Mask ventilation was not difficult, and endotracheal intubation was performed using a direct laryngoscope. During endotracheal intubation, the airway view was well secured as Cormack-Lehane grade 1, and intubation was successful using an endotracheal tube without cuff with an internal diameter of 3.0. General anesthesia was maintained using sevoflurane, O\(_2\), and N\(_2\)O (Table 1). Using a forced air warming system, the body temperature was maintained within the normal range.

The operation took 42 min. At the end of the surgery, the train-of-four (TOF) count was expected to be at least 3, as inferred from the clinical duration of rocuronium. Although neuromuscular monitoring should have been used, considering the clinical effects of the drug, the authors decided to administer the reversal agent empirically. Neostigmine 0.25 mg was intravenously administered to reverse neuromuscular blockade at the end of the surgery. The patient was manually ventilated, and the authors waited for a return to spontaneous breathing. However, recovery was not observed even approximately 35 min after neostigmine administration. Dose of anticholinesterase needed to reverse neuromuscular blockade is 0.07 mg/kg at TOF count 2–3. An additional dose of neostigmine was administered under the suspicion of a lack of adequate dose of reversal agent.

The continued effect of atropine given by premedication was expected considering patient’s heart rate, so instead of administering neostigmine/glycopyrrolate mixture, we planned to administer neostigmine firstly and monitor changes in EKG, heart rate, then secondly administer glycopyrrolate. Heart rate and EKG remained stable after the sole administration of neostigmine. The pupil reflex was normal, but spontaneous respiration did not return. Approximately 30 min after the second dose of neostigmine (approximately 1 h after the first dose of neostigmine), the post-tetanic count (PTC) of 0 was measured using a neuromuscular monitoring device (TOF-Watch, Organon Ltd., Ireland). Manual ventilation was maintained for approximately 20 min, and the PTC of 2 was measured. Sugammadex 25 mg was administered because it was determined that reversal of

<table>
<thead>
<tr>
<th>Time</th>
<th>Heart rate (beats/min)</th>
<th>Respiratory rate (breaths/min)</th>
<th>ETCO(_2) (mmHg)</th>
<th>SpO(_2) (%)</th>
<th>Tidal volume (ml)</th>
<th>Sevoflurane (vol %)</th>
<th>O(_2)::N(_2)O (L/min)</th>
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</tr>
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<tbody>
<tr>
<td>12:45</td>
<td>210</td>
<td>23</td>
<td>100</td>
<td></td>
<td></td>
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<td>202</td>
<td>28</td>
<td>100</td>
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<td>25</td>
<td>100</td>
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<td>22</td>
<td>100</td>
<td></td>
<td>40</td>
<td>2,5</td>
<td>1.5;1.5</td>
<td>Thiotepal 25 mg IV</td>
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<td>197</td>
<td>20</td>
<td>36</td>
<td>100</td>
<td>40</td>
<td>2,5</td>
<td>1.5;1.5</td>
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<td>22</td>
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<td>2,5</td>
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<td>36.8°C</td>
</tr>
</tbody>
</table>

**Table 1.** Pre- and Intra-operative Vital Sign and Administered General Anesthetics

ETCO\(_2\): end-tidal CO\(_2\), SpO\(_2\): saturation of percutaneous oxygen, IV: intravenous.

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neuromuscular blockage was incomplete. After administration of sugammadex, the patient began to move slightly, measuring up to 77% of the TOF ratio, with recovery of spontaneous respiration (Table 2, Fig. 1). The TOF was > 90% at the time of extubation. The patient was transported to the post-anesthesia care unit (PACU) thereafter.

After arriving at the PACU, 5 L/min of O₂ was administered through a mask with a reservoir bag for 20 min, and oxygen saturation was between 98% and 100%. The patient stayed in the PACU for about 50 min and was transferred to the ward without any problems. In the ward, an antipyretic was prescribed because of the high body temperature of 38°C the day after the surgery, and he was discharged after the fever subsided. The surgical site was observed to be clean five days after the discharge. The patient was active, and no specific neurological symptoms were observed.

**DISCUSSION**

As children are immature in the development of neuro-

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**Table 2. Postoperative Anesthesia Recovery Progress after Administration of Neostigmine and Sugammadex**

<table>
<thead>
<tr>
<th>Time</th>
<th>Time elapsed since the first injection of reverse medication</th>
<th>IV drug</th>
<th>Dose</th>
<th>Neuromuscular blockade monitoring</th>
<th>BT</th>
<th>Note</th>
</tr>
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<tr>
<td>13:42</td>
<td>36 min</td>
<td>Neostigmine</td>
<td>0.25 mg</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>14:18</td>
<td>1 h 3 min</td>
<td>Neostigmine</td>
<td>0.25 mg</td>
<td></td>
<td>PTC 0</td>
<td></td>
</tr>
<tr>
<td>14:45</td>
<td>1 h 23 min</td>
<td>Neostigmine</td>
<td>0.25 mg</td>
<td></td>
<td>PTC 2</td>
<td>35.9°C</td>
</tr>
<tr>
<td>15:05</td>
<td></td>
<td>PTC 3</td>
<td></td>
<td></td>
<td></td>
<td>Forced air warming</td>
</tr>
<tr>
<td>15:06</td>
<td></td>
<td>Sugammadex</td>
<td>25 mg</td>
<td>TOF 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15:11</td>
<td>1 h 29 min</td>
<td>Sugammadex</td>
<td></td>
<td>TOF 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15:12</td>
<td></td>
<td>Sugammadex</td>
<td></td>
<td>TOF 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15:13</td>
<td></td>
<td>Sugammadex</td>
<td></td>
<td>TOF 74%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15:14</td>
<td></td>
<td>Sugammadex</td>
<td></td>
<td>TOF 77%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15:15</td>
<td>1 h 33 min</td>
<td>Sugammadex</td>
<td></td>
<td>TOF 77%</td>
<td>36.3°C</td>
<td>Extubation*</td>
</tr>
</tbody>
</table>

BT: body temperature, IV: intravenous, EMR: electronic medical record, TOF: train-of-four, PTC: post-tetanic count. *Due to the limitations of the EMR system, the last TOF ratio recorded was 77%, but actual extubation was performed after confirming that the TOF ratio was 95%.

---

**Fig. 1.** The monitoring device was attached on the patient’s arm. (A) The size of lead for stimulation was inappropriate for an infant, so the edge was cut and used. (B) Neuromuscular blockade reversed as TOF 4 after administration of sugammadex. TOF: train-of-four.
Sugammadex in an infant

muscular junctions and differ in pharmacokinetics of drugs from adults, caution is needed when using a variety of drugs, including NMBDs and their reversal agents. In particular, the effective use of NMBDs in acetylcholine receptors in infants and acetylcholine deficiency in their developing motor nerves may make them vulnerable to the action of a non-depolarizing NMBD [1,8]. This delays recovery from neuromuscular blockade and increases the risk of RNMB after surgery. Therefore, for general anesthesia, it is desirable to confirm the TOF ratio before and after the administration of NMBDs and its reversal agent.

Recently, there have been continuous reports of reversal of neuromuscular blockade without adverse events by administering sugammadex in pediatric patients diagnosed with genetic disease accompanied by decreased muscle tone. Kim and Chun [9] used 2 mg/kg of sugammadex in an 11-year-old child diagnosed with Duchenne muscular dystrophy. Sung et al. [10] also used 2 mg/kg of sugammadex in a 4-year-old child diagnosed with Prader-Willi syndrome. In both cases, the neuromuscular blockade was effectively reversed without any side effects.

In addition, the number of cases of sugammadex use in infants is increasing. Franz et al. [11] recently reported 331 cases of sugammadex used in infants under 2-year-olds. According to the report, 2 mg/kg of sugammadex for 223 cases, 4 mg/kg for 98 cases, and 16 mg/kg for 10 cases were used, with no notable adverse events. However, the use of sugammadex has only been approved in adults. Therefore, anesthesiologists cannot help hesitating regarding using it in infants.

In this case, the patient was not diagnosed with any genetic disease accompanied by decreased muscle tone or abnormal liver or kidney function. Therefore, other causes had to be identified initially before determining that the cause of delayed recovery was due to RNMB. Delayed recovery from anesthesia has a variety of causes, including pharmacokinetics, pharmacodynamics, and neurological reasons [12]. Firstly, cerebral ischemia was considered, the most likely neurological reason. However, there was no history of cerebrovascular disease and no special events during surgery to suspect air embolism, and relatively stable vital signs were maintained and pupil reflexes were intact; thus, neurological causes were excluded. In addition, the end-tidal concentration of sevoflurane gas was reduced to less than 0.1% at the time of arousal, and opioids were not used; therefore, excessive sedation was ruled out. To prevent hypoxia and hypothermia, which can affect the recovery of spontaneous respiration, the end-tidal carbon dioxide (ETCO₂) was maintained between 35 and 40 mmHg, and the normal body temperature was maintained by applying a forced air warmer. Finally, RNMB was identified by monitoring the TOF ratio, and recovery was achieved without adverse effects using sugammadex.

PTC of 2, even with administration of a neuromuscular blockade reversal agent, can be caused by a variety of causes. First, a residual neuromuscular blockade was considered. The criteria for appropriate reversal of neuromuscular blockade is 0.90 or higher on TOF monitoring. Although PTC of 2 is of unclear cause, it can be determined that it was caused by insufficient reversal of neuromuscular blockade. The factors that can cause insufficient reversal can be divided into three categories: pre-, intra-, and post-operative. Preoperative factors include patient’s age, sex, preoperative conditions, and medications that can affect neuromuscular transmission. The most likely explanation for this case was age. Anderson reported that the effectiveness of NMBD increases in neonates because of altered pharmacodynamics [13]. The type of NMBD could be considered as an intraoperative factor. Rocuronium was used as an intermediate-acting drug, but the dose was not excessive. Although electrolyte imbalance could not be confirmed intraoperatively, preoperative laboratory tests showed normal electrolyte levels. Moreover, there were few factors that could affect the patient’s general status during surgery, so electrolyte imbalance could be excluded. The inhaled anesthetics could affect the effect of neuromuscular blockade, but most anesthetics were removed because sufficient time had passed. Hypothermia could be considered a postoperative factor, but it did not occur in this case.

Second, neostigmine-induced muscle weakness could be considered as the cause of PTC of 2. Neostigmine administration after complete reversal of neuromuscular blockade potentially has a negative effect on respiratory muscles. Changed sensitivity of the upper airway muscles in the presence of overabundant acetylcholine can lead to desensitization of the acetylcholine receptor, depolarizing blockade, or an open channel blockade [4]. Neostigmine-induced muscle weakness could be ruled out because neuromuscular blockade was reversed immediately after administration of sugammadex. Comprehensively, the most likely factor for this case was the extension of the neuromuscular blockade duration due to age.

In this case, using sugammadex seems appropriate to complete insufficient reversal of neuromuscular blockade.
Moreover, it is very important to monitor neuromuscular blockade before induction of anesthesia in infants as well as in all patients. After the surgery, the patient and patient’s parents were interviewed to check for further medical and family history, and there were no specifics other than hypertension on the paternal side. However, there is a possibility that the patient may have had an undiagnosed genetic condition associated with neuromuscular junctions, such as congenital myasthenic syndrome. The parents were given an explanation that the patient may experience a delayed recovery from general anesthesia again in the future.

In conclusion, RNMB can occur in anyone, and a present, waiting for spontaneous respiration recovery is the usual option to manage it. In case of an incomplete recovery even after waiting, a decision to wait more or to give sugammadex for full recovery needs to be made. Although the use of sugammadex in children has not yet been approved by the FDA, according to continuously reported studies, the use of sugammadex at 2–4 mg/kg is reasonable considering the risk caused by RNMB.

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CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

Not applicable.

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Living-donor ABO-incompatible (ABOi) liver transplantation (LT) is now recognized as the only way to overcome blood type barriers and successfully expand donor pools [1]. However, in case of ABOi LT, hyperacute rejection could be occurred because of immune response by anti-A or anti-B antibodies [2]. Therapeutic plasma exchange (TPE) decreases the naturally occurring anti-A or anti-B isoagglutinin titer. However, TPE, on the morning of LT, is occasionally inevitable in TPE-resistant patients who struggle to lower anti-A or anti-B isoagglutinin titers [3]. The isoagglutinin titers should be dropped below 1:8 to avoid hyperacute rejection [4,5]. However, an excessive citrate load during TPE can cause hypocalcemia and hypomagnesemia and acid-base imbalances [6]. Therefore, metabolic alkalosis with compensatory hypercarbia and electrolyte disturbances occurred before LT [7,8]. If TPE was performed the day before surgery, patients
may have time to correct acid-base imbalance and electrolyte disturbances by respiratory compensation or supplementation of electrolytes. On the contrary, TPE was performed even on the day of surgery, this imbalance will be further exacerbated, which can cause severe arrhythmias and fatal outcomes.

We report on two ABOi LT cases including severe metabolic alkalosis and ventricular tachycardia who received TPE on the day of surgery. One case had a surprisingly high metabolic alkalosis of pH 7.73 immediately after tracheal intubation and the other had sudden ventricular tachycardia after surgical incision accompanied with severe hypokalemia of 1.8 mmol/L.

**CASE REPORT**

These case reports were approved by the Institutional Review Board (no. 2021-0691).

**Case 1**

A 58-year-old male with alcoholic cirrhosis (Model for End-Stage Liver Disease [MELD] score: 17) received ABOi LT with TPE on the operative morning. The initial isoagglutinin titer of the patient was 1:2,048, and even after TPE was performed eight times up to the day before surgery, the titer was 1:32. The 9th TPE was performed on the morning of surgery, with 29 units (replaced volume 4,759 ml) of fresh frozen plasma (FFP) replaced and an acid-citrate-dextrose solution used as an anticoagulant. LT was then performed, with the final titer of 1:8.

Room air arterial blood gas analysis (ABGA) ([Table 1](#)) was performed after entering the operating room. The arterial partial pressure of carbon dioxide (PaCO₂) and bicarbonate (HCO₃⁻) were unexpectedly high and were reexamined after encouraging deep breathing. Although we tried to avoid an unintentional increase of minute ventilation during anesthesia induction and manual bagging, which may disrupt compensatory hypercarbia, we found that PaCO₂ was decreased from 75 mmHg to 46 mmHg. Consequently, this caused uncompensated severe metabolic alkalosis (pH, 7.53 to 7.73) with sustained HCO₃⁻ retention (> 60 mmol/L). Severe hypokalemia (2.1 mEq/L) was also noted.

### Case 2

A 39-year-old male with alcoholic cirrhosis (MELD score: 18) received ABOi LT with an 8th TPE the operative morning. The initial isoagglutinin titer of the patient was 1:4,096. The titer was 1:16, even though TPE was performed seven times until the day before surgery. Therefore, the 8th TPE was performed on the morning of surgery, with 20 units (replaced volume 3,287 ml) of FFP replaced and an acid-citrate-dextrose solution used as an anticoagulant. LT was then performed with the final titer of 1:8.

Metabolic alkalosis was revealed on room air ABGA ([Table 2](#)).

### Table 1. Artery Blood Gas Analysis after Entering the Operating Room

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>FiO₂</th>
<th>EtCO₂</th>
<th>pH</th>
<th>pCO₂</th>
<th>pO₂</th>
<th>HCO₃⁻</th>
<th>BE</th>
<th>Sat</th>
<th>Na</th>
<th>K</th>
<th>Ca</th>
<th>Lac</th>
<th>Hct</th>
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<tbody>
<tr>
<td>14:46</td>
<td>Room air</td>
<td>0.21</td>
<td>51</td>
<td>7.53</td>
<td>75</td>
<td>233</td>
<td>&gt; 60</td>
<td>?</td>
<td>?</td>
<td>140</td>
<td>2.2</td>
<td>1.24</td>
<td>1.1</td>
<td>24</td>
</tr>
<tr>
<td>14:49</td>
<td>Re-check</td>
<td>0.21</td>
<td>47</td>
<td>7.63</td>
<td>60</td>
<td>173</td>
<td>&gt; 60</td>
<td>?</td>
<td>?</td>
<td>142</td>
<td>2.1</td>
<td>1.31</td>
<td>1.1</td>
<td>25</td>
</tr>
<tr>
<td>15:01</td>
<td>After intu.</td>
<td>0.5</td>
<td>35</td>
<td>7.73</td>
<td>46</td>
<td>100</td>
<td>&gt; 60</td>
<td>?</td>
<td>?</td>
<td>139</td>
<td>2.1</td>
<td>1.2</td>
<td>1.3</td>
<td>23</td>
</tr>
<tr>
<td>15:27</td>
<td>Before inc.</td>
<td>0.5</td>
<td>43</td>
<td>7.66</td>
<td>56</td>
<td>72</td>
<td>&gt; 60</td>
<td>?</td>
<td>?</td>
<td>141</td>
<td>2.0</td>
<td>1.31</td>
<td>1.6</td>
<td>23</td>
</tr>
</tbody>
</table>


### Table 2. Artery Blood Gas Analysis after Entering the Operating Room

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>FiO₂</th>
<th>EtCO₂</th>
<th>pH</th>
<th>pCO₂</th>
<th>pO₂</th>
<th>HCO₃⁻</th>
<th>BE</th>
<th>Sat</th>
<th>Na</th>
<th>K</th>
<th>Ca</th>
<th>Lac</th>
<th>Hct</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:40</td>
<td>Room air</td>
<td>0.21</td>
<td>42</td>
<td>7.61</td>
<td>42</td>
<td>77</td>
<td>42.2</td>
<td>19.0</td>
<td>97</td>
<td>141</td>
<td>2.0</td>
<td>0.98</td>
<td>1.7</td>
<td>23</td>
</tr>
<tr>
<td>13:40</td>
<td>After intu.</td>
<td>0.5</td>
<td>42</td>
<td>7.56</td>
<td>45</td>
<td>183</td>
<td>40.3</td>
<td>16.5</td>
<td>100</td>
<td>142</td>
<td>1.8</td>
<td>1.02</td>
<td>2.0</td>
<td>20</td>
</tr>
<tr>
<td>14:35</td>
<td>10 min. before VT</td>
<td>0.5</td>
<td>41</td>
<td>7.56</td>
<td>44</td>
<td>136</td>
<td>39.4</td>
<td>15.7</td>
<td>99</td>
<td>142</td>
<td>2.2</td>
<td>1.04</td>
<td>2.3</td>
<td>19</td>
</tr>
<tr>
<td>15:06</td>
<td>20 min. after VT</td>
<td>0.5</td>
<td>42</td>
<td>7.51</td>
<td>47</td>
<td>135</td>
<td>37.5</td>
<td>13.1</td>
<td>99</td>
<td>143</td>
<td>2.6</td>
<td>1.02</td>
<td>2.2</td>
<td>24</td>
</tr>
</tbody>
</table>

after entering the operating room. Anesthesia was induced, with careful attention to avoid hyperventilation by bag and mask ventilation. After anesthesia induction, metabolic alkalosis and respiratory compensation were shown on ABGA with severe hypokalemia (1.8 mEq/L). Potassium chloride was supplemented, and hypokalemia was slightly resolved. However, ventricular tachycardia with severe blood pressure drop occurred for 10 s about 40 min after the incision, but the patient spontaneously recovered (Fig. 1).

**DISCUSSION**

According to the World Health Organization and the Spanish Transplant Organization, Organización Nacional de Trasplantes Global Observatory on Donation and Transplantation, more than 30,000 LTs per year are performed worldwide as a potential curative treatment for patients with end-stage liver disease or hepatocellular carcinoma. However, a donor organ shortage in Korea has led to high waiting lists and increased mortality rates. Therefore, to overcome organ shortage, living-donor ABOi LTs have become increasingly popular [9,10].

Historically, ABOi LT has been challenged with various desensitization methods, such as TPE, direct graft infusion therapy, cyclophosphamide, splenectomy, and intraarterial or intravenous immunoglobulin therapies [2,8]. Currently, desensitization protocol of TPE with preemptive rituximab administration has been standardized and has allowed ABOi living donor liver transplantation (LDLT) to become more successful [1–3].

Pre-LT TPEs are typically performed many times until the day before LT to effectively decrease anti-A or anti-B isoagglutinin titers until dropped below 1:8 [4,5]. The titers were followed up daily before liver transplantation to ensure that the titer decreased below 1:8. Through the procedure, the incidence of hyperacute rejection in ABOi LT can be reduced. Usually, TPE was performed using a dual lumen central venous catheter in the internal jugular vein. The infusion rate was set at approximately 40 ml/min and was adjusted according to the patient’s tolerance. Albumin, which role a significant part in blood osmotic pressure, was the preferred replacement fluid as long as coagulation lab test was within the normal range [11]. Regional citrate anticoagulation (RCA) was infused with a huge amount of FFP as replacement fluid. The FFP infused approximately 1.5 times the plasma volume [4]. The FFP can compensate for the loss of coagulation factors accompanied by plasma drainage. The RCA used in TPE, which was combined with ionized calcium, which was a necessary cofactor of the coagulation cascade [12]. Accumulation of citrate causes systemic hypocalcemia, which leads to tetany, QT prolongation and life-threatening arrhythmias may occur [13]. Therefore, during TPE, calcium gluconate was continuously infused to prevent hypocalcemia [14]. However, the massive citrate load from the RCA solution and FFPs might shift the acid-base status in liver cirrhosis patients from respiratory alkalosis to metabolic alkalosis [8]. Consequently, with pre-existing electrolyte disturbances, the risk of severe hypokalemia and hypomagnesemia are aggravated in ABOi LDLT recipients [8].

Therefore, anesthesiologists should be alert in patients with ABOi LT because inadvertent hyperventilation might take place during anesthesia induction with manual bagging. Such hyperventilation may lead to severe alkalosis because rapid respiratory alkalosis initiated by an unintentional fall in PaCO₂ profoundly aggraves preexisting metabolic

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**Fig. 1.** (A) ECG and (B) arterial pressure before and after ventricular tachycardia. Just before ventricular tachycardia, hypokalemic ECG findings, such as ST-segment depression, T-wave flattening, and prominent U waves were seen. ECG: electrocardiography.
In our first case, we were surprised to find that a pH of 7.7 and severe hypokalemia after tracheal intubation developed, even though we intended to avoid hyperventilation. This implies we should have paid more attention and been more careful during manual bagging. After finding this severe alkalosis, we decreased minute ventilation to compensate severe alkalosis and small amount of potassium chloride was supplemented.

Our second case developed ventricular tachycardia with severe hypokalemia (1.8 mmol/L) after surgical incision. Fortunately, the ventricular tachycardia running time was short and recovered spontaneously without treatment. We therefore could begin to manage the acid-base and electrolyte disturbances without further ventricular arrhythmias.

Potassium’s the arrhythmogenic potential on the heart has been extensively studied [15]. If severe, it is associated with life-threatening ventricular arrhythmias. Various literatures demonstrated a significant positive correlation between hypokalemia and the incidence of malignant ventricular arrhythmias. Therefore, in case of severe hypokalemia, potassium supplementation should be actively carried out within the recommended infusion rate.

The electrocardiographic (ECG) criteria for hypokalemia include the presence of U waves greater than 1 mm and U waves larger than the T wave with associated ST-segment depression [15]. Before developing ventricular tachycardia, our second case of hypokalemia also showed similar hypokalemic ECG changes.

In conclusion, our cases report strongly suggests that anesthesiologists should pay particular attention to PaCO₂ changes and hypokalemia in ABOi LT, particularly at the start of anesthesia and mechanical ventilation in patients who just finished TPE the operative day morning. This may disturb the acid-base homeostasis and electrolyte balance, resulting in life-threatening ventricular tachycardia.

**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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Spontaneous intracranial hypotension (SIH) occurs due to cerebrospinal fluid (CSF) leakage from the spinal column. Underlying dural sac weakness associated with meningeal diverticula, dural weakness caused by minor trauma, ventral dural tears of intervertebral disc material, and CSF-venous fistulas are common causes of SIH. However, in some cases, the exact cause of SIH is completely unknown \[1,2\]. Orthostatic headache is the most common and important manifestation of SIH patients. Various clinical presentations such as nausea, vomiting, photophobia, hearing impairment and dizziness can be observed with orthostatic headache \[1\]. Diagnostic measures for suspected SIH are radioisotope (RI) cisternography, computed tomography myelography, and magnetic resonance imaging (MRI) myelography \[1,2\].

Conservative treatment for headache due to SIH includes bed rest, theophylline, intravenous fluid infusion, caffeine, and an epidural blood patch (EBP). Among such treatment, an EBP is considered the treatment of choice for those patients whose headache did not improve with initial conservative treatment.

Greater occipital nerve (GON) blockade has been performed widely to relieve symptoms of migraine, tension-type headache of spontaneous intracranial hypotension. This study describes successful treatment of SIH with bilateral GON blockade in a 40-year-old male who presented with severe orthostatic headache.

Case Report

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Greater occipital nerve blockade using ultrasound guidance for the headache of spontaneous intracranial hypotension - A case report -

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Background: Spontaneous intracranial hypotension occurs due to cerebrospinal fluid leakage from the spinal column, and orthostatic headache is the most common clinical presentation. Recent studies showed that bilateral greater occipital nerve blockade demonstrated clinical efficacy in relieving post-dural puncture headache after caesarean section.

Case: A 40-year-old male who presented severe orthostatic headache was consulted to our pain clinic from neurology department. He initially felt a dull nature pain over the whole occipital area which then spread over the frontal and parietal areas. His headache was combined with nausea and vomiting. An epidural blood patch was delayed until final cisternography, and bilateral greater occipital nerve blockade using ultrasound guidance was performed instead. After the blockade, the previously existing headache around the occipital and parietal areas disappeared completely, but mild headache persisted around the frontal area.

Conclusions: Greater occipital nerve blockade could be a good therapeutic alternative to improve headache resulting from spontaneous intracranial hypotension.

Keywords: Greater occipital nerve; Orthostatic headache; Spontaneous intracranial hypotension; Ultrasound.
headache, and cluster headache [3]. Recent studies showed that bilateral GON blockade demonstrated clinical efficacy in relieving post-dural puncture headache after caesarean sections [4].

We encountered a patient with severe orthostatic headache who was diagnosed as SIH after admission to the neurology department. Herein, we report this case as GON blockade using ultrasound guidance was performed successfully, and it demonstrated a dramatic improvement of the headache. Before the preparation of this case report, written informed consent for publication was obtained from the patient.

**CASE REPORT**

A 40-year-old male with a height of 173 cm and a weight of 68 kg, who presented severe orthostatic headache, was consulted to our pain clinic from neurology department. The headache started three weeks prior to the admission with a characteristic orthostatic nature. The patient had no history of headache prior to this ongoing orthostatic headache. He initially felt a pain over the whole occipital area which then spread over the frontal and parietal areas. He described his headache as dull nature pain accompanied by pressure sensation, and it was associated with nausea and vomiting. He graded his headache as 9/10 on a numerical rating scale (NRS) before admission to the neurology department. After strict bed rest and intravenous hydration therapy, his NRS decreased to 7/10. The headache persisted for whole day during his admission. Physical examination did not reveal any specific neurologic abnormality or symptoms. He did not have any special history of trauma or accidental dural puncture prior to the onset of this headache. He showed slightly decreased kidney function due to IgA nephropathy which was diagnosed three years ago. He could not maintain his daily activity due to headache. Contrast enhanced MRI revealed bilateral symmetric curvilinear dural enhancement along both cerebral high convexities. Both internal carotid artery angiography and vertebral artery angiography were performed, but they did not demonstrate any suspicious lesion of cerebral venous thrombosis. To identify the leakage level of CSF, cisternography was planned. However, cisternography was only possible at least three weeks later due to an overloaded schedule.

Before the planned cisternography, this patient was consulted to our pain clinic for an EBP. Since we thought that targeted EBP after confirmation of leakage level of CSF is more appropriate for headache improvement, an EBP was delayed until the cisternography was performed. Instead of an EBP, we suggested a bilateral GON blockade using ultrasound guidance for symptom improvement.

The GON blockade was performed by a pain physician who had more than five years of experience in ultrasound guided procedures. The patient was asked to lie with his face down and his head was flexed slightly. Afterward, the spinous process of C2 was palpated and marked. Sterile draping was done using a povidone swab. A linear probe with a frequency of 4–15 MHz was used (Logiq S8, GE Healthcare, USA). After identifying the spinous process of C2, we placed the probe in a parallel direction to the laminae of C2 and then rotated it along the long axis of the obliquus capitis inferior (OCI) (Fig 1A). Since the GON always passes by the OCI, the OCI muscle was first identified [5]. After this identification, our final target site was the intermuscular fatty layer between the OCI and semispinalis capitis (SSC) muscle (Fig. 1B). Local infiltration using 1% lidocaine was done before needle insertion. A 23 G needle was inserted slowly toward the intermuscular fatty layer between the OCI and SSC using an in-plane method. When the needle tip was confirmed to have reached the final target site, 0.1% ropivacaine 3 ml was injected. We could check the accumulation of the local anesthetics at the intermuscular fatty layer (Fig. 1C). Both sides of the GON blockade were performed using the same local anesthetics and technique.

After completing the bilateral GON blockade, the patient was lay down in bed for 20 min and was monitored for the appearance of any possible side effect. He was asked to sit up for a while in order to confirm the improvement of the orthostatic headache. He reported that the previous headache which existed around the occipital and parietal areas had disappeared completely, but that mild headache persisted at the frontal area. On the next day after the GON blockade, the significant improvement of headache was still maintained and NRS of the headache was approximately 1–2/10. Two days after GON blockade, he was discharged with mild headache at the frontal area. He was fully educated about the importance of absolute bed rest at home to prevent the aggravation of the intracranial hypotension and headache.

Three weeks after his discharge, he was readmitted for the cisternography. The test demonstrated multiple CSF leakages at the upper thoracic spine, and lumbar puncture opening pressure was as low as 5 cmH2O. Although the headache was mild with NRS of 1–2/10, an EBP was performed to pre-
vent any unwanted complication due to low intracranial pressure. The EBP was performed using the C-arm guided technique. For epidural entry at the specific spinal level, the midline approach via loss-of-air resistance was used. Autologous blood of 10 ml was injected using a 22-G Tuohy epidural needle. The blood was injected very slowly to minimize any discomfort during the injection. Before the blood injection, 3 ml of contrast medium was injected to confirm the epidural space.

One month after the GON blockade and EBP were performed, the orthostatic headache had almost completely disappeared but mild tinnitus remained.

**DISCUSSION**

This case of orthostatic headache due to SIH demonstrated a dramatic improvement after bilateral GON blockade using ultrasound guidance. Peripheral nerve blockade including GON has been performed widely to relieve cervicogenic headache, cluster headache, tension-type headache, occipital neuralgia and migraine [3]. The clinical features and mechanism of the headache which occurs due to SIH are distinct compared to common primary headache. Headache of SIH is a clinical result of CSF leakage, leading to a decreased CSF pressure, which eventually triggers a movement of intracranial structures and traction of pain-sensitive structures in the upright position [1,2]. Although such a distinctive nature of the headache is present in SIH, GON blockade resulted in good therapeutic efficacy. There is only one case report which demonstrated an efficacy of GON blockade for the headache due to SIH. GON blockade resulted in short-term benefit lasting four month, and subsequent pulsed radiofrequency of GON showed significant pain relief lasting 10 months [6].

GON originates from the medial branch of the C2 dorsal ramus with variable contributions from the C3 dorsal ramus, and ascends superior to the posterior scalp. GON is always situated between the OCI and SSC muscle and then pierces to the SSC muscle [7]. The trigeminal and upper cervical nerve provide sensory innervation to the face and scalp. The trigeminal nucleus caudalis is located near the upper cervical spinal neuron. The convergence of sensory input from the upper cervical and trigeminal nerves to the trigeminal nucleus caudalis is present. However, in cases of SIH, the activity in the trigeminal and greater occipital nerves can be increased due to a dural stretch caused by a low intracranial pressure [6]. GON blockade can result in the inhibition of sensory input to the trigeminal nucleus caudalis from upper cervical nerves [8]. A “winding down” of the central sensitization caused by the reduction in afferent input to the trigeminal nucleus caudalis can provide a neuromodulatory effect of the headache [6,8].

Many pain physicians still perform a GON blockade using the conventional approach which depends on the palpation of external anatomic landmarks at the level of the superior nuchal line. However, we should keep in mind that the course of GON presents diverse variations at the level of the superior nuchal line [7,9]. We used a proximal approach at the C2 level suggested by Greher et al. [7] targeting GON superficial to the OCI muscle. Their study revealed that the proximal-level GON blockade showed a higher success rate and was more accurate than the conventional blockade at

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Fig. 1. Photography showing the proper position of the linear probe for greater occipital nerve blockade (A). Ultrasound image showing the obliquus capitis inferior (OCI), and the semispinalis capitis (SSC) muscle. Asterisk (*) indicates intermuscular fatty layer between the OCI and the SSC muscle, which is the final target site (B). Red arrow indicates an accumulation of local anesthetics in the intermuscular fatty layer between the OCI and the SSC muscle (C).
the level of the superior nuchal line [7]. Moreover, proximal-level GON blockade provided more sustained analgesic benefit compared with the distal-level GON blockade [10]. Considering a constant relationship between the GON and OCI muscle [7,8], GON blockade at the C2 level provides many advantages compared to the conventional method at the level of the superior nuchal line.

In this case, we delayed the EBP to perform leakage level targeting EBP afterward. In a retrospective study of EBP, site-directed EBP correlated well with a greater likelihood of first EBP efficacy [11]. SIH and post-dural puncture headache have similar pathophysiologic mechanism and clinical manifestation. However, computed tomography-myelography or radionuclide cisternography often revealed multiple levels of CSF leakage throughout the spine in SIH, and the efficacy of EBP was lower in SIH than in post-dural puncture headache [1,2,11].

An EBP has been the treatment of choice for intractable orthostatic headache due to SIH or post-dural puncture headache. However, there is no consensus about the actual blood volume needed for an EBP. A previous study which was performed in SIH patients demonstrated that an epidural blood volume greater than 22.5 ml resulted in a higher success rate compared to a volume less than 22.5 ml (67.9% vs. 47.0%) [12]. However, if a higher volume of epidural blood is used, we should consider the possibility of rebound intracranial hypertension. The main clinical manifestation of rebound intracranial hypertension is headache, nausea, vomiting, and blurred vision [13], which makes it difficult to distinguish from the clinical manifestation of SIH. Recently reported fatal complications such as acute vision loss [14] and arachnoiditis [15] secondary to an EBP, raise the necessity for the further alternative treatment options.

If an EBP shows minimal efficacy in headache improvement or an unwanted complication is expected, combining a bilateral GON blockade with an EBP can be a good alternative. However, further studies with a larger patient group are required to confirm the clinical efficacy.

**FUNDING**

None.

**CONFLICTS OF INTEREST**

No potential conflict of interest relevant to this article was reported.
479-85.
Analgesic efficacy of ultrasound-guided transversus abdominis plane block for laparoscopic gynecological surgery: a randomized controlled trial

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Background: This study aimed to determine whether ultrasound-guided transversus abdominis plane (TAP) block is more effective in reducing postoperative pain and analgesic consumption than local anesthetic infiltration (LAI) at the port site for elective laparoscopic gynecological surgeries.

Methods: Eighty patients with the American Society of Anesthesiologists status I/II undergoing laparoscopic gynecology surgery were enrolled for this randomized control trial. After general anesthesia was administered, patients in group C received LAI at each port site, and patients in group T received bilateral ultrasound-guided TAP block. Postoperative pain was assessed at time intervals of 1/2, 2, 4, 6, 8, and 24 h using the numeric rating scale (NRS). Clinical metrics such as postoperative analgesic diclofenac consumption, need for rescue fentanyl, nausea-vomiting scores, and antiemetic requirements were also recorded.

Results: Seventy-four patients were included in the final analysis. Postoperatively, patients in group T had significantly lower NRS than those in group C (P < 0.05). The highest difference in the postoperative NRS was observed at 2 h (median [1Q, 3Q]; group C = 3 [2, 4]; group T = 1 [0, 2]; P < 0.001). A statistically significant difference was observed in the frequency of diclofenac (75 mg intravenous) requirement between the groups (P = 0.010). No significant difference was observed between the groups in need of rescue fentanyl or antiemetic and the nausea-vomiting scores.

Conclusions: In patients undergoing laparoscopic gynecological surgery, ultrasound-guided TAP block provided greater postoperative analgesic benefits in terms of lower NRS and reduced analgesic requirements than port site LAI.

Keywords: Analgesia; Laparoscopy; Local anesthetic; Transversus abdominis.

INTRODUCTION

Although laparoscopic gynecological surgery is less invasive than open gynecological surgery, significant postoperative pain remains possible. Trocar insertion, tissue dissection, and the creation of pneumoperitoneum contribute to postoperative pain in laparoscopic surgery [1,2]. Undertreatment of this pain can lead to patient discomfort, nausea, vomiting, and consequently delay the patient’s recovery and discharge. Commonly, local anesthetic infiltration (LAI), in-
traperitoneal instillation of local anesthetic, or neuraxial anesthesia are used along with systemic drugs such as opioids, non-steroidal anti-inflammatory drugs (NSAIDs), and dexamethasone for the treatment of postoperative pain from laparoscopic surgery [3,4].

The ultrasound-guided transversus abdominis plane (TAP) block is simple to perform and has recently become a popular technique for reducing postoperative pain after abdominal surgery. It has been shown to provide effective postoperative analgesia in a variety of open abdominal surgical procedures with an opioid-sparing effect and allowing faster patient recovery [5-8]. For laparoscopic surgery, the TAP block has been found to be effective in reducing postoperative pain at rest and opioid consumption. A dose-response relationship was also observed between the local anesthetic dose used in the TAP block and its effect on late pain at rest and opioid consumption [9].

While studies have been conducted to evaluate TAP block in laparoscopic hysterectomy, only a few studies have assessed its benefit in laparoscopic gynecological surgeries [10,11]. Therefore we planned the present study to evaluate whether ultrasound-guided TAP block provided any postoperative analgesic benefits over LAI in patients undergoing laparoscopic gynecological surgery. Our study was based on the hypothesis that ultrasound-guided TAP block is more effective in reducing postoperative pain and analgesic consumption than LAI at the port insertion site in elective gynecologic laparoscopic surgeries under general anesthesia. We considered postoperative pain score at 2 h as an indicator of early post-surgical pain and discomfort. Therefore, the primary outcome of the study was postoperative numeric rating scale (NRS) at 2 h. Postoperative NRS at 1/2, 4, 6, 8, and 24 h, postoperative analgesic requirement (diclofenac), need for rescue analgesia (fentanyl), postoperative nausea and vomiting (PONV) scores, and requirement of antiemetics were the secondary outcomes measured in the first 24 h after surgery.

MATERIALS AND METHODS

This prospective randomized control study was conducted at a tertiary care teaching institute after approval from the Institutional Ethics Committee. Ethics committee approval was received for this study from the ethics committee of Employees’ Insurance Cooperation Postgraduate Institute of Medical Sciences and Research (no. DM(A)H-9/14/17-2012 PGIMSR). This study was registered at Central Trial Registry India (CTRI/2018/05/013625). Eighty patients with the American Society of Anesthesiologists status I/II in the age group of 18–60 years undergoing elective laparoscopic gynecologic surgery excluding laparoscopic hysterectomy were enrolled in this prospective randomized trial from February 2017 to February 2018. Patients with obesity (body mass index > 30 kg/m²), hypersensitivity to amide local anesthetics, steroids, anticoagulant treatment, or with bleeding disorders were excluded from the study. The principal investigator enrolled all patients for the study after a thorough pre-anesthetic check, and written informed consent was obtained. The patients were randomized to group C (general anesthesia with LAI) or group T (general anesthesia with TAP block) using a computer-generated random numbers list, and the allotment was concealed using sealed envelopes. All procedures involving human participants were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

On the day of surgery, the sealed envelope containing the group allotment was handed over to the anesthesia consultant in the operation theater. All patients received oral alprazolam 0.25 mg on the night before and on the morning of surgery. After shifting to the operation theater, all monitors including electrocardiogram, pulse oximetry, and non-invasive blood pressure were attached to each patient, and a Ringers’ lactate drip was started. General anesthesia was induced with fentanyl 2 μg/kg intravenous (IV), propofol 2–3 mg/kg IV, vecuronium 0.1 mg/kg IV, and after adequate muscle relaxation, an appropriately sized pro-seal laryngeal mask airway was inserted. Anesthesia was maintained with 50% O₂, 50% N₂O, and 1–2% sevoflurane and positive pressure ventilation to maintain an end-tidal carbon dioxide concentration of 30–40 mmHg.

Laparoscopic surgeries were performed by insertion of four ports, one at the level of the umbilicus and three at the infra-umbilical level. Patients in group C were given LAI at the port insertion sites before trocar insertion at the start of surgery; a 20 ml syringe of 0.25% levobupivacaine was drawn up and 5 ml of the local anesthetic was infiltrated at each port site. Patients in group T received bilateral ultrasound-guided mid-axillary TAP block with 20 ml of 0.25% levobupivacaine on each side before the start of surgery. After cleaning the skin with 2% chlorhexidine solution, a high frequency 6–13 MHz linear ultrasound transducer probe (Sonosite, USA) was placed at the level of the mid-axillary
line between the 12 ribs and the iliac crest. The three abdominal wall muscle layers, external oblique, internal oblique (IO), and transversus abdominus (TA) were visualized. A 10 cm long 22-gauge TAP block needle (SonoTAP, Pa-junk, Germany) was inserted until the needle tip reached the plane between the IO and TA (Fig. 1). The correct placement of the needle tip in the TAP block plane was confirmed by visualizing the separation of the fascial plane between the IO and TA on the injection of a small volume (up to 5 ml) of saline. Thereafter, 20 ml of 0.25% levobupivacaine was injected, and the spread of the drug in the TAP block plane was seen as an elliptical hypoechoic shadow (Fig. 2).

During the surgery, the patient’s hemodynamic parameters including heart rate, systolic blood pressure (BP), diastolic BP, and mean BP were recorded at five minutes interval. Additional IV dose of fentanyl 1ug/kg was administered if there was a 15% increase in hemodynamic parameters from baseline, and the total requirement of fentanyl during surgery was recorded. After completion of the surgery, inhalation anesthetic agents were turned off, the neuromuscular blockade was reversed, and the patient was extubated.

The patients were transferred to the recovery room where they were assessed for pain by another anesthesiologist who was blinded to the group allocation. Pain was assessed on 11 points per NRS (0, no pain; 10, worst imaginable) at 1/2, 2, 4, 6, 8, and 24 h. The postoperative analgesic regimen comprised diclofenac 75 mg intravenously for NRS ≥ 3. For acute pain (NRS > 5), IV dose of fentanyl 1ug/kg was administered as rescue analgesia. No additional analgesic medications were administered to the patients. The total diclofenac consumption and need for rescue analgesia (fentanyl) in the 24 h postoperative period was recorded. PONV was assessed on the categorical scale: 0, none (no nausea or vomiting); 1, mild (nausea only); 2, moderate (nausea with retching); 3, severe (nausea with vomiting); ondansetron 4 mg IV was administered for PONV score > 2. The next day, the site of the TAP block was inspected for swelling, infection, or hematoma before discharge from the hospital.

Based on the pilot cases in patients receiving general anesthesia with LAI (group C), the highest anticipated NRS for patients at 2 h in the postoperative period was 5 (SD = 2.5). We considered a 40% (i.e. 2 points on NRS score) reduction in NRS scores to be of clinical relevance. With a type I error of 0.05, and a type II error of 0.10, a sample size estimated was 33 patients per group with an effect size of 0.80 to detect a significant difference in NRS scores. We recruited 80 patients to allow for any dropouts and exclusions. Details of the recruitment of patients are shown in the Consolidated Standards for Reporting of Trials (CONSORT) flow diagram for the study (Fig. 3), the demographic profile and surgical characteristics of patients in the two groups are shown in Table 1.

Statistical analyses were performed using the SPSS program for Windows (version 17.0, SPSS Inc., USA). Data were checked for normality prior to the statistical analyses. Continuous variables are presented as mean ± SD or median (1Q, 3Q), categorical variables are presented as absolute numbers and percentages. Normally distributed continuous variables including age, weight, intraoperative fentanyl dose,
Table 1. Demographic Profile and Surgical Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group C (n = 37)</th>
<th>Group T (n = 37)</th>
<th>Mean difference (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>27.1 ± 4.1</td>
<td>28.6 ± 3.9</td>
<td>-1.64 (-3.34 to 0.42)</td>
<td>0.126</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>52.6 ± 9.1</td>
<td>53.8 ± 9.3</td>
<td>-1.22 (-5.47 to 3.30)</td>
<td>0.570</td>
</tr>
<tr>
<td>ASA (1/2)</td>
<td>33/4</td>
<td>36/1</td>
<td>-</td>
<td>0.358</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chromo-intubation and salpingostomy</td>
<td>12</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clipping or excision of hydrosalpinx</td>
<td>6</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tube-ovarian mass excision</td>
<td>5</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fulguration of endometriosis and adenomyosis</td>
<td>7</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovarian cystectomy</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myomectomy</td>
<td>4</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgical time (min)</td>
<td>65.6 ± 18.2</td>
<td>75.9 ± 25.9</td>
<td>-11.89 (-22.39 to -1.39)</td>
<td>0.053</td>
</tr>
<tr>
<td>Anesthesia time (min)</td>
<td>83.1 ± 8.7</td>
<td>89.6 ± 24.8</td>
<td>-11.62 (-22.29 to -0.95)</td>
<td>0.208</td>
</tr>
<tr>
<td>Fentanyl dose (μg)</td>
<td>105.0 ± 21.2</td>
<td>112.2 ± 23.9</td>
<td>-7.16 (-17.63 to 3.31)</td>
<td>0.177</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number only. CI: confidence interval. Group C patients received general anesthesia with local anesthetic infiltration; group T patients received general anesthesia with a transversus abdominis plane (TAP) block. Independent Student’s t-test was used for statistical comparison of age, weight, surgical time, anesthesia time, and intraoperative fentanyl dose. Fisher’s exact test was used for statistical comparison of American Society of Anesthesiologists (ASA) status. Four patients in group C and five in group T needed additional fentanyl 1 μg/kg during surgery after the induction dose of fentanyl 2 μg/kg (P value > 0.999). Fisher’s exact test was used for statistical comparisons.
surgical and anesthesia times, total 24 h diclofenac requirement were compared using independent Student’s t-test. Non-normally distributed continuous variables, including postoperative NRS and PONV scores, were analyzed using the Mann–Whitney U test. Categorical variables including the American Society of Anesthesiologists status, number of patients needing additional intraoperative fentanyl, frequency of requirement of postoperative analgesics, and antiemetic were compared using the Fisher’s exact test. Statistical significance was set at P < 0.05.

RESULTS

Of the 80 patients enrolled in the study, six were excluded from the final analysis due to the conversion of the laparoscopic procedure to open surgery by the surgeon (Fig. 3). Patients in groups C and T had comparable demographic and surgical characteristics (Table 1). Table 2 shows the postoperative NRS (primary outcome) for the two groups, these were significantly lower in group T than in group C at 1/2, 2, 4, 6, 8, and 24 h. The highest difference in the postoperative NRS was observed at 2 h (median [1Q, 3Q]; group C = 3 [2, 4]; group T = 1 [0, 2]; P < 0.001).

The mean total fentanyl requirement during surgery for patients in two groups was statistically comparable (mean ± SD; group C = 105.0 ± 21.2 μg, group T = 112.2 ± 23.9 μg; P = 0.177) (Table 1). Four patients in group C and five in group T needed additional fentanyl 1 μg/kg during surgery after the induction dose of fentanyl 2 μg/kg (P value > 0.999). The requirement of analgesics and antiemetics for patients in groups C and T in the 24 h postoperative period is shown in Table 3. A statistically significant difference was observed in the requirement of diclofenac (75 mg IV) between groups C and T (P = 0.010). Postoperatively, 32 patients (86.5%) in group C and 25 patients in group T (67.6%) required diclofenac medication for analgesia. The highest number of patients (16/37, 43.2%) in group C required two doses of diclofenac; the majority in group T (19/37, 51.4%) required only one dose of diclofenac for pain relief. The total diclofenac requirement over the 24 h postoperative period was also significantly lower in group T (68.6 ± 63.4 mg) than in group C (113.5 ± 61.0 mg; P = 0.003). No statistical difference was observed in the requirement of rescue fentanyl or ondansetron between the groups.

The PONV scores were statistically comparable at all points of time in the postoperative period for patients in both groups (median [1Q, 3Q]; group C = 0 [0, 1], group T = 0 [0, 1]; P value >0.999). None of the patients had swelling, hematoma, or infection at any site of the abdominal wall on follow-up on the first postoperative day.

DISCUSSION

The study showed that ultrasound-guided TAP block significantly lowered the postoperative NRS in patients undergoing laparoscopic gynecological surgery. The reduction in NRS was both statistically and clinically significant as a 2-point difference was seen at 2, 4, 6, 8, and 24 h postoperatively. Furthermore, the patients who received TAP block had lower consumption of analgesics (diclofenac) and res-

Table 2. Postoperative NRS

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Group C (n = 37)</th>
<th>Group T (n = 37)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2</td>
<td>3 (2, 4.5)</td>
<td>2 (0, 4)</td>
<td>0.013</td>
</tr>
<tr>
<td>2</td>
<td>3 (2, 4)</td>
<td>1 (0, 2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>4</td>
<td>2 (0, 3)</td>
<td>0 (0, 2)</td>
<td>0.001</td>
</tr>
<tr>
<td>6</td>
<td>2 (1, 3)</td>
<td>0 (0, 2)</td>
<td>0.001</td>
</tr>
<tr>
<td>8</td>
<td>2 (1, 3)</td>
<td>0 (0, 2)</td>
<td>0.001</td>
</tr>
<tr>
<td>24</td>
<td>2 (0, 3)</td>
<td>0 (0, 2)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are presented as median (1Q, 3Q). NRS: numeric rating scale. Group C: patients received general anesthesia with local anesthetic infiltration. Group T: patients received general anesthesia with transversus abdominis plane (TAP) block. Mann-Whitney U test used for statistical comparison.

Table 3. Requirement of Analgesics and Antiemetic in 24 h Postoperative Period

<table>
<thead>
<tr>
<th>Number of doses</th>
<th>Group C (n = 37)</th>
<th>Group T (n = 37)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac (75 mg IV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 dose</td>
<td>5 (13,5)</td>
<td>12 (32,4)</td>
<td>0.010*</td>
</tr>
<tr>
<td>1 dose</td>
<td>13 (35.1)</td>
<td>19 (51.4)</td>
<td></td>
</tr>
<tr>
<td>2 dose</td>
<td>16 (43.2)</td>
<td>4 (10.8)</td>
<td></td>
</tr>
<tr>
<td>3 dose</td>
<td>3 (8.1)</td>
<td>2 (5.4)</td>
<td></td>
</tr>
<tr>
<td>Fentanyl (1 μg/kg IV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 dose</td>
<td>27 (73.0)</td>
<td>34 (91.9)</td>
<td>0.079</td>
</tr>
<tr>
<td>1 dose</td>
<td>8 (21.6)</td>
<td>3 (8.1)</td>
<td></td>
</tr>
<tr>
<td>2 dose</td>
<td>2 (5.4)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Ondansetron (4 mg IV)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 dose</td>
<td>34 (91.9)</td>
<td>32 (86.5)</td>
<td>0.711</td>
</tr>
<tr>
<td>1 dose</td>
<td>3 (8.1)</td>
<td>5 (13.5)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number (%). IV: intravenous. Group C: patients received general anesthesia with local anesthetic infiltration. Group T: patients received general anesthesia with a transversus abdominis plane (TAP) block. Fisher’s exact test was used for statistical comparisons. *Statistically significant difference was seen between group C and group T in frequency of requirement of diclofenac (75 mg IV) in 24 h postoperative period.
cue analgesia (fentanyl) in the 24 h postoperative period compared to those with a given LAI. However, the TAP block group did not differ from the control group in terms of the PONV scores or antiemetic requirements.

The findings of our study are similar to previous studies of Kawahara et al. [12] and De Oliveira et al. [13] showing the significant analgesic effect of TAP block in laparoscopic gynecology surgery. However, these studies differ in the approach of the TAP block, the local anesthetic used, and the comparator control group. In a study by Kawahara et al. [12], patients undergoing laparoscopic gynecological surgery receiving mid-axillary TAP block with 0.35% ropivacaine (20 ml each side) had significantly reduced postoperative pain, analgesic consumption, and nausea-vomiting compared to patients receiving TAP block with saline. Similarly, De Oliveira et al. [13] found that a posterior TAP block with 0.25% or 0.5% ropivacaine to improve the quality of recovery scores and reduce postoperative pain and opioid consumption in patients undergoing daycare gynecological laparoscopy surgery. Conversely, El Hachem et al. [14] reported no postoperative analgesic benefit of TAP block over trocar site LAI in laparoscopic gynecological surgery. In their study, each patient was given a TAP block on one side and LAI on the other side of the abdomen; thereafter, the postoperative pain on both sides was compared.

The pain associated with laparoscopic gynecological surgery includes visceral pain from manipulation of the uterus, fallopian tube, and vagina, and parietal pain from stretching of the parietal peritoneum by pneumoperitoneum and port insertion in the abdominal wall. Commonly, LAI at the port site or intraperitoneally has been used together with opioids, NSAIDs, dexamethasone, and lidocaine infusion for multimodal analgesia for laparoscopic gynecological surgeries [15,16]. Despite several studies on LAI at port sites or intraperitoneally, the results of its analgesic effect are controversial. While Pellicano et al. [17] and Ceyhan et al. [18] found LAI intra-peritoneally and at the port site reduced the postoperative pain, other researchers demonstrated LAI at the port wound did not result in significant analgesia [19,20]. The meta-analysis by Mark et al. [4] concluded that the analgesic effect of LAI was short-lived and limited only to the early postoperative period (6 h).

In contrast to LAI, the TAP block has been found to provide a longer duration of analgesia, lasting up to 24 h, along with a greater opioid-sparing effect for lower abdominal surgery [21,22]. The spread of the local anesthetic in the plane between the TA and IO muscles and the consequent block-

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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Analgesic effects of ultrasound-guided four-quadrant transversus abdominis plane in patients with cytoreductive surgery with hyperthermic intraperitoneal chemotherapy: a prospective, randomized, controlled study

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Background: Postoperative pain occurring after cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is difficult to control because of extensive surgical injuries and long incisions. We assessed whether the addition of a four-quadrant transversus abdominis plane (4Q-TAP) block could help in analgesic control.

Methods: Seventy-two patients scheduled to undergo elective CRS with HIPEC and intravenous patient-controlled analgesia (IV PCA) were enrolled. The patients received 4Q-TAP blocks in a 10 ml mixture of 2% lidocaine and 0.75% ropivacaine per site (4Q-TAP group, n = 36) or normal saline (control group, n = 33). Oxycodone in the post-anesthesia care unit (PACU) and pethidine or tramadol in the ward were used as rescue analgesics. The primary outcome was less than 3 times of rescue analgesic administration (%) in the ward for 5 postoperative days. Secondary endpoints included oxycodone requirement in PACU, fentanyl doses of IV PCA, morphine milligram equivalent (MME) of total opioid use, hospital stay, and postoperative complications.

Results: During 5 postoperative days, there was no difference in pain scores and total rescue analgesic administration between two groups. However, the use of oxycodone in PACU (P = 0.011), fentanyl requirement in IV PCA (P = 0.029), and MME/kg of total opioid use (median, 2.35 vs. 3.21 mg/kg, P = 0.009) were significantly smaller in the 4Q-TAP group. Hospital stay and incidence of postoperative morbidity were similar in both groups.

Conclusions: The 4Q-TAP block enhanced multimodal analgesia and decreased opioid requirements in patients with CRS with HIPEC, but did not change postoperative recovery outcomes.

Keywords: Cytoreduction surgical procedure; Hyperthermic intraperitoneal chemotherapy; Nerve block; Postoperative complications; Postoperative pain.
INTRODUCTION

Thoracic epidural analgesia has been recognized by various guidelines as the treatment of choice among analgesic methods after open abdominal surgery due to a significant improvement in pain control, less opioid consumption, and enhancement of clinical outcomes [1,2]. However, there are still risks of infection, epidural hematoma, and failure of epidural analgesia [3].

Multimodal intravenous patient-controlled analgesia (IV PCA) contributes to enhanced recovery after surgery (ERAS) by reducing the total amount of opioids used and mixing various drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, ketamine, lidocaine [4], dexmedetomidine [5], or nefopam [6] into the IV PCA instead. With the increasing use of minimally invasive techniques, fast-track protocols, and multimodal analgesic techniques, multimodal analgesia with IV PCA has been shown to be comparable to epidural analgesia in postoperative pain control after abdominal surgery [3].

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS with HIPEC) causes severe postoperative pain due to the long incision from the xiphoid process to the pelvic cavity and the severe invasiveness of the surgery, despite the use of IV PCA [7]. However, the effect of the transversus abdominis plane (TAP) block with opioid-reduced multimodal IV PCA on the efficacy of the analgesic in patients with severe surgical pain, such as CRS with HIPEC, remains to be investigated. We hypothesized that the addition of a four-quadrant TAP (4Q-TAP) block [8], which is both a bilateral subcostal TAP block and a bilateral lateral TAP block, in patients who underwent CRS with HIPEC using multimodal IV PCA would effectively control severe postoperative pain and enhance postoperative recovery.

The purpose of this randomized double-blinded controlled study was to investigate whether the 4Q-TAP block could effectively reduce the opioid requirement in patients undergoing elective CRS with HIPEC using multimodal IV PCA, and whether it could be beneficial for postoperative recovery.

MATERIALS AND METHODS

Patients

After an Institutional Review Board approved this prospective randomized double-blinded controlled study (no. 2020-11-022-002), 72 adult patients aged 26–81 years, with an American Society of Anesthesiologists physical status ≤ III, and who were scheduled to undergo elective CRS with HIPEC under general anesthesia provided informed consent to receive the 4Q-TAP block and were enrolled in the study. Patients who had local infections or coagulation abnormalities, could not communicate, were drug-addicts, or were using opioids by various routes before surgery were excluded from the study.

Randomization, allocation, and blinding

On the day of the surgery, the 72 patients were randomly assigned to either the 4Q-TAP group or the control group using a computer-generated randomization table. We used a block randomization method where block sizes of 2 and 4 were also randomly mixed. We used sealed, opaque, sequentially numbered envelopes that were opened by a single investigator when the patient arrived at the operating room (Fig. 1).

The 4Q-TAP group received a postoperative, ultrasound-guided, four-quadrant TAP block, and the control group received an equivalent volume of normal saline. The same type of syringe was used for administering the study drugs; the color of the syringe and that of the study drugs was identical, and eventually the syringes containing the study drugs were indistinguishable. A designated independent investigator prepared four syringes containing equal volume mixtures of 0.75% ropivacaine and 2% lidocaine (10 ml × 4) or normal saline (10 ml × 4) according to the assignment, and did not participate in any other study processes. All patients, surgeons, anesthesiologists, and follow-up observers were blinded to the assignment.

Anesthesia

The patients were taken to the operating room where standard monitors were applied, including pulse oximetry, electrocardiography, blood pressure and temperature monitoring, capnography, and end-tidal gas analysis. Before the induction of anesthesia, all patients were asked about experiencing motion sickness, smoking history, and current smoking habits. Anesthesia was performed by an attending anesthesiologist. None of the patients received any premedication. Total intravenous anesthesia with propofol and remifentanil was administered to the patients, the blood pressure was adjusted to approximately 20% of the preoper-
ative blood pressure, and the bispectral index level was maintained between 40 and 60. Neuromuscular blockage was performed with 0.8 mg/kg of rocuronium iv, and for sustained relaxation, 5 µg/kg/min of rocuronium was infused continuously. The lungs were ventilated with O₂ air to maintain normocapnia with a basal positive end-expiratory pressure of 5–7 cmH₂O. All patients underwent goal-directed fluid therapy wherein the total volumes of fluids and transfusion, urinary output, and estimated blood loss were examined. To avoid surgical site infections, antibiotics were administered 1 h before skin incision, and 30 mg of ketorolac and 5 mg of dexamethasone were administered to relieve excess abdominal inflammation, if not contraindicated. Ketonolac was not used in patients with elevated creatinine concentrations to avoid the possibility of acute kidney injury in perioperative patients [9]. Just before HIPEC, 2 g of propacetamol was prophylactically administered to avoid profound systemic hyperthermia. HIPEC was performed for 90 min in all patients. On completion of HIPEC, the abdominal cavity was opened again, and the surgical field was checked for bleeding or injury due to HIPEC. The abdomen was finally closed, and stoma formation was performed as necessary.

After suturing, all patients received ultrasound-guided bilateral TAP block from an experienced anesthesiologist. After the block, the neuromuscular blockade was reversed, and the endotracheal tube was extubated. IV PCA (Autoselector®, ACE Medical Co., Ltd., Korea) containing fentanyl (0.1 µg/kg/ml), nefopam (60 mg), and lidocaine (400 mg) in 100 ml was applied to the patients, and maintenance infusion was started at 2 ml/h in both groups and titrated appropriately to the pain level. Considering the postoperative pain period of 4–5 days, the total amount of IV PCA was prepared at 200 ml for the 4Q-TAP group and 300 ml for the control group. The programmed bolus dose was 1 ml and the lock-out time was 15 min. The routine postoperative use of NSAIDs was prohibited because of the risk of acute kidney injury after CRS [9].

In the PACU, recovery profiles and pain scores of all patients were measured, and 0.1 mg/kg of oxycodone [10] was administered as a rescue analgesic when the numerical rating scale (NRS) was 5 or higher. The number of rescue anal-

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**Fig. 1.** Flow chart of the study. 4Q-TAP: four-quadrant transabdominal plane.
were evaluated at NRS of < 5. If a patient was calm during sleep, they were not disturbed and were evaluated at NRS of < 5.

The skin was prepared for sterilization, and the position of the transverse abdominis muscle was confirmed using ultrasound. Due to peritonectomy, the peritoneal line was not well differentiated and the intestine was often in an ileus state with little movement; therefore, the correct block point was carefully confirmed by moving the probe back and forth widely. First, the position of the transverse abdominis muscle was confirmed in the midaxillary line between the costal margin and the iliac crest. Then, the linear probe was moved forward until it met the rectus abdominis muscle. Between the transversus abdominis and rectus abdominis muscles, bilateral subcostal TAP blocks were performed with a 10 ml mixture of 2% lidocaine and 0.75% ropivacaine per site. The operator carefully inserted the needle using the in-plane ultrasound technique to avoid bowel perforation. When the target point was reached, 0.5 ml of the mixture was injected after confirming the negative pressure. If there was a spread of local anesthetics between the target muscles, the remaining 9.5 ml was injected. For the lateral approach, the probe was positioned in the midaxillary line between the costal margin and the iliac crest, and the same amount of drug was injected between the transversus abdominis and internal oblique muscles. If the lateral approach in the midaxillary line was challenging due to stoma formation or drainages, the probe was moved slightly to the rear.

Outcome measurements

The primary endpoint was less than 3 times of the rescue analgesic administration (%) for 5 postoperative days. Secondary endpoints included fentanyl doses of IV PCA every 6 h for 5 days, oxycodone requirement in PACU, total opioid consumption converted to morphine milligram equivalent (MME), local anesthetic toxicity, hospital stay, and postoperative morbidity and mortality.

Maintenance doses of IV PCA were started at 2 ml/h and titrated according to the patients’ NRS and complications, if any. When a patient’s NRS was 5 or higher and not controllable with the IV PCA bolus, the patient was administered 25 mg of pethidine or 50 mg of tramadol as rescue analgesics. If a patient was calm during sleep, they were not disturbed and were evaluated at NRS of < 5.

Despite the use of the bolus injection, if the patient’s NRS score was higher than 5 and they frequently requested additional rescue analgesics, we increased the dose of IV PCA by 1 ml/hr. If the patient’s NRS score was less than 3, or they had opioid-related side effects such as sedation, dizziness, nausea, retching, or vomiting, we reduced the maintenance dose of IV PCA to 1 ml/h. If opioid-related side effects persisted without improvement, IV PCA was temporarily stopped, and symptoms were observed. When symptoms subsided and an NRS score higher than 5 was reached, IV PCA infusion was restarted at 1 ml/h.

The total frequency of additional analgesic administration for 5 postoperative days was recorded. The NRS scores and maintenance dose of IV PCA were also recorded every 6 h for 5 postoperative days. The IV PCA duration was checked, and if it was stopped, the reason and the time of stopping were recorded. Any adverse events associated with TAP block or IV PCA, hospital stay, and postoperative morbidity and mortality were recorded. As an index of the recovery profile following surgery, postoperative morbidity scores were evaluated in nine domains including infectious, pulmonary, renal, gastrointestinal, cardiovascular, hematological, wound, neurological, and pain problems at 3, 5, 8, 15, and 30 days postoperatively [11]. Pulmonary complications were evaluated based on the requirement of supplemental oxygen, and the infectious domain was evaluated by the current use of antibiotics or body temperature of > 38°C. Renal complications were evaluated by oliguria, increased serum creatinine (> 30% of baseline), or urinary catheter placement, while the gastrointestinal domain was evaluated by an inability to tolerate an enteral diet, including a feeding tube, for any reason. A case wherein a normal diet could not be processed even on the 5th day after CRS with HIPEC was defined as prolonged postoperative ileus, and its incidence was also compared. Cardiovascular domains were evaluated with the following criteria: de novo myocardial infarction or ischemia, hypotension requiring drugs or fluids, arrhythmia, pulmonary edema, or thromboembolic events. Neurological deficits, including confusion and delirium, wound problems, and bleeding requiring blood transfusion were evaluated in each domain. Surgical pain requiring parenteral opioids or regional blocks was also evaluated in the pain domain.

Sample size estimation

The primary outcome was the percentage of patients who
received less than three rescue analgesics administered for 5 postoperative days. Seventy-two patients were required to have an 80% chance of detecting, as significant at the 5% level, an increase in the primary outcome measure from 20% in the control group to 50% in the 4Q-TAP group.

**Statistical analysis**

Data are presented as mean ± SD or number of patients (%). Nonparametric data are presented as median (1Q, 3Q). Quantitative variables were analyzed using the independent t-test or Mann–Whitney U test after normality assumption test with Kolmogorov–Smirnov test. Qualitative variables were analyzed using the chi-square test or Fisher’s exact test. Repeated measure of analysis of variance (RM ANOVA) was performed for repeatedly measured data such as NRS and the amount of fentanyl in IV PCA. All data were analyzed using SPSS software (version 26.0, IBM Co., USA) and GraphPad Prism (version 7.05, GraphPad Software, USA). Statistical significance was set at P < 0.05.

### Table 1. Demographic Data and Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 33)</th>
<th>4Q-TAP (n = 36)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>14/19</td>
<td>16/20</td>
<td>0.866</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>59.4 ± 12.5</td>
<td>60.5 ± 11.1</td>
<td>0.690</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.4 ± 9.7</td>
<td>160.9 ± 8.4</td>
<td>0.839</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>61.0 ± 12.7</td>
<td>61.9 ± 12.2</td>
<td>0.772</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.6 ± 3.5</td>
<td>23.8 ± 3.4</td>
<td>0.814</td>
</tr>
<tr>
<td>ASA (I/II/III)</td>
<td>12/16/5</td>
<td>17/16/3</td>
<td>0.552</td>
</tr>
<tr>
<td>Original source of cancer</td>
<td></td>
<td></td>
<td>0.799</td>
</tr>
<tr>
<td>Stomach</td>
<td>4 (12.1)</td>
<td>4 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>19 (57.6)</td>
<td>23 (63.9)</td>
<td></td>
</tr>
<tr>
<td>Appendiceal</td>
<td>4 (12.1)</td>
<td>2 (5.6)</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>4 (12.1)</td>
<td>6 (16.7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 (6.1)</td>
<td>1 (2.8)</td>
<td></td>
</tr>
<tr>
<td>Motion sickness or PONV Hx</td>
<td>7 (21.9)</td>
<td>8 (24.2)</td>
<td>0.821</td>
</tr>
<tr>
<td>Current smoking</td>
<td>3 (9.1)</td>
<td>6 (16.7)</td>
<td>0.351</td>
</tr>
<tr>
<td>Apfel’s risk scores (1/2/3/4)</td>
<td>3/9/15/5</td>
<td>5/10/12/6</td>
<td>0.811</td>
</tr>
<tr>
<td>PCI</td>
<td>22.0 ± 9.5</td>
<td>17.0 ± 13.7</td>
<td>0.202</td>
</tr>
<tr>
<td>CC</td>
<td>1.4 ± 1.0</td>
<td>1.1 ± 1.4</td>
<td>0.446</td>
</tr>
</tbody>
</table>

All measured values are presented as number only, mean ± SD, or number (%). M/F: male/female, 4Q-TAP: four-quadrant transabdominal plane, ASA: American Society of Anesthesiologists, CC: completeness of cytoreduction, PCI: peritoneal carcinomatosis index, PONV Hx: History of Postoperative Nausea and Vomiting. The Apfel simplified score includes female sex, history of PONV and/or motion sickness, non-smoking status, and postoperative use of opioids. When 0, 1, 2, 3, or 4 factors are present, the risk of PONV is 10, 20, 40, 60, or 80% respectively [12]. PCI is a diagnostic and prognostic tool that is the sum of the scores of 13 abdominal regions. Each region is assigned a score of 0–3 based on the largest tumor size in each region. The scores ranged from 0 to 39. Higher scores indicated more widespread and/or larger tumors in the peritoneal cavity. The CC score is an assessment of residual disease after maximal surgical cytoreduction. According to the size of the residual tumor, the score is graded with CC0 (none), CC1 (< 2.5 mm), CC2 (2.5–25 mm), or CC3 (> 25 mm) [13].

**RESULTS**

### Study patients

A total of 72 patients were approached for the study and randomized into two groups (Fig. 1). Three patients in the control group were excluded from the study. In 2 patients, palliative surgery was performed instead of CRS, and 1 patient had no CRS and no HIPEC due to poor general condition. Consequently, 36 patients in the 4Q-TAP group and 33 patients in the control group participated in this study. There was no significant difference in the demographic characteristics, Apfel’s postoperative nausea and vomiting (PONV) risk scores, and cancer origin (Table 1) [12,13].

### Intraoperative variables

Peritoneal carcinomatosis index (PCI) scores and completeness of cell reduction were not different between the two groups.

Estimated blood loss was significantly higher in the control group than in the 4Q-TAP group (400 ml vs. 350 ml, me-
RM ANOVA was performed to compare the two groups of NRS scores measured repeatedly every 6 h for 5 postoperative days. However, the sphericity assumption was not satisfied (P < 0.001, Mauchly’s sphericity test); hence, the degrees of freedom were adjusted with the Greenhouse-Geisser sphericity correction (adjustment factor = 0.484) [14,15]. No significant difference was observed in the two groups for the NRS scores measured every 6 h for 5 postoperative days. (RM ANOVA with Greenhouse-Geisser sphericity correction, between-subject effect, P = 0.407). The NRS score was significantly different with the passage of time (within-subject effect, P = 0.008), but there was no interaction effect between time and group (P = 0.686) (Fig. 2).

Rescue analgesic consumption was divided into the PACU and the ward. In the PACU, the 4Q-TAP group had a significantly smaller oxycodone requirement compared to the control group. The dose of oxycodone was mean ± SD, 0.04 ± 0.07 mg/kg in 4Q-TAP group and 0.09 ± 0.08 mg/kg in control group (P = 0.011). The number of patients who did not receive analgesics in the PACU was also significantly smaller oxycodone requirement compared to the control group. The dose of oxycodone was mean ± SD, 0.04 ± 0.07 mg/kg in 4Q-TAP group and 0.09 ± 0.08 mg/kg in control group (P = 0.011). The number of patients who did not receive analgesics in the PACU was also significantly higher in the 4Q-TAP group (24 patients, 66.7%) than in the control group (10 patients, 30.3%) (P = 0.003). However, in the ward, the total frequency of rescue analgesic administration < 3 times for 5 postoperative days was not different between the two groups (24 patients [66.7%] in 4Q-TAP group vs. 15 patients [45.5%] in the control group, P = 0.076).

The administration of fentanyl dose in IV PCA was also analyzed using the RM ANOVA. It also did not satisfy the sphericity assumption (P < 0.001, Mauchly’s sphericity test), and the degree of freedom was adjusted with the Greenhouse-Geisser sphericity correction (Adjustment factor = 0.203) [14]. The fentanyl dose administered by IV PCA for 5 postoperative days was significantly lower in the 4Q-TAP group than in the control group (RM ANOVA with Greenhouse-Geisser sphericity correction, between-subject effect, P = 0.038). The fentanyl dose in IV PCA was significantly different with the passage of time (within-subject effect, P < 0.001), and there was also a significant interaction effect between the two variables (P = 0.029) (Fig. 3). A significant dose reduction of fentanyl in IV PCA of the 4Q-TAP block was maintained for 36 h after surgery (Fig. 3).

To specify the effects of the 4Q-TAP block, we converted all administered opioid doses, including IV PCA and rescue an-

**Table 2. Intraoperative Variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control (n = 33)</th>
<th>4Q-TAP (n = 36)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of operation (min)</td>
<td>474.2 ± 177.7</td>
<td>457.3 ± 160.1</td>
<td>0.680</td>
</tr>
<tr>
<td>Duration of anesthesia (min)</td>
<td>538.4 ± 184.7</td>
<td>533.5 ± 155.3</td>
<td>0.906</td>
</tr>
<tr>
<td>Propofol (mg)</td>
<td>2,756.2 ± 1,710.3</td>
<td>3,066.1 ± 1,540.2</td>
<td>0.547</td>
</tr>
<tr>
<td>Remifentanil (mg)</td>
<td>2,875.0 ± 1,674.0</td>
<td>2,825.0 ± 1,978.5</td>
<td>0.358</td>
</tr>
<tr>
<td>Intraoperative fluid (ml)</td>
<td>6,485.2 ± 3,471.6</td>
<td>5,151.7 ± 2,257.0</td>
<td>0.061</td>
</tr>
<tr>
<td>Urine output (ml)</td>
<td>1,450.0 ± 1,067.0</td>
<td>1,318.7 ± 1,022.7</td>
<td>0.585</td>
</tr>
<tr>
<td>Estimated blood loss (ml)</td>
<td>400 (200, 1,500)</td>
<td>350 (200, 600)</td>
<td>0.039*</td>
</tr>
<tr>
<td>Transfusion (%)</td>
<td>13 (39.4)</td>
<td>12 (33.3)</td>
<td>0.601</td>
</tr>
</tbody>
</table>

*All measured values are presented as mean ± SD, median (1Q, 3Q), or number (%). 4Q-TAP: four-quadrant transversus abdominis plane.*

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Fig. 2. Numeric rating scale (NRS) every 6 h for 5 postoperative days. Repeatedly measured NRS for 5 postoperative days was not different for both the groups (repeated measures of analysis of variance with Greenhouse-Geisser correction, between-subject effect, P = 0.407, within-subject effect, P = 0.008, and interaction effect, P = 0.686). 4Q-TAP: four-quadrant transversus abdominis plane.
The incidence of pulmonary morbidity was similar in both groups. Time of liquid diet and regular diet were similar in both groups and no patient in either group required ventilator care for 5 postoperative days.

Consequently, the 4Q-TAP group effectively reduced total opioid consumption during the 5 days after CRS with HIPEC.

**Adverse events and outcomes**

Hospital stay and mortality rates were not significantly different between the two groups (Table 3).

In the postoperative morbidity score, not all domains of postoperative complications differed between the groups (Table 3). The incidence of pulmonary morbidity was similar between the groups. There was no difference in the duration of supplementary oxygen use (6.3 vs. 7.5 days, P = 0.348), and no patient in either group required ventilator care for 5 postoperative days.

The incidence and duration of gastrointestinal morbidity were not significantly different between the two groups (Table 3). Time of liquid diet and regular diet were similar in both groups and prolonged postoperative ileus also occurred at a similar frequency (4Q-TAP, 33.4% vs. Control, 36.0%) in both groups.

The total period of parenteral opioid administration was not different between the groups (mean, 15.3 vs. 16.9 days).

**Table 3. Postoperative Outcomes**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n = 33)</th>
<th>4Q-TAP group (n = 36)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital stay (d)</td>
<td>25.1 ± 11.5</td>
<td>24.7 ± 12.5</td>
<td>0.891</td>
</tr>
<tr>
<td>Postoperative stay (d)</td>
<td>20.0 ± 10.7</td>
<td>19.4 ± 9.3</td>
<td>0.790</td>
</tr>
<tr>
<td>ICU (%)</td>
<td>5 (15.2)</td>
<td>4 (11.1)</td>
<td>0.619</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>1 (3.0)</td>
<td>2 (5.6)</td>
<td>0.607</td>
</tr>
<tr>
<td>Time of supplementary oxygen (d)</td>
<td>6.3 ± 4.5</td>
<td>7.5 ± 5.3</td>
<td>0.348</td>
</tr>
<tr>
<td>Time of liquid diet (d)</td>
<td>2.7 ± 1.8</td>
<td>2.5 ± 1.9</td>
<td>0.607</td>
</tr>
<tr>
<td>Time of regular diet (d)</td>
<td>5.1 ± 3.0</td>
<td>4.8 ± 2.1</td>
<td>0.656</td>
</tr>
<tr>
<td>Parenteral opioid period (d)</td>
<td>16.9 ± 9.4</td>
<td>15.3 ± 7.1</td>
<td>0.411</td>
</tr>
<tr>
<td>Postoperative morbidity score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>11 (33.3)</td>
<td>15 (41.7)</td>
<td>0.475</td>
</tr>
<tr>
<td>Infectious</td>
<td>3 (9.1)</td>
<td>7 (19.4)</td>
<td>0.222</td>
</tr>
<tr>
<td>Renal</td>
<td>0 (0)</td>
<td>1 (2.8)</td>
<td>0.335</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>12 (36.4)</td>
<td>12 (33.3)</td>
<td>0.792</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>1 (3.0)</td>
<td>4 (11.1)</td>
<td>0.196</td>
</tr>
<tr>
<td>Neurological</td>
<td>1 (3.0)</td>
<td>0 (0)</td>
<td>0.293</td>
</tr>
<tr>
<td>Wound</td>
<td>2 (6.1)</td>
<td>1 (2.8)</td>
<td>0.504</td>
</tr>
<tr>
<td>Bleeding</td>
<td>8 (24.2)</td>
<td>12 (33.3)</td>
<td>0.406</td>
</tr>
<tr>
<td>Pain &gt; 15 days</td>
<td>13 (39.4)</td>
<td>17 (47.2)</td>
<td>0.512</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or frequency (%). ICU: intensive care unit, 4Q-TAP group: 4 quadrant transversus abdominis plane block group.
Local anesthetic toxicity, such as seizures, metallic taste, blurred vision, ear fullness, or fatal arrhythmia, did not occur in either group.

During 5 days after the surgery, there was no significant difference between the groups in the incidence of IV PCA-related adverse events, including sedation, PONV, dizziness, headache, and heartburn (Table 4). Sedation developed in 2 patients in both the groups. PONV within 24 h developed in 8 patients (22.2%) in the 4Q-TAP group and 4 patients (12.1%) in the control group (P = 0.269). The overall incidence of nausea for 5 days was higher in the 4Q-TAP group (33.3%, 12 patients) than in the control group (18.2%, n = 6), but the difference was not significant (P = 0.152).

The incidence of temporary clamping of IV PCA was 6.1% in the control group and 22.2% in the 4Q-TAP group (P = 0.057), but most of them used IV PCA again without further side effects. The PCA duration was shorter in the control group (89.8 ± 37.1 h) than in the 4Q-TAP group (97.1 ± 38.1 h), but the difference was not statistically significant.

**DISCUSSION**

In the present study, the addition of a 4Q-TAP block to multimodal IV PCA effectively enhanced postoperative analgesia in patients undergoing CRS with HIPEC.

Postoperative analgesia is an essential part of ERAS. Introduction of the ERAS protocol has also been reported to be related to an increase in survival rates of patients with CRS with HIPEC [1]. Particularly, the use of an opioid-sparing regimen for pain management is emphasized to avoid delayed recovery and multimodal analgesia techniques, including various drugs and epidural analgesia [2].

However, epidural analgesia should be used with caution in patients with CRS and HIPEC. Although not many cases are reported of coagulation abnormalities that are insufficient to maintain and remove the epidural catheter after surgery [17], but massive bleeding may occur during the surgery, according to the severity or invasiveness of the cancer. Hurdle et al. [18] reported that postoperative coagulopathy occurred in approximately 40% of patients who underwent CRS with HIPEC, and the incidence was higher with intraoperative blood transfusion or higher PCI scores. Therefore, careful attention should be given to the management of epidural catheters in high-risk patients. However, since it is difficult to predict the patient’s PCI score and bleeding volume before surgery, it is difficult to guarantee the safety of preoperative epidural catheterization. Moreover, to cover the long dermatome of CRS with HIPEC [19], the dose of local anesthetics for epidural analgesia should be greatly increased. Hemodynamic stability, which is an advantage of thoracic epidural analgesia, is difficult to expect and thus hypotensive complications are inevitable. Poorer analgesia compared to a well-controlled IV PCA may also reduce patient satisfaction [3]. Some studies have shown that thoracic epidural analgesia increased the complexity of recovery and rather increased the total hospital stay [20]. These studies explained that if epidural analgesia were performed in surgeries with short recovery periods, the start of anticoagulation after surgery was delayed, and the voiding rehabilitation period due to Foley catheter placement would be also required, which in turn delayed the recovery.

Recently, TAP blocks have been implemented as a new alternative to epidural analgesia [21]. However, in CRS with HIPEC, postoperative pain is extremely severe and has a long duration. The pain not only is because of the abdominal wall but also manifests through various mechanisms such as inflammatory, neuropathic pain, visceral, and positional back pain. We also believe that the TAP block alone

**Table 4. IV PCA Complications for 5 Postoperative Days**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n = 33)</th>
<th>4Q-TAP group (n = 36)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCA duration (h)</td>
<td>89.8 ± 37.1</td>
<td>97.2 ± 38.1</td>
<td>0.421</td>
</tr>
<tr>
<td>Temporary clamp</td>
<td>2 (6.1)</td>
<td>8 (22.2)</td>
<td>0.057</td>
</tr>
<tr>
<td>Sedation</td>
<td>2 (6.1)</td>
<td>2 (5.6)</td>
<td>0.929</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (15.2)</td>
<td>12 (30.5)</td>
<td>0.152</td>
</tr>
<tr>
<td>0–24 h</td>
<td>4 (12.1)</td>
<td>8 (22.2)</td>
<td>0.269</td>
</tr>
<tr>
<td>24–102 h</td>
<td>2 (6.1)</td>
<td>4 (11.1)</td>
<td>0.457</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (12.1)</td>
<td>3 (8.3)</td>
<td>0.603</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (3.0)</td>
<td>0 (0.0)</td>
<td>0.293</td>
</tr>
<tr>
<td>Heartburn</td>
<td>0 (0.0)</td>
<td>1 (2.8)</td>
<td>0.335</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or frequency (%). IV PCA: intravenous patient-controlled analgesia, 4Q-TAP group: 4 quadrant transversus abdominis plane block group. P < 0.05 was considered significant, chi-square test or independent t-test.
was insufficient to replace the epidural block. Cata et al. [22] reported that 4Q-TAP block after CRS with HIPEC did not delay recovery profiles, but significantly increased opioid consumption compared with thoracic epidural analgesia. Therefore, we decided to implement multimodal analgesia with low-dose fentanyl, nefopam, lidocaine, NSAIDs, steroids, and a 4Q-TAP block.

The transversus abdominis plane is a potential anatomical space between the transversus abdominis and the internal oblique muscles [23]. Therefore, the TAP block is a kind of “field block” by infiltration of TAP with local anesthetics, not a specific nerve block. There are several routes to block the abdominal walls, including the subcostal, lateral, posterior, and oblique subcostal approaches [23].

The 4Q-TAP block is a bilateral dual TAP block. Borglum et al. first introduced the “four-point approach,” [21] and Niraj et al. [8] also called it the “four-quadrant” TAP block. The 4Q-TAP block, which technically combines subcostal with lateral or posterior TAP blocks, provides a wider coverage of the upper and lower abdominal walls. Some studies have shown that the posterior TAP block and the posteromedial quadratus lumborum block were more effective than the lateral TAP block [24]. However, in this study, the procedure was performed in the lithotomy position in the operating room, and a lateral TAP block was preferred for positional merit in our study.

The implementation of TAP block in patients with CRS with HIPEC requires careful attention. Due to extensive peritoneectomy, the peritoneal lining was unclear, and the remaining intestine was almost in an ileus state and edematous. Therefore, it is often difficult to distinguish between the abdominal anatomical layers. Additionally, it was challenging to secure the location of the block because of various drains and stoma formations. To safely perform the block, it was started from the lateral wall where the three abdominal muscle layers of the external oblique, internal oblique, and transversus abdominis muscles were clearly visible, then moved along the subcostal line to the point where the internal oblique muscle disappeared and met the rectus abdominis muscle. At that point, the subcostal TAP block was performed with 10 ml of an equal volume mixture of 0.75% ropivacaine and 2% lidocaine. The same dose of an equal volume mixture of ropivacaine and lidocaine was also injected in the lateral TAP block site. The procedure was repeated on the other side.

A field block or a plane block, such as TAP, may have a satisfactory effect when a sufficient volume is injected. Generally, it is recommended to inject at least 15 ml of a single TAP block. According to a pilot study [25], in the case of the same dose of local anesthetics, even if the volume increased by changing the concentration, the height of the dermatomal blockade could not be increased, but rather the block duration was decreased. When multiple blocks are required, safe dose selection is important and should be calculated in advance. We mixed 0.75% ropivacaine and 2% lidocaine in a 1:1 ratio to reduce systemic toxicity and to accelerate the onset. Generally, the median effective analgesic dose (ED$_{50}$) of ropivacaine for TAP block is approximately 2.7 mg/kg, which is close to the toxic concentration (3 mg/kg) [26]. In our study, all patients received ropivacaine (37.5 mg) per site, and the total dose of ropivacaine was 150 mg.

It has been reported that the TAP block duration of long-acting local anesthetics is 6–24 h with no definite preemptive analgesic effects [27]. In this study, we used a local anesthetic mixture, not just a long-acting one. An equal volume mixture has been reported to have a shorter duration owing to the diluted concentration of local anesthetics [27]. The 4Q-TAP group required a significantly smaller amount of rescue analgesics in the PACU than the control group. We did not examine the exact onset time of 4Q-TAP block, but the reduced opioid requirement in the PACU suggests the influence of the nerve block. After the PACU, rescue analgesic consumption was not different, but the IV PCA requirement was significantly reduced in the 4Q-TAP group and stable pain control was achieved by IV PCA maintenance.

Although total opioid usage was reduced with the TAP block, opioid-related complications such as PONV, dizziness, sedation, or prolonged postoperative ileus were not different between the groups. Although not statistically significant, the incidence of PONV was slightly higher in the 4Q-TAP group from the day after surgery, and the number of transient PCA clamps was also higher in the 4Q-TAP group (22.2%) compared to the control group (6.1%) (P = 0.058). A meta-analysis study by Zhao et al. [28] also reported that PONV significantly increased after the TAP block in laparoscopic intestinal surgery. The increased PONV was presumed to be caused by a temporary opioid overdose because the IV PCA dose titration was not performed quickly for the fear of pain. From the day after surgery, IV PCA dose reduction may be necessary in patients with a TAP block, and further prospective studies on IV PCA maintenance doses with TAP blocks are needed.

Additionally, despite the opioid-reducing effect in the 4Q-TAP group, there was no significant difference in the
overall outcome or morbidity compared to the control group. Various multimodal analgesic regimens have enhanced recovery by lowering the opioid requirement to increase gastrointestinal motility, reducing pulmonary complications, and promoting ambulation [4,29]. In this study, no recovery outcomes, including hospital stay and various morbidities were different. We speculate that this might be because various analgesic drugs such as lidocaine, NSAIDs, steroids, or nefopam were used together in all patients. Moreover, although the opioid dose of IV PCA in the control group was higher than that in the TAP group, the total amount of opioids administered was not large enough to delay the recovery, even in the control group.

This study has some limitations. First, we titrated the IV PCA according to the NRS score and the presence of complications. Rescue analgesics and IV PCA could be administered in a complementary manner. Therefore, this may have been another intervention other than the 4Q-TAP block. To eliminate this effect, we calculated MME of total opioid use and compared the difference between the two groups. Second, we did not examine the plasma concentrations of long-acting local anesthetics in the 4Q-TAP group. All patients were administered ropivacaine (150 mg). Approximately 15.2% of the 4Q-TAP group exceeded the toxic concentration of ropivacaine (approximately 3 mg/kg). However, owing to the nature of the field block, injecting a smaller dose per site may lead to block failure, and diluted concentrations lead to a shorter duration of block. Moreover, the addition of a small dose of 2% lidocaine in IV PCA also has the potential to augment the effect of systemic toxicity of local anesthetics. International guidelines for the safe use of parenteral lidocaine have not yet been developed, however, the recently published international consensus statement also recommends that parenteral lidocaine should be used at an interval of 4 h after nerve block [30]. Fortunately, there was no systemic toxicity in this study, but it would be influenced by the small sample size and would not guarantee safety. Further studies on the safe dose and various methods to reduce the systemic toxicity of multiple TAP blocks are needed. Clinicians performing multiple TAP blocks should always be thoroughly prepared for the risk of systemic toxicity of local anesthetics.

In conclusion, the addition of ultrasound-guided 4Q-TAP block with multimodal IV PCA effectively reduced total opioid requirements in the postoperative period in patients who underwent CRS with HIPEC. However, it did not change recovery outcomes and hospital stay.

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None.

**CONFLICTS OF INTEREST**

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

**DATA AVAILABILITY STATEMENT**

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

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**REFERENCES**


Approaching trauma analgesia using prolonged and novel continuous peripheral nerve blocks
- A case report -

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Case Report

Background: A supraclavicular brachial plexus nerve block provides analgesia for the shoulder, arm, and hand; however, the maximum safe duration for a continuous infusion remains controversial. A novel continuous peripheral nerve block (CPNB) technique combining the Lateral, Intermediate, and Medial femoral cutaneous nerves (termed the ‘LIM’ block) to provide analgesia to the lateral, anterior, and medial cutaneous areas of the thigh while preserving quadriceps strength will also be described in detail here.

Case: We present a complex case in which simultaneous utilization of an unilateral supraclavicular CPNB (5 weeks) and bilateral LIM CPNB (5 days) are successfully performed to provide analgesia for a traumatic degloving injury resulting in multiple surgeries.

Conclusions: The analgesic plan in this case study eliminated previous episodes of opioid-induced delirium, facilitated participation in recovery, and removed concerns for respiratory depression and chronic opioid use in a patient at particular risk for both issues.

Keywords: Acute pain service; Amputation; Analgesia; Anesthesia; Local anesthesia; Nerve block.

Traumatic injuries often cause significant acute pain, intensified by required surgeries and painful dressing changes. The amalgamation of complicated injuries and pain intensity requires complex analgesia to achieve adequate pain control. Prolonged healing time, combined with opioid-centric analgesia regimens expose patients to harmful, potentially avoidable, opioid-related adverse drug events (ORADEs) [1].

Continuous peripheral nerve blocks (CPNB) carry proven advantages in the setting of acute traumatic and post-surgical pain, including improved provision of analgesia and reduced ORADE’s [2]. Post-intervention immobility is a disadvantageous limitation of some CPNB techniques such as the fascia iliaca block due to the decrease in quadricep muscle strength and resulting increased risk in patient falls [3]. Further, the maximum safe duration for a continuous infusion remains controversial [4]. Herein, the authors present a case of simultaneous, continuous, and prolonged analgesia by employing a supraclavicular CPNB combined with a novel CPNB technique which provides continuous cutaneous analgesia to the thigh, while preserving motor strength and facilitating productive physical and occupational therapy sessions.
CASE REPORT

The patient provided written informed consent for publication of this case report and the associated images.

A 76-year-old male patient sustained injuries that included a comminuted left humerus midshaft fracture and a thermal contact abrasion with full thickness burns and degloving of the left shoulder, upper arm, and extensor surface of the lower arm and hand. His past medical history was significant for obesity, obstructive sleep apnea, type 2 diabetes mellitus, hypertension, and gastroesophageal reflux disease.

The patient immediately underwent an open reduction and internal fixation of the left humerus, followed by burn wound excision and application of allograft to the left upper extremity. Pain intolerance with dressing changes and opioid–associated delirium prompted an Acute Pain Service (APS) consultation. Accordingly, APS performed an ultrasound-guided, left supraclavicular CPNB (B Braun Contiplex Needle, B-Braun Medical Inc., USA) using 20 ml of 0.5% bupivacaine followed by a 10 ml/h continuous infusion of 0.125% bupivacaine through an electronic infusion pump (CADD Solis infusion system, Smiths Medical, USA). Analgesia dramatically improved, and symptoms of delirium abated in parallel to reduced opioid consumption (Table 1). Prior to each of the remaining 7 surgeries performed under general anesthesia, APS bolused the supraclavicular CPNB with 20 ml of 0.5% bupivacaine.

Thereafter, the patient underwent a below elbow amputation on hospital day (HD) 15. The supraclavicular CPNB was utilized as the primary anesthetic along with intravenous

Table 1. Opioids, Antibiotics, and Local Anesthetic Received During 5 Weeks of Procedures

<table>
<thead>
<tr>
<th>Opioids/Other</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>50 μg x 4, 100 μg x 5, 50 μg x 2</td>
<td>50 μg x 4</td>
<td>100 μg x 3, 50 μg x 2</td>
<td>100 μg x 1, 25 μg x 2</td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>1 mg x 1, 0.5 μg x 3</td>
<td>0</td>
<td>0</td>
<td>0.25 mg</td>
<td>0</td>
</tr>
<tr>
<td>Morphine, IV</td>
<td>2 mg x 5, 4 mg x 2</td>
<td>2 mg x 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oxycodone, oral</td>
<td>10 mg x 4, 5 mg x 1</td>
<td>5 mg</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>1 mg x 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bupivacaine use</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Individual bupivacaine bolus quantity by surgery/events</td>
<td>(HD 2) 100 mg</td>
<td>(HD 8) 100 mg</td>
<td>(HD 15) 100 mg</td>
<td>(HD 23) 100 mg</td>
<td>(HD 30) 100 mg</td>
</tr>
<tr>
<td></td>
<td>0.77 mg/kg bolus(^{1})</td>
<td>0.77 mg/kg(^{1})</td>
<td>0.77 mg/kg(^{1})</td>
<td>0.77 mg/kg(^{1})</td>
<td>0.77 mg/kg(^{1})</td>
</tr>
<tr>
<td></td>
<td>(HD 4) 100 mg</td>
<td>(HD 17) 25 mg</td>
<td>(HD 24) 25 mg</td>
<td>(HD 28) 100 mg</td>
<td>(HD 35) All CPNBs removed</td>
</tr>
<tr>
<td></td>
<td>0.77 mg/kg(^{1})</td>
<td>0.19 mg/kg(^{1})</td>
<td>0.19 mg/kg(^{1})</td>
<td>0.77 mg/kg(^{1})</td>
<td></td>
</tr>
<tr>
<td>24-hour total dose from 0.125% bupivacaine continuous infusion per week</td>
<td>10 ml/hr</td>
<td>10 ml/hr</td>
<td>10 ml/hr</td>
<td>10 ml/hr</td>
<td>18 ml/hr</td>
</tr>
<tr>
<td></td>
<td>300 mg</td>
<td>300 mg</td>
<td>300 mg</td>
<td>300 mg</td>
<td>540 mg</td>
</tr>
<tr>
<td></td>
<td>2.3 mg/kg(^{1})</td>
<td>2.3 mg/kg(^{1})</td>
<td>2.3 mg/kg(^{1})</td>
<td>4.15 mg/kg(^{1})</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cefepime</td>
<td>2 g x 14 (q12 hr)</td>
<td>2 g x 14 (q12 hr)</td>
<td>2 g x 14 (q12 hr)</td>
<td>2 g x 14 (q12 hr)</td>
<td>2 g x 14 (q12 hr)</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>160 mg x 1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Piperacillin and tazobactam</td>
<td>3,375 g x 5</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>2.25 g x 14 (q12 hr)</td>
<td>2.25 g x 4 (q12 hr), 1.75 g x 10 (q12 hr)</td>
<td>1.75 g x 14 (q12 hr)</td>
<td>1.75 g x 14 (q12 hr)</td>
<td>1.75 g x 5 (q18 hr)</td>
</tr>
<tr>
<td>Surgery/events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(HD 1) Open Reduction and Internal Fixation left Humerus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(HD 2) Wound Excision &amp; Allograft</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(HD 2) Supraclavicular CPNB performed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(HD 4) Muscle flap with allograft</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(HD 24) Supraclavicular CPNB Replaced</td>
<td>(HD 28) Dressing Change Surgery, Major</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(HD 30) Wound Excision &amp; Bilateral thigh autograft</td>
<td>(HD 30) Bilateral ‘LIM’ CPNB performed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(HD 35) All CPNBs removed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IV: intravenous, HD: hospital day, CPNB: continuous peripheral nerve block. \(^{1}\)Intraoperative opioid administration. \(^{1}\)Based on patient’s 130 kg body weight.
propofol sedation and replaced on HD 17. Amputation formalization occurred on HD 23, and APS carried out routine exchange of the supraclavicular CPNB catheter on HD 17 and HD 24 to reduce the potential risk for catheter site infection. The patient then underwent a burn wound excision of the left arm and received an extensive split thickness skin graft (1,140 cm²) from both thighs on HD 30. For donor site analgesia and to further mitigate opioid-induced delirium, APS performed an ultrasound-guided bilateral Lateral, Intermediate, and Medial femoral cutaneous nerves (LIM) CPNB intraoperatively using a total of 40 ml of 0.375% bupivacaine. The novel LIM CPNB technique was performed by directing the needle caudally and medially above the fascia iliaca along the lateral border of the sartorius muscle. The sartorius muscle serves as an anatomical landmark as the lateral femoral cutaneous nerve enters the thigh lateral to the sartorius muscle near the LIM block insertion site. The intermediate and medial cutaneous branches of the femoral nerve respectively supply anterior and medial cutaneous thigh sensation and pierce the fascia iliaca just lateral to the sartorius muscle distally. Hydrodissection with local anesthetic allows the needle to advance easily in the correct plane just above the fascia iliaca. Ultrasound and anatomy images describe the nerve block procedure and relevant sonoanatomy (Figs 1–4) [5].

For the next 5 days, APS continuously infused a total of 8 ml/hr of 0.125% bupivacaine through a second electronic infusion pump utilizing a catheter tubing splitter (6 inch Bifurcated Blue Stripe Extension, ICU medical, USA) to the LIM blocks. On HD 35, APS held the supraclavicular and LIM block infusions to evaluate for remaining underlying pain. After confirming adequate analgesia without requirements for opioids, APS removed all three CPNB catheters without complication or evidence of infection.

DISCUSSION

The authors report this complex case demonstrating the successful use of a continuous unilateral supraclavicular nerve block for 5 weeks for ongoing left upper extremity pain supplemented with a novel LIM CPNB technique performed to control pain in the lateral, anterior, and medial cutaneous portions of both thighs. This comprehensive regional analgesic approach helped control postoperative pain, reduce opioid consumption, and facilitate therapy participation.

Throughout the 5-week supraclavicular CPNB infusion, the patient confirmed adequately controlled pain, utilizing only scheduled acetaminophen and requiring minimal opioids (Week 1 [prior to CPNB]: 159 oral morphine milligram equivalents [MME]; Week 2–5 average weekly oral MME: 89.

Fig. 1. Lateral femoral cutaneous (LFC) nerve & local anesthetic in fat pad over fascia iliaca and iliopsoas muscle lateral to sartorius muscle with probe in transverse view (post-block).

Fig. 2. Lateral femoral cutaneous (LFC) nerve & local anesthetic in fat pad over fascia iliaca and iliopsoas muscle lateral to sartorius muscle with probe in near sagittal view (post-block).
8.88) for pain despite several painful surgeries, dressing changes, and participation with physical and occupational therapy. The patient exhibited no signs of local infection, local anesthetic systemic toxicity (LAST), and no evidence of residual weakness or numbness to the left arm. Throughout the 5-day continuous LIM block infusion, the patient denied thigh tenderness to palpation. Physical examination by APS demonstrated decreased temperature sensation to the lateral, anterior, and medial thigh and bilateral 5/5 strength of quadriceps each day. Consequently, the patient remained able to participate in physical and occupational therapy with LIM block infusions and without limitation due to quadriceps weakness or pain.

Adequate pain control facilitates earlier ambulation and discharge, improves functional recovery, and helps prevent other consequences of traumatic amputation, such as phantom and residual limb pain [6]. Utilization of long-term CPNB can reduce the risk of chronic post-surgical pain and mitigate downstream effects of prolonged exposure to opioids and related ORADEs, such as post-operative respiratory insufficiency, opioid dependence, and opioid-induced delirium experienced by this patient [7]. Patients suffering severe traumatic injuries are at risk for prolonged opioid exposure and, ultimately, opioid dependence [1]. This patient presented with a high risk for multiple ORADEs, given his past medical history and sustained trauma.

Significant aspects of the LIM CPNB for thigh autograft pain include requiring a relatively low bupivacaine infusion rate to reduce the risk for developing LAST and preserving quadriceps muscle strength to lower the risk of falls. Furthermore, the combined LIM CPNB consisting of the lateral, intermediate, and medial femoral cutaneous nerves performed in a single block provided reliable analgesia for the lateral, anterior, and medial cutaneous regions of both thighs. The anterior femoral cutaneous nerve, which carries the intermediate and medial femoral cutaneous nerves, additionally supplies cutaneous analgesia to the anteromedial knee [8]. In contrast to the novel technique described herein, other CPNB techniques traditionally utilized to control pain from thigh autograft harvesting, such as the femoral or fascia iliaca nerve blocks, produce quadriceps weakness and can lead to the common complication of patient falls [3]. The combined CPNBs provided an efficacious, alternative approach for analgesia, while promoting patient safety and participation in therapy.

Infection remains one of many concerns with CPNBs and has been associated with duration of catheter use [9]. Though the patient’s requirement for antibiotics (Table 1) helped reduce the local infection due to prolonged catheter
utilization risk, clinicians must keep the infection concern in mind during treatment. Many clinical practices have evolved by including the routine use of chlorhexidine skin preparation and cyanoacrylate glue for catheter site entry [4]. A specific recommendation regarding the duration of epidural or CPNB catheterization that is associated with an increased risk of infectious complications has not been issued, and studies have demonstrated minimal evidence of CPNB catheter-related infections despite prolonged use [10].

Concerns regarding nerve injury risk while replacing CPNBs with partially anesthetized nerves are valid, but ultrasound guidance and clinical experience mitigate this risk [11]. Given the extended infusion of CPNBs in this case, clinicians should consider the risk of LAST [12]. As standard practice, total daily local anesthetic usage is carefully calculated, and patients are continually monitored and verbally screened for LAST every 6 hours. As a final mitigation strategy, nurses maintain APS generated annual competencies for managing patients receiving CPNB.

While these risks are not trivial, the short and long-term risks associated with extended opioid exposure remain significant and should equally be considered [1,7]. Post-operative pain management with opioids independently serves as a risk factor for chronic opioid use even in opioid naïve patients [1,2]. This patient’s injuries required multiple surgeries and would have required multiple weeks of escalating opioid doses.

Anesthesiologists involved in trauma and burn injuries could consider these techniques, particularly for patients with risk factors for addiction and ORADEs. Further investigation is needed to examine the risks and benefits of prolonged CPNBs and dressing management protocols in trauma patients. Evaluating optimal dosing for initial LIM block boluses and infusion rates, the risks and benefits of single injection and continuous LIM blocks versus fascia iliaca blocks or lateral femoral cutaneous blocks for thigh autografts are needed. Given the utilization of multiple CPNB, uncertainty arises regarding the efficacy and practicality of such approaches outside the trauma setting.

This case study demonstrates successful, prolonged usage of a supraclavicular CPNB in a patient with complex injuries. Further, the authors demonstrate a novel LIM CPNB requiring less anesthetic and providing extensive analgesia for bilateral thigh autografts while maintaining quadriceps strength. The analgesic plan in this case study eliminated previous episodes of opioid-induced delirium, facilitated participation in recovery, and removed concerns for respiratory depression and chronic opioid use in a patient at particular risk for both issues.

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None.

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Figs. 1–3 courtesy of Jerry Jones, MD.

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

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

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Based on the local data provided by the Department of Health through the Online National Electronic Injury Surveillance System in 2014, only 1.64% of all recorded injuries were due to fracture of the clavicle, scapula, or humerus [1]. Moreover, most clavicle fractures (81%) in both adults and children were located at the midshaft [2]. General anesthesia has traditionally been the preferred anesthesia for clavicle fractures because regional anesthesia via peripheral nerve block can be challenging [3]. Several case reports and series have already been published to support the use of brachial plexus block (interscalene approach) or combination blocks (interscalene with superficial cervical plexus) in clavicle surgeries. However, these techniques can be time-consuming as two separate ultrasound-guided injections are needed to provide the surgical block. Besides its ease of performance, the clavipectoral plane block (CPB) can avoid the possible adverse events associated with an interscalene block, such as ipsilateral phrenic nerve palsy, vocal cord paralysis, vertebral artery injection, total spinal anesthesia, and pneumothorax [4].

This case report discusses the use of a clavipectoral block as the sole nerve block that provides surgical anesthesia and analgesia in a midshaft clavicle fracture. Evaluation of postoperative pain control using the Numerical Rating Scale (NRS) and opioid consumption showed the effectiveness of this plane block.

This article adheres to the applicable Enhancing the Quality and Transparency of Health Research Guidelines and Case Reports (CARE) Checklist.

**CASE REPORT**

The patient signed an informed consent, which stated that the clinical images taken would be used for medical teaching and in a journal publication. The Makati Medical Center Institutional Review Board (MMC IRB) approved this case report.
A 39-year-old male patient with no known comorbidities or allergies had a closed, complete, displaced fracture in the middle third shaft of the right clavicle due to a history of trauma. The patient underwent open reduction and internal fixation of the right clavicle with plates and screws.

A peripheral nerve block was administered preoperatively under sedation with midazolam (2–5 mg) and fentanyl (50–100 µg) intravenously. Monitoring was set to 5-min intervals with supplemental oxygen at 3 L/min via nasal cannula. In the supine position, the head was turned to the contralateral side (left). The block was administered with appropriate antisepsis. The affected clavicle was surrounded by sterile drapes. A high-frequency linear probe dressed with a sterile sonography cover was used to scan the length of the clavicle.

Fig. 1A and 1B show the probe positions for this block. The probe was initially placed 2 to 3 cm proximal to the fracture line to mark the first injection (Fig. 1A), and a similar marking was performed 2 to 3 cm distal to the fracture line to mark the second injection (Fig. 1B). Fig. 1C shows the sonoanatomy of the clavicle and its surrounding structures. The periosteum of the clavicle as well as the surrounding fascia were visualized for both the medial and lateral injection sites. An in-plane technique was used to view the 80-mm ultrasound-visible stimulation needle advancing in a caudad to cephalad direction until it rested on the clavipectoral fascia.

Fig. 2A and 2B show the needle in-plane at the medial and lateral clavicles, respectively. Aspiration was performed before the injection of local anesthesia. An injection pressure monitor attached to the syringe objectively measured the injection pressure during the administration of the peripheral nerve blocks. The total amount of local anesthetic mixture used was 30 ml (1:1 of 0.25% levobupivacaine and 1% lidocaine), divided into 15 ml medial and 15 ml lateral. The first
injection was deposited on the medial side. The same steps were followed to block the lateral fracture line. Local anesthesia spread was observed on the medial (Fig. 2C) and lateral (Fig. 2D) sides of the clavicle.

Sensory and motor assessment of the arm and shoulder was performed 15 min after the nerve block. The right supraclavicular and infraclavicular areas were mapped for coverage of the block, which were both insensate to needle pricks. Additionally, the right upper extremity retained a full range of motion.

Sedation with dexmedetomidine (2 µg/ml) at 0.5–0.7 µg/kg/h was initiated before positioning the patient in a beach chair position. A Ramsey sedation score of 3 to 5 was maintained, leading to unremarkable surgery for almost two hours. The patient was monitored for pain control at the post-anesthesia care unit for two hours, with an NRS score of 0/10. Twelve hours after the nerve block, the patient sat comfortably on the bed while wearing an arm sling, retaining an NRS of 0/10. The right clavicle area was insensate. The patient was able to perform a range of motion over the right elbow and wrist. However, 16 h post-block, the patient had a pain score of NRS 7/10 on the postoperative site. It was immediately relieved by a dose of intravenous tramadol (50 mg), decreasing the pain score to NRS 0/10.

The patient was administered intravenous acetaminophen (every 6 h for a total of three doses) and cyclooxygenase-2 inhibitor (every 12 h for a total of two doses) and was sent home the day after the surgery, with oral medications (non-steroidal anti-inflammatory drug with an opioid).

**DISCUSSION**

There is limited data on regional anesthesia for clavicle surgeries, probably due to the complex innervation of the clavicle...
clavicular region [5]. The supraclavicular nerve of the superficial cervical plexus (SCP) innervates the skin above the clavicle. However, the sensory innervation of the clavicle remains questionable. Terminal branches of the sensory nerves, such as the suprascapular, subclavian, lateral pectoral, and long thoracic nerves pass through the plane between the clavipectoral fascia and the clavicle itself. Hence, the sensory innervation of the clavicle should penetrate the clavipectoral fascia [6].

Posterior to the clavicular part of the pectoralis major muscle is a tough fascia called the clavipectoral fascia (Fig. 1D). Superiorly, this fascia splits to envelop the subclavian muscle. Medially, it connects to the first rib, before joining the fascia over the first intercostal space [7]. To form the costocoracoid ligament, the clavipectoral fascia thickens between the first rib and the coracoid process of the scapula. The structures that penetrate the clavipectoral fascia include the cephalic vein, thoracoacromial artery and vein, lymphatics, and lateral pectoral nerve. Ultimately, since this fascia envelopes the clavicle, its nerve endings pierce through this structure [7].

Sensory innervation of the clavicle originates from the cervical and brachial plexuses. The chosen regional anesthesia technique should cover all the necessary innervations of the skin, muscles, and bones of the clavicle, and should correlate well with the planned surgical approach. Therefore, depositing local anesthesia between the clavipectoral fascia and periosteum may block the complete innervation [7].

Thus, the CPB has been speculated to provide effective regional anesthesia and perioperative analgesia in clavicle surgeries. However, it can only provide a surgical block if the fracture is located midshaft [6].

A recent paper by Yoshimura and Morimoto [8] presented two patients who received CPB after induction with general anesthesia. CPB combined with a block of the supraclavicular branch of the SCP was used to anesthetize the skin above the clavicle. CPB provided a similar analgesic effect as did the brachial plexus, but without the upper limb motor block, and the possible complication of phrenic nerve paralysis. Another recent study by Kukreja et al. [4] was conducted, wherein CPB was used as an adjunct peripheral nerve block. Three patients who underwent CPB preoperatively then received general anesthesia.

In this case report, a CPB with intravenous sedation provided adequate surgical anesthesia in a patient with a midshaft clavicle fracture. Instead of performing two peripheral nerve blocks (interscalene brachial plexus and superficial cervical plexus blocks), CPB provides an alternative option if either of the two mentioned blocks is contraindicated [6].

A supplemental block in the form of a “hematoma block” may be administered to cover the areas lost due to a possible break in the continuity of the fascia surrounding the fractured clavicle. Local infiltration over the subcutaneous plane of the clavicle may be provided to avoid sparing when performing CPB [7]. Neither of the two aforementioned techniques were employed in this case.

The integrity of the fascia may be lost through tissue injury and trauma caused by the surgical procedure. Hence, in fascial plane blocks, these two factors may play a major role in providing effective and successful anesthesia: integrity of the fascia and potentiality of the interfascial plane [7]. In this case, the trauma that caused the fracture might have created only a mild disruption in the fascial plane architecture, thereby not compromising the spread of the local anesthesia.

This nerve block technique may provide benefits to patients with difficult airways and in trauma patients with rib fractures and pneumothorax, where general anesthesia may increase the risk of expansion of the pneumothorax [4]. Using CPB with light sedation in this case avoided the added cost of administering general anesthesia and manipulating the airway during intubation. Further, it could gauge the coverage of the sensory and motor involvement before and after the procedure, which would have been difficult if the patient had received general anesthesia.

The midshaft location of the fracture might have also contributed to the usefulness of CPB for surgical fixation of clavicle fractures in this patient. Further studies with larger sample sizes are required to gather sufficient evidence to support the effectiveness of this novel block.

This case report supports the use of a CPB for anesthesia and analgesia in midshaft clavicle surgeries. In addition to its safety and ease of use, CPB with light sedation is a good alternative, especially if general anesthesia is not warranted.

**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

Endotracheal tube cuff pressure during laparoscopic bariatric surgery: highs and lows

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Background: Gastric calibration tubes (GCTs) are a unique component of bariatric surgery. This study aimed to assess changes in the endotracheal tube (ETT) cuff pressure during laparoscopic bariatric surgery.

Methods: This was a prospective observational study consisting of 124 American Society of Anesthesiologists class I–III morbidly obese patients (body mass index > 40 kg/m²) undergoing elective laparoscopic bariatric surgery under general anesthesia. The baseline ETT cuff pressure was 28 cmH₂O. Cuff pressure, peak airway pressure, and hemodynamic changes were observed during various steps of bariatric surgery. Immediate postoperative complications during the first 24 h were recorded.

Results: ETT cuff pressure increased significantly from the baseline (28 cmH₂O) after insertion of GCT (36.3 ± 7.3 cmH₂O) and creation of carboperitoneum (33.3 ± 3.8 cmH₂O). Cuff pressure decreased significantly on GCT removal (24.0 ± 3.0 cmH₂O) and release of carboperitoneum (24.7 ± 3.0 cmH₂O). Peak airway pressure increased from the initial baseline value of 25.1 ± 3.7 to 26.5 ± 4.5 after GCT insertion, creation of carboperitoneum (32.6 ± 4.4), attainment of reverse Trendelenburg position (32.3 ± 4.0), and subsequent return to supine position 32.5 ± 4.8.

Conclusions: The endotracheal cuff pressure significantly varies during the intraoperative period. Routine monitoring and readjustment of cuff pressure are advisable in all laparoscopic bariatric surgeries to minimize the possibility of postoperative complications.

Keywords: Adult; Bariatric surgery; Calibration; Laparoscopic surgical procedures; Manometry; Morbid obesity; Trachea.

INTRODUCTION

Obesity can be defined as a “disease,” which is prevalent in both developing and developed nations. Currently, laparoscopic bariatric surgery is an efficient method of weight reduction and is generally associated with low morbidity and mortality [1]. General anesthesia in patients with morbid obesity presents a challenging task.

Laparoscopic surgery is performed under general anesthesia with mechanical ventilation. A high-volume, low-pressure cuffed endotracheal tube (ETT) with a sealing cuff pressure of approximately 20–30 cmH₂O is commonly used for proper sealing and avoidance of over-inflation [2]. The main symptoms associated with tracheal intubation are sore throat, hoarseness, and dysphagia [3]. Although the exact pathophysiology of post-intubation airway symptoms is not fully known,
mucosal damage at the cuff level is thought to be an important cause of tracheal morbidity [4].

Insertion of gastric calibration tubes (GCTs) is required during bariatric surgery, especially sleeve gastrectomy, to drain and remove gastric fluid and provide calibration for gastric pouch and leak testing. The complications associated with GCT insertion include pharyngeal and esophageal tears, which increase morbidity and cost in these patients [5,6]. Another important aspect of GCT insertion, which is usually ignored, is the pressure exerted on the trachea, with the resultant increase in cuff pressure of the ETT in situ. Hence, this study aimed to observe the changes in cuff pressure during various steps of laparoscopic surgery and the complications arising from it.

**MATERIALS AND METHODS**

This prospective observational study was conducted for 4 months in a tertiary, high-volume bariatric center after obtaining Institutional Ethics Committee approval (no. SAIMS/IEC/16/02) and written informed consent. A total of 289 patients underwent surgery during the study period, comprising 182 morbidly obese patients (body mass index [BMI] > 40 kg/m²) who were admitted for laparoscopic bariatric surgery. One hundred and twenty-four American Society of Anesthesiologists grade I, II, and III morbidly patients of both the sexes taken in the operating theater with bispectral index (BIS) monitoring under the same anesthesiologist and consenting to be a part of the study were included in the study (Fig. 1). Patients who did not fulfill the inclusion criteria, American Society of Anesthesiologists grade IV patients, and those with predicted difficult intubation or tracheostomy in situ were excluded from the study.

After being transferred to the operating theater, all patients were administered general anesthesia using a standard protocol. Pre-oxygenation with 100% oxygen for 3 min was carried out. Induction of anesthesia was started with IV glycopyrrolate 0.2 to 0.4 mg, IV fentanyl 30–40 µg, and IV propofol 1% 7.5–12.5 ml (BIS guided). Endotracheal intubation with a cuffed ETT was facilitated by the neuromuscular blocker cisatracurium IV, 0.15 mg/kg as per total body weight. For female patients, a size 7 cuffed ETT was used, and for males, a size 8 cuffed ETT was used. Anesthesia was maintained with oxygen and air (60:40) along with desflurane and controlled mechanical ventilation with cisatracurium injection. A high-volume, low-pressure ETT (Rüsch®, Teleflex Medical, Malaysia) was placed in situ, and the ETT cuff pressure was adjusted to 28 cmH₂O using a manometer (Posey®, Portex, Germany). We ensured that there was no leakage by stethoscopic auscultation. After induction, a 38 Fr (12.7 mm) GCT (Ethicon Endo-Surgery, Germany) was inserted blindly in a slightly head-up position. Abdominal insufflation of carbon-dioxide was performed in the supine position. The patients were placed in the reverse Trendelenburg position to facilitate surgery and consequent cuff pressure changes, and changes in peak airway pressure were recorded at the following steps of surgery: 2 min after insertion of GCT, creation of carboperitoneum in supine position, reverse Trendelenburg position, final removal of GCT, return to supine position, and release of carboperitoneum. The cuff pressure recordings were performed at the end of expiration.

Immediate postoperative complications during the first 24 h such as sore throat, cough, hoarseness of voice, and aspiration pneumonia were also recorded. The target cuff pressure was set at 28 cmH₂O and adjusted after each recording at various surgical steps. The manometer was calibrated every month. It was kept attached to the pilot balloon throughout surgery. Intra-abdominal pressure was maintained between 14 and 16 mmHg during the carboperitoneum. Measurements were taken with the patient’s head and neck in the neutral position and occiput on the same type of pillow.

**Statistical analysis**

The results obtained were collected, tabulated, and analyzed using appropriate statistical tests. Statistical analysis was performed using IBM SPSS 20 version (IBM Co., USA). Normality of distribution was assessed using the Kolmogorov-Smirnov test. Continuous variables were expressed as
mean ± standard deviation or range, while non-continuous variables were expressed as the number of occurrences and percentages. The ETT cuff pressure and peak pressure at various surgical steps were compared using multiple paired t-tests. Statistical significance was set at P < 0.05.

RESULTS

In total, 124 patients were included in this study (Fig. 1). In the study population, mean age was 44.5 ± 12.6 years and mean BMI was 46.1 ± 6.0 kg/m². Majority of the patients belonged to the age group of 40–60 years (51.7%), with a preponderance of females (55%). The mean duration of surgeries was 1.2 h. Most patients underwent sleeve gastrectomy, Roux-en-Y gastric bypass, or mini-gastric bypass (Table 1).

The baseline cuff pressure was set to 28 cmH₂O. Mean ETT cuff pressure was found to be significantly increased from the baseline after insertion of GCT (36.3 ± 7.3 cmH₂O; P < 0.001) and creation of carbo-peritoneum (33.3 ± 3.8 cmH₂O; P < 0.001). ETT cuff pressure was frequently higher than 30 cmH₂O after GCT insertion, which may lead to impaired tracheobronchial mucosal blood flow. Clinically significant increase in cuff pressure (> 35 cmH₂O) was observed in 55 of 120 patients (45.8%). We also found that there was an approximately twofold increase in endotracheal cuff pressure in 3 out of 120 patients (2.5%). In addition, cuff pressure significantly decreased from the baseline after GCT removal (24.0 ± 3.0 cmH₂O; P < 0.001) and release of carbo-peritoneum (24.7 ± 3.0 cmH₂O; P < 0.001). No significant changes were observed in cuff pressure after giving reverse Trendelenburg position (28.0 ± 1.4 cmH₂O) and return to supine position (27.9 ± 1.3 cmH₂O) (Table 2).

There was a significant increase (P < 0.05) in peak airway pressure from the initial baseline value of 25.1 ± 3.7 to 26.5 ± 4.5 cmH₂O (P < 0.001) after GCT insertion, creation of carbo-peritoneum (32.6 ± 4.4) (P < 0.001), attainment of reverse Trendelenburg position (32.3 ± 4.0) (P < 0.001), and subsequent return to supine position 32.5 ± 4.8 (P < 0.001). Furthermore, peak airway pressure decreased and returned to baseline values after the release of the carbo-peritoneum (Table 3). Only 2 of the patients had hoarseness of voice as a postoperative complication, while 10 patients had sore throat and discomfort. No other complications such as aspiration were noted in this study (Table 2).

DISCUSSION

Our study emphasizes the importance of intraoperative ETT cuff pressure monitoring, particularly in laparoscopically performed bariatric surgery. We found that cuff pressure not only increases with GCT insertion and creation of the carbo-peritoneum but also decreases significantly with GCT removal and release of carbo-peritoneum. Both scenarios can prove harmful if adequate measures are not taken.

Laparoscopy in bariatric surgery is associated with lower morbidity and mortality than the traditional surgical approach [7]. The physiological changes associated with laparoscopic bariatric surgery include those associated with tilting the patient to facilitate instrumentation and surgical exposure, pressure effects of instilled gas into a closed cavity

<table>
<thead>
<tr>
<th>Table 1. Demographic Data</th>
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<tr>
<td>Variable</td>
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<tr>
<td>Age (yr)</td>
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<tr>
<td>Sex, F/M (%)</td>
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<tr>
<td>BMI (kg/m²)</td>
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<tr>
<td>Duration of surgery (min)</td>
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<td>Type of surgery, sleeve/gastric bypass</td>
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Values are presented as mean ± SD or number only. BMI: body mass index. *Total patients.

| Table 2. Comparison of Cuff Pressure between Baseline and Various Steps During Surgery |
|-----------------------------------------|---------------------------------|
| Steps during surgery                   | Cuff pressure (cmH₂O)          |
| Baseline                                | 28                             |
| GCT insertion                           | 36.3 ± 7.3                     |
| Creation of carbo-peritoneum            | 33.3 ± 3.8                     |
| Reverse Trendelenburg position          | 28.0 ± 1.4                     |
| Final removal of GCT                    | 24.0 ± 3.0                     |
| Return to supine                        | 27.9 ± 1.3                     |
| Release of carbo-peritoneum             | 24.7 ± 3.0                     |

Values are presented as mean ± SD. Cuff pressure was adjusted to 28 cmH₂O at each step. GCT: gastric calibration tube.

| Table 3. Comparison of Peak Airway Pressure between Baseline and Various Steps During Surgery |
|-----------------------------------------|---------------------------------|
| Steps during surgery                   | Peak airway pressure (cmH₂O)   |
| Baseline                                | 25.1 ± 3.7                     |
| GCT insertion                           | 26.5 ± 4.5                     |
| Creation of carbo-peritoneum            | 32.6 ± 4.4                     |
| Reverse Trendelenburg position          | 32.3 ± 4.0                     |
| Final removal of GCT                    | 31.7 ± 4.5                     |
| Return to supine                        | 32.5 ± 4.8                     |
| Release of carbo-peritoneum             | 25.3 ± 3.9                     |

Values are presented as mean ± SD. GCT: gastric calibration tube.
Endotracheal tube cuff pressure during laparoscopic bariatric surgery

Further increasing the gastric pressure, systemic effects of carbon dioxide, and pressure effect associated with GCT. Thus, endotracheal intubation is mandatory in obese patients. Studies conducted to date have assessed cuff pressure changes during one aspect of laparoscopic surgery, such as position or carboperitoneum [3,8]. This study evaluated changes in cuff pressure during various steps of laparoscopic bariatric surgery.

The ETT cuff pressure must be adjusted to ensure delivery of the prescribed mechanical ventilation tidal volume and reduce the risk of aspiration of secretions that accumulate above the cuff without compromising tracheal perfusion [9]. A minimal pressure of 20 cmH₂O is recommended to prevent aspiration and ventilator-associated pneumonia [10,11]. There is a lack of uniformity in the desired value of cuff pressure, but a range of 20–30 cmH₂O can be considered safe. Lomholt [12] recommended selecting a cuff pressure of 25 cmH₂O as the safe minimum cuff pressure to prevent aspiration and leakage of ventilator gases. The cuff pressure was adjusted to 28 cmH₂O to ensure safety.

Hung [13], in their study on patients undergoing laparoscopic bariatric surgery, had concluded that after insertion of the calibrating orogastric tube, the median tracheal cuff pressure increased from 28 to 36 cmH₂O (P < 0.001) and was greater than 35 cmH₂O in 30 of 60 patients (50%). Our study showed that cuff pressure increases not only at the time of GCT insertion but also at the time of creation of the carboperitoneum. Fifty-five percent of the patients had ETT cuff pressure greater than 35 cmH₂O on GCT insertion, and 17.5% patients had increased cuff pressure at the time of pneumoperitoneum creation. Kim et al. [14] observed a similar increase in cuff pressure after insertion of a transesophageal echocardiography probe.

Wu et al. [8] evaluated ETT cuff pressure changes in the head-up or head-down position during laparoscopic surgery. They found that the head-up position in laparoscopic cholecystectomy causes no significant change in cuff pressure, which is similar to our results. BMI did not show any correlation with an increase in cuff pressure in our study, similar to the aforementioned study. The peak airway pressure did not change significantly in their study. In our study, a significant increase was seen from the baseline value, but when compared with the value of peak pressure at the time of creation of the carboperitoneum, no significant change was observed (Table 3). The reverse Trendelenburg position reduces breathing by shifting the abdominal viscera caudally away from the diaphragm. Hence, it is expected that the airway pressure should decrease, but this was not observed. The increase in compliance with the reverse Trendelenburg position could have been nullified by the carboperitoneum. Carboperitoneum decreases thoracopulmonary compliance by 30–50% in healthy and obese patients [15].

Hemodynamic parameters were also recorded during the various surgical steps. Heart rate did not vary much with GCT insertion, carboperitoneum, reverse Trendelenburg position, return to supine position, or release of carboperitoneum. However, in the reverse Trendelenburg position, systolic and diastolic blood pressure fell significantly below baseline. Hence, it is vital for patients to be adequately hydrated to prevent adverse outcomes due to hypotension, such as stroke.

The drop in ETT cuff pressure observed when the GCT was removed in the present study can be explained by the removal of an external force on the posterior membranous tracheal wall exerted by the GCT into the esophagus. The cuff pressure also decreases significantly when the carboperitoneum is released. These periods of insufficient pressure leave the patient susceptible to micro-aspiration as secretions or hemorrhagic acidic gastric content pooled on top of the ETT cuff as the GCT is removed, may move past it, and trickle down into the lungs. Accumulating evidence suggests that obesity is associated with complications due to longstanding reflux, such as erosive esophagitis, Barrett’s esophagus, and esophageal adenocarcinoma [16]. Thus, microaspiration or frank aspiration of gastric contents intraoperatively, especially when the GCT is pulled out, is a serious risk in these patients. Therefore, proper suctioning as the GCT is removed is recommended.

Fluid leakage around the ETT cuff into the airway is a potentially serious form of microaspiration. The cuff is designed to seal the airway, allowing airflow through the ETT, but preventing the passage of air or fluids around the ETT. When this seal is compromised, microaspiration contaminated with gastric contents or bacterially colonized oral secretions can occur, leaving the patient susceptible to a host of problems, such as hypoxia, pneumonitis, and respiratory infection.

In our study, 9.7% of the patients had throat pain or hoarseness of voice. Liu et al. [17] had found the incidence of sore throat to be 44% when cuff pressure was not monitored, whereas adjustment of cuff pressure reduced the incidence to 33%. However, this study was not specific to laparoscopic bariatric surgeries. Hung [13] did not consider the postoperative complications. None of the patients in our study had severe complications such as aspiration. This may be the result of

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cuff pressure adjustment to 28 cmH$_2$O at every step. If this is not done, the increase or decrease in cuff pressure and the subsequent complication rate can be quite high.

A major limitation of our study is that at each step, the endotracheal cuff pressure was readjusted to 28 cmH$_2$O. If the pressure was not adjusted, the incidence of complications may have been higher. Neuromuscular monitoring was not performed in this study.

Sengupta et al. [18] concluded in their study that there is a tendency to overinflate the cuff by manual palpation, and increased training does not improve cuff management. Thus, in this study, we conclude that there is a significant increase in cuff pressure at the time of GCT insertion, as well as creation of pneumoperitoneum, while a significant drop is seen at the time of GCT removal and release of pneumoperitoneum. ETT cuff pressure monitoring using a manometer is a simple and effective method of decreasing tracheal mucosal injury and aspiration-related complications. Its use is recommended not only in bariatric surgery but also in all laparoscopic surgeries.

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CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

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Comparison between GlideRite® rigid stylet and Parker Flex-It™ stylet to facilitate GlideScope intubation in simulated difficult intubation: a randomized controlled study

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Background: The GlideScope® videolaryngoscope (GVL) is widely used in patients with difficult airways and provides a good glottic view. However, the acute angle of the blade can make insertion and advancement of an endotracheal tube (ETT) more difficult than direct laryngoscopy, and the use of a stylet is recommended. This randomized controlled trial compared Parker Flex-It™ stylet (PFS) with GlideRite® rigid stylet (GRS) to facilitate intubation with the GVL in simulated difficult intubations.

Methods: Fifty-four patients were randomly allocated to undergo GVL intubation using either GRS (GRS group) or PFS (PFS group). The total intubation time (TIT), 100-mm visual analog scale (VAS) for ease of intubation, success rate at the first attempt, use of laryngeal manipulation, tube advancement rate by assistant, and complications were recorded.

Results: There was no significant difference between the GRS and PFS groups regarding TIT (50.3 ± 12.0 s in the GRS group and 57.8 ± 18.8 s in the PFS group, P = 0.108). However, intubation was more difficult in the PFS group than in the GRS group according to VAS score (P = 0.011). Cases in which the ETT was advanced from the stylet by an assistant, were more frequent in the GRS group than in the PFS group (P = 0.002). The overall incidence of possible complications was not significantly different.

Conclusions: In patients with a simulated difficult airway, there was no difference in TIT using either the PFS or GRS. However, endotracheal intubation with PFS is more difficult to perform than GRS.

Keywords: Airway management; General anesthesia; Intubation; Laryngoscopes.
tracheal intubation because of the large angle of the curved blade, which has the potential to make insertion and advancement of an endotracheal tube (ETT) relatively difficult with the possibility of intraoral damage [1].

Owing to the curvature of the GVL blade, a stylet must be used to position the ETT tip at the glottic opening [1]. The GlideRite® rigid stylet (GRS) (Fig. 1) is a reusable dedicated stylet provided by the manufacturer with an angle of approximately 90° and radius of 6 cm to fit the GVL [2]. Various authors have recommended different curvatures of the ETT/stylet to optimally place it into the trachea, including matching the blade’s 60° angle, configuring the ETT with a 90° bend [1,3], or using a J-shaped ETT [4]. Other potential strategies may include the use of a flexible stylet that allows active adjustment of the ETT tip angle during tracheal intubation [5]. The Parker Flex-It™ stylet (PFS, Parker Medical, USA) (Fig. 2) is a two-piece plastic stylet allowing active modification of the tip of the ETT during use, and fixation at a specific curvature using a locking clip. Its ability to “relax” the curvature after the ETT tip has passed the vocal cords, facilitates the advancement of the ETT following the curvature of the airway [5,6].

To simulate a difficult airway, we used an adjustable cervical collar, which could be customized for individual cervical lengths. Immobilization using a cervical collar is a method commonly used in patients with cervical spine injuries, and there is no risk caused by the fixation itself [7,8]. This method has been used intentionally to simulate a difficult airway in several previous studies [7,9–11], and different aids for intubation have been studied in simulated difficult airways [7,12]. The Ambu® Perfit ACE cervical collar (Ambu Inc., Denmark) used in this study is different from the rigid or semi-rigid collars used in previous studies [13–15]. It is adjustable to any neck size with 16 different settings ranging from “Neckless” to “Tall” sizes, allowing to size the collar exactly to the individual’s neck size. Therefore, we expected to reconstruct a difficult case precisely.

Previous studies comparing the PFS with the GRS or malleable stylet investigated each stylet in patients with normal airways [5,16]; however, no study has been conducted for difficult airways. Therefore, the purpose of this study was to compare the usefulness of the GRS and PFS during intubation with GVL in a simulated difficult airway, and the alternative hypothesis was that there would be difference in TIT between the two groups.

**MATERIALS AND METHODS**

This randomized controlled study was approved by the Institutional Review Board of the our hospital (no. 2016-11-005-010). Written informed consent was obtained from all patients before enrollment in the study. The inclusion criteria were patients with American Society of Anesthesia physical status I & II, aged 19–60 years, and scheduled for elective surgery requiring general anesthesia and tracheal intubation. Patients with a body mass index > 35 kg/m², who needed emergency operations and rapid sequence intubation, had pre-existing dental pathology, and were expected to have difficult airways were excluded from the study. Potentially difficult intubation was defined as the presence of Mallampati class > III, mouth opening < 2.5 cm, thyromental distance < 6 cm, and history of previous difficult intubation.

The patients were randomly assigned to either the GRS group or the PFS group using a random number table generated using the randomization plan generator provided at http://www.randomization.com. In the GRS group, tracheal

![Fig. 1](image1.png) The GlideRite® rigid stylet (GRS, Verathon, USA), a dedicated stylet provided by the manufacturer.

![Fig. 2](image2.png) The Parker Flex-It™ stylet (PFS, Parker Medical, USA), shown individually and inserted into an endotracheal tube.
intubation was performed with the GVL, and the tracheal tube was used with the manufacturer’s stylet, the GRS. In the PFS group, tracheal intubation was performed with PFS.

We recruited 60 patients for this study, and six of them were not eligible because of the Mallampati class IV (n = 2), cancellation of the surgery (n = 2), and invalid informed consent (n = 2) (Fig. 3). The remaining 54 patients fulfilled all criteria and subsequently consented to participate in the study (n = 27 per group). Each patient was allocated to a group using a sealed opaque envelope, which was opened as the patient entered the operating room. The assigned stylet was inserted into the ETT by one of the study investigators, who concealed the stylet and ETT with a towel and then had no further involvement with clinical care or outcome assessment. An independent anesthesiologist, higher than 3rd grade resident doctor who was clinically experienced in handling GVL dozens of times and had practiced intubation with PFS over 30 times to become skilled, performed all tracheal intubations, and was not involved in the collection or analysis of the data.

Before the induction of general anesthesia, we measured the neck circumference, inter-incisor distance (mouth opening), and thyromental distance while awake. After preoxygenation with 100% oxygen for > 3 min, induction was started with 2 mg/kg of 1% propofol and 2 μg/kg of fentanyl. When the patient lost consciousness and manual ventilation with a face mask was well performed, 0.6 mg/kg of rocuronium was administered. Three minutes later, the Cormack-Lehane grade was evaluated using a Macintosh laryngoscope, and the cervical collar was applied to simulate the difficult airway. To evaluate whether the simulated difficult tracheal intubation would be appropriately functioning, the Cormack-Lehane grade was assessed using a Macintosh laryngoscope once more after applying the neck collar. Tracheal intubation was performed using either the GRS or PFS according to each group using 7.5-mm tubes for men and 7.0-mm tubes for women. We allowed the involvement of an assistant with laryngeal manipulation or ETT advancement, if necessary, and recorded it. If the operator removed the GVL blade or ETT from the mouth, this was counted as an additional attempt at intubation.

The primary outcome was total intubation time (TIT), which was defined as the time from insertion of the blade of the GVL into the oral cavity to the appearance of end-tidal carbon dioxide (EtCO₂) curve of at least 30 mmHg after intubation of the ETT. TIT was divided into two detailed phases, including endotracheal tube insertion time (EIT) and endotracheal tube advancement time (EAT). After the timer was initiated, the blinded observer measured not only the TIT but also each section of the time. Their definitions are as follows:

- EIT: the time from insertion of the blade of the GVL into the oral cavity to the moment just before the ETT con-
contacts the glottic opening.

- EAT: the time from the passing of the ETT through the glottis to the appearance of the EtCO$_2$ curve of at least 30 mmHg on the anesthesia monitor.

Data were collected by one investigator to eliminate observer interpreter bias. We defined failure of tracheal intubation as one of the following cases: three failed attempts, prolonged intubation time $>120$ s, or SpO$_2$ $<90\%$ during intubation. In case of failed intubation, we planned to remove the cervical collar and conduct a bag-and-mask ventilation with 100% oxygen, and then perform tracheal intubation with the stylet that the operator preferred to use with the GVL. These cases were excluded from the analysis, and the TIT of the final trial was counted and used for analysis. The time required for intermittent mask ventilation was subtracted from the TIT.

Prespecified secondary outcomes included ease of intubation using a visual analog scale (VAS) ($0 =$ extremely easy to $100 = $ extremely difficult), the number of attempts, success rate for the first attempt, whether external laryngeal manipulation was used, and whether the ETT was advanced along the stylet by an assistant. During intubation, we also evaluated the occurrence of severe hypoxemia, which was defined as peripheral oxygen saturation (SpO$_2$) $<90\%$, and laryngospasm. Intraoral examination was performed to confirm the presence of lip, mucosal, or tooth injury immediately after tracheal intubation. After surgery, we examined oropharyngeal trauma with GRS and performed extubation. Subsequently, the presence of blood in the tracheal tube was identified. One hour after the extubation, the patients were interviewed if they had symptoms of complications, such as sore throat, hoarseness, and dysphagia by an independent anesthetist blinded to group allotment in the post-anesthesia care unit; the complications were reevaluated after 24 h in the general ward in the same manner. Hemodynamic data, such as blood pressure, heart rate, and SpO$_2$, were consistently monitored and recorded since the patients entered the operating room until the operation finished, especially before and after tracheal intubation and extubation.

Statistical analyses

The primary outcome was TIT, and the secondary outcomes were VAS score for ease of intubation, success rate at the first attempt, use of laryngeal manipulation, tube advancement rate by assistant, and complications. A pilot study was conducted in 20 patients (10 patients per group) to determine the required sample size. All cases were not included in our present study. The mean ± standard deviation (SD) of the TIT was 52.4 ± 23.1 s for the GRS group and 67.7 ± 14.0 s for the PFS group. Using a statistical significance level of 0.05 ($\alpha = 0.05$) and 80% power ($\beta = 0.2$), we estimated that 26 patients would be required per group. We selected a sample size of 30 patients per group to compensate for potential dropouts (about 10%).

Statistical analysis was performed using the SPSS ver. 23 (IBM Corp., USA). Values are expressed as median (1Q, 3Q), or mean ± SD, or as the number of patients. The normality of the distribution of continuous variables was analyzed using the Shapiro–Wilk test. We used independent t-tests to analyze continuous, normally distributed variables and the Mann–Whitney U test to analyze continuous, non-normally distributed variables. Chi-squared or Fisher’s exact tests were used, as appropriate, for categorical data. The limit of statistical significance was set at $P < 0.05$.

RESULTS

The demographic and airway assessment data of the patients showed no differences between the GRS and PFS groups, as shown in Table 1. All tracheal intubations were successfully performed within three attempts and there were no cases of failed intubation. The Cormack-Lehane grade of the simulated difficult airway evaluated with the Macintosh laryngoscope was greater than III. No statistically significant differences were observed between the two groups concerning the TIT, which was 45.9 s (41.8, 52.8) in the GRS group and 49.5 s (46.2, 64.5) in the PFS group ($P = 0.108$). The EIT ($P = 0.257$) and EAT ($P = 0.863$) also showed no differences between the groups. However, the difference in ease of intubation between the two groups was statistically significant, with a mean VAS score of 40.8 ± 12.7 mm in the GRS group and 52.1 ± 18.3 mm in the PFS group ($P = 0.011$). The successful tracheal intubation rate at the first attempt was 92.6% in the GRS group and 74.1% in the PFS group ($P = 0.142$). One case of a third intubation attempt occurred in the PFS group, and the stylets were broken during tracheal intubation in three cases in the PFS group. Cases in which the ETT was advanced along the stylet by an assistant were 11 (40.7%) and 1 (3.7%) in the GRS and PFS groups, respectively ($P = 0.002$) (Table 2). The incidence of complications, including hypoxemia and dental damage during intubation, was not observed in either group. In addition, there were no significant differences in the incidence
Table 1. Patient Demographics and Airway Assessment Data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GRS group (n = 27)</th>
<th>PFS group (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>47 (37, 54)</td>
<td>51 (44, 56)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>11/16</td>
<td>11/16</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.1 ± 3.3</td>
<td>24.0 ± 2.4</td>
</tr>
<tr>
<td>ASA (I/II)</td>
<td>17/10</td>
<td>17/10</td>
</tr>
<tr>
<td>Thyromental distance (cm)</td>
<td>9.0 (8.5, 10.0)</td>
<td>9.5 (8.5, 10.0)</td>
</tr>
<tr>
<td>Neck circumference (cm)</td>
<td>38.0 ± 4.0</td>
<td>37.1 ± 2.8</td>
</tr>
<tr>
<td>Mouth opening without collar (cm)</td>
<td>4.8 (4.3, 5.0)</td>
<td>4.6 (3.9, 4.8)</td>
</tr>
<tr>
<td>Mouth opening with collar (cm)</td>
<td>1.9 ± 0.4</td>
<td>1.9 ± 0.4</td>
</tr>
<tr>
<td>Mallampati class (I/II)</td>
<td>10/17</td>
<td>12/15</td>
</tr>
<tr>
<td>Cormack-Lehane grade (I/II/III/IV)</td>
<td>10/14/3/0</td>
<td>10/17/0/0</td>
</tr>
<tr>
<td>Cormack-Lehane grade with collar (I/II/III/IV)</td>
<td>0/0/3/24</td>
<td>0/0/2/25</td>
</tr>
<tr>
<td>Cormack-Lehane grade with collar by the GVL (I/II/III/IV)</td>
<td>19/6/2/0</td>
<td>22/4/1/0</td>
</tr>
</tbody>
</table>

Values are presented as median (1Q, 3Q), number of patients, or mean ± SD. GRS: GlideRite® rigid stylet (Verathon, USA), PFS: Parker Flex-It™ stylet (Parker Medical, USA), BMI: body mass index, ASA: American Society of Anesthesiologists physical status classification, GVL: GlideScope® videolaryngoscope.

Table 2. Intubation Data of 54 Patients Compared Using Either the GRS or PFS

<table>
<thead>
<tr>
<th>Intubation data</th>
<th>GRS group (n = 27)</th>
<th>PFS group (n = 27)</th>
<th>MD (95% CI)</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIT (s)</td>
<td>45.9 (41.8, 52.8)</td>
<td>49.5 (46.2, 64.5)</td>
<td>−7.5 (−16.1 to 1.1)</td>
<td>0.108</td>
<td></td>
</tr>
<tr>
<td>EIT (s)</td>
<td>21.2 (18.3, 26.3)</td>
<td>23.2 (17.0, 40.3)</td>
<td>−7.4 (−15.1 to 0.2)</td>
<td>0.257</td>
<td></td>
</tr>
<tr>
<td>EAT (s)</td>
<td>26.7 (22.7, 30.0)</td>
<td>26.2 (22.7, 30.6)</td>
<td>−0.1 (−4.1 to 4.0)</td>
<td>0.863</td>
<td></td>
</tr>
<tr>
<td>Ease of intubation (100-mm VAS)</td>
<td>40.8 ± 12.7</td>
<td>52.1 ± 18.3</td>
<td>−11.3 (−19.9 to −2.8)</td>
<td>0.011*</td>
<td></td>
</tr>
<tr>
<td>Intubation attempts 1/2/3/fail</td>
<td>25/2/0/0</td>
<td>20/6/1/0</td>
<td>0.142</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Success rate for the first attempt (%)</td>
<td>92.6</td>
<td>74.1</td>
<td>0.229 (0.043 to 1.224)</td>
<td>0.085</td>
<td></td>
</tr>
<tr>
<td>ETT advanced from stylet by assistant</td>
<td>11 (40.7)</td>
<td>1 (3.7)</td>
<td>0.056 (0.007 to 0.475)</td>
<td>0.008*</td>
<td></td>
</tr>
<tr>
<td>Laryngeal manipulation</td>
<td>0 (0)</td>
<td>1 (3.7)</td>
<td>1.000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as median (1Q, 3Q), mean ± SD, or number of patients (%). GRS: GlideRite® rigid stylet (Verathon, USA), PFS: Parker Flex-It™ stylet (Parker Medical, USA), MD: mean difference, 95% CI: 95% confidence interval, OR: odds ratio, TIT: total intubation time, EIT: endotracheal tube insertion time, EAT: endotracheal tube advancement time, VAS: visual analog scale, ETT: endotracheal tube. *Significantly different between the groups (P < 0.05).

Of oropharyngeal trauma, blood on the tube, sore throat, hoarseness, and dysphagia between the groups (Table 3). Perioperative hemodynamic data also showed no significant differences.

**DISCUSSION**

In this study, we assessed the TIT of two different stylets, the GRS and PFS, during tracheal intubation with the GVL in a simulated difficult airway. Our results revealed that there was no difference in TIT using either of the two stylets. We also found that the performance of intubation with the GRS was subjectively easier than that with the PFS according to the VAS score. Less assistance was needed from the assistant in advancing the ETT into the trachea using the PFS in the simulated difficult airway.

The GVL is easy to use and provides a good glottic view during intubation with less cervical movement and lower applied forces; therefore, it is widely used in patients with difficult airways. Despite the excellent glottic visualization provided by the screen of the GVL, it does not guarantee easy and fast tracheal intubation [1]. The dedicated stylet, the GRS, can occasionally make intubation difficult and may impinge on the laryngeal structures around the vocal cords with potential risk of trauma because of its rigidity [17]. Efforts to determine optimal stylets for GVL intubation have been made by many researchers for several years [1,3,4,18]. Although the PFS was originally designed for use with the Macintosh laryngoscope, we expected that the PFS, with its capability to actively angulate the distal ETT, could facilitate insertion and advancement of the ETT during GVL intubation, especially in simulated difficult airways.
Contrary to our expectations, the TIT was not statistically different between the GRS and PFS. We divided the TIT into two phases, namely EIT and EAT. For EIT, we expected that the ETT with the PFS would approach the vocal cords faster than the GRS could because of its flexible feature to actively control the curvature of the ETT following the structure of the airway. For EAT, we expected that the time to advance the ETT/PFS into the trachea would be shortened by releasing the locking clip and relaxation of the active adjustment of the PFS angle, following the natural angle of the ETT, without assistance. However, the EIT and EAT also showed no statistical differences between the two groups. The reason for the absence of differences in the TIT, EIT, and EAT in our study is that handling the PFS is difficult in the limited intraoral space because of the interference of adjacent intraoral structures, unlike in the air without hindrance, thus it could not shorten the EIT. This study showed an advantage regarding the advancement of the ETT off the stylet by an assistant in the PFS group. Only one case (3.7%) in the PFS group needed the help of an assistant while advancing the ETT/stylet into the trachea, while 11 cases (40.7%) in the GRS group required it. It was anticipated that relaxation of the curvature of the PFS after passing the glottic opening would facilitate ETT advancement smoothly, reducing the need for help from an assistant to advance the ETT. However, the PFS group did not present a shorter EAT than that of the GRS group. According to the study by Sheta et al. [16], which investigated the difference in the GRS and PFS in patients with normal airways, PFS had no benefit in shortening the TIT in normal airways.

Tracheal intubation with the GRS was significantly easier than that with the PFS during the use of GVL, based on the VAS score of the experienced operators. However, we need to reconsider the ease of intubation. Careful consideration of the factors that can affect the VAS score is needed. From another perspective, the number of attempts, ability to control the stylet, frequency of usage of external laryngeal manipulation, and advancement of ETT along the stylet by an assistant could influence the evaluation of the VAS score. In our study, even though there were more cases of advancement of ETT requiring an assistant in the GRS group than in the PFS group, difficulty in manipulating the ETT/PFS in the narrow oral cavity, the breakage of the PFS, and a higher frequency of intubation attempts might have resulted in higher VAS scores in the PFS group.

The success rates for the first attempt were 92.6% in the GRS group and 74.1% in the PFS group. Although the difference may not be not statistically significant, but could be clinically significant. It is thought that the rigid GRS was easier to manipulate in the limited intraoral space than the flexible PFS. Repeated intubation attempts in the PFS group were conducted more often than in the GRS group. In three cases in the PFS group, the stylets broke because of their thin and fragile plastic material. In cases of rapid sequence intubation or situations in which successful tracheal intubation must be performed at once, the use of PFS may not be appropriate as a first choice. In such cases, the GRS might be better utilized because of its higher success rate in the first attempt. If the PFS must be used in the first attempt, a “back-up” stylet should be arranged in advance. In addition, we believe that it is necessary to replace the fragile plastic part of the PFS with a durable metallic material.

There is also variation between studies in the type of collar used. In our study, the application of the adjustable cervical collar to the patients facilitated more restricted mouth opening than without the collar, presenting an airway diameter of

### Table 3. Incidence of Complications

<table>
<thead>
<tr>
<th>Parameters</th>
<th>GRS group (n = 27)</th>
<th>PFS group (n = 27)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sore throat at 1 h</td>
<td>12 (44.4)</td>
<td>15 (55.6)</td>
<td>0.587</td>
</tr>
<tr>
<td>Sore throat at 24 h</td>
<td>3 (11.1)</td>
<td>7 (25.9)</td>
<td>0.293</td>
</tr>
<tr>
<td>Hoarseness at 1 h</td>
<td>6 (22.2)</td>
<td>5 (18.5)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hoarseness at 24 h</td>
<td>1 (3.7)</td>
<td>2 (7.4)</td>
<td>1.000</td>
</tr>
<tr>
<td>Dysphagia at 1 h</td>
<td>3 (11.1)</td>
<td>2 (7.4)</td>
<td>1.000</td>
</tr>
<tr>
<td>Dysphagia at 24 h</td>
<td>1 (3.7)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hypoxemia (SpO₂ &lt; 90%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Dental damage</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Oropharyngeal trauma</td>
<td>8 (29.6)</td>
<td>4 (14.8)</td>
<td>0.327</td>
</tr>
<tr>
<td>Blood on the tube</td>
<td>5 (18.5)</td>
<td>3 (11.1)</td>
<td>0.704</td>
</tr>
</tbody>
</table>

Values are presented as number of patients (%). GRS: GlideRite® rigid stylet (Verathon, USA), PFS: Parker Flex-It™ stylet (Parker Medical, USA). SpO₂: peripheral oxygen saturation.
4.8 to 1.9 cm in the GRS group and 4.6 to 1.9 cm in the PFS group, thereby sufficiently increasing the Cormack-Lehane grades for glottic view. This implies that the proper simulation of a difficult airway was set up.

Various complications related to the use of the GVL with the GRS or other rigid stylets have been reported by many authors. Previously reported cases of tonsillar and palatopharyngeal injury during intubation with GVL were shown to be related to the rigidity of the stylet and the ‘potential blind spot’ of the GVL [17,19,20]. While concentrating on the GVL monitor to visualize the tip of the ETT adjacent to the glottic opening, a “blind spot” might present in the passage of the styletted ETT from the mouth opening to the vocal cords [17,19]. Our study showed no significant difference in intubation-related complications between the GRS and PFS groups. We first expected that intubation with the PFS would be less traumatic because of its capability to modify the curvature in the oral cavity and its flexible features. Perhaps because of use in the simulated narrow oral environment, both GRS and PFS touched oropharyngeal and laryngeal structures with higher frequency than in the normal airway. The incidence of sore throat 1 h after surgery has been reported as 18.3% in the normal airway [16] and was 50.0% in this study, irrespective of the type of stylet. Moreover, the incidence of oropharyngeal trauma has been reported as 10.0% in the normal airway [16] and was 22.2% in this study. Although the studies were not compared under the same design, the incidence of trauma was higher when intubation was performed in a narrow oral cavity in a simulated difficult airway.

This study has several limitations. First, since most anesthesiologists including the operator in this study are usually familiar with use of the GRS, there might be a possibility of difference in learning curve from that of the PFS. In order to overcome this point, the operator had sufficiently practiced intubation using the PFS prior to study participation. However, we think that it is inevitable that the differences in the learning curve of using the GRS and PFS can sometimes occur, which might have affected estimation of the sample size. If the sample size increases, it could make a statistically significant difference, but it will not be a clinically significant difference. Therefore, the authors believe that the conclusions will be the same as this study. This is one of the major study limitations. Second, the anesthesiologist who performed tracheal intubation could not be blinded to the stylet used. Although the assigned stylet and ETT were concealed before intubation, it was impossible to prevent the anesthesiologist from knowing which stylet was being used during intubation. Third, we tried to simulate a difficult airway with a cervical collar, but it could not reflect an actual difficult airway. Difficult airways include not only neck immobilization and limited mouth opening, but also many structural problems of the airway. Tongue swelling, abnormal dentition, and distorted pharyngeal or laryngeal anatomy can affect the difficulty of tracheal intubation. Therefore, this simulated method is limited in reflecting the actual difficult cases.

In conclusion, in patients with a simulated difficult airway, there was no difference in TIT using either the PFS or GRS. However, endotracheal intubation with the PFS is more difficult to perform than with the GRS.

**FUNDING**

This study was supported by 2017 Kangwon National University Hospital Grant.

**ACKNOWLEDGEMENTS**

Flex-It™ stylet has been changed manufacturer name since submitting a manuscript (changed from Parker Medical to Salter Labs).

**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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REFERENCES

Management of renin-angiotensin-aldosterone inhibitors and other antihypertensives and their clinical effects on pre-anesthesia blood pressure

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Background: Blood pressure fluctuations appear more significant in patients with poorly controlled hypertension and are known to be associated with adverse perioperative morbidity. In the present study, we aimed to determine the effects of antihypertensive drug treatment strategies on preanesthetic operating room blood pressure measurements.

Methods: A total of 717 patients participated in our study; 383 patients who were normotensive based on baseline measurements and not under antihypertensive therapy were excluded from the analysis. The remaining 334 patients were divided into six groups according to the antihypertensive drug treatment. These six groups were examined in terms of preoperative baseline and pre-anesthesia blood pressure measurements.

Results: As a result of the study, it was observed that 24% of patients had high blood pressure precluding surgery, and patients using renin-angiotensin-aldosterone system inhibitors (RAASI) had higher pre-anesthesia systolic blood pressure than patients using other antihypertensive drugs. Patients who received beta-blockers were also observed to have the lowest pre-anesthesia systolic blood pressure, diastolic blood pressure, and mean blood pressure, compared to others.

Conclusions: Recently, whether RAASI should be continued preoperatively remains controversial. Our study shows that RAASI cannot provide optimal pre-anesthesia blood pressure and lead to an increase in the number of postponed surgeries, probably due to withdrawal of medication before the operation. Therefore, the preoperative discontinuation of RAASI should be reevaluated in future studies.

Keywords: Anti-Hypertensive agents; Blood pressure; Pre-operative hypertension; Pre-anesthesia hypertension.

INTRODUCTION

Hypertension is a global public health problem and a preventable cause of mortality and morbidity. It has an estimated prevalence of 30% [1]. In untreated patients, hypertension is known to increase the risk of cardiovascular and cerebrovascular events, bleeding, kidney injury, and mortality [2,3]. In addition, poorly controlled blood pressure leads to cancellation or postponement of surgery [3]. Table 1 presents the classification of hypertension, as recommended by the 2018 European Society of Cardiology (ESC) and European Society of Hypertension (ESH) guidelines for the management of arterial hypertension (Table 1) [4]. It is generally accepted that patients with grade 1 hypertension have little or no in-
creased risk of perioperative cardiac morbidity, and anesthesia can be performed as planned, whereas patients with grade 3 hypertension have an increased risk of severe end-organ damage and cardiac morbidity [5]. In this context, the 2018 ESC/ESH guidelines for the management of arterial hypertension and the 2017 American College of Cardiology (ACC) and American Heart Association (AHA) guidelines for the prevention, detection, evaluation, and management of high blood pressure in adults suggest that in those with systolic blood pressure (SBP) ≥ 180 mmHg and/or diastolic blood pressure (DBP) ≥ 110 mmHg, deferring the intervention until blood pressure is reduced or controlled is advisable, except for emergencies [4,6].

In patients receiving antihypertensive therapy, an important issue in the perioperative period is to avoid large blood pressure fluctuations. Fluctuations appear more significant in patients with poorly controlled hypertension and are usually accompanied by a significant increase during anesthesia induction followed by a serious decrease [7]. Intraoperative blood pressure instability is known to be associated with adverse perioperative morbidity, the most important of which are major adverse cardiac events and acute kidney injury [1,2].

Antihypertensive treatment strategies have not been proven to be superior to each other in patients undergoing non-cardiac surgery; therefore, general antihypertensive treatment algorithms are applied in the perioperative period [8,9]. Accordingly, tight control of blood pressure in the perioperative period is more important than the type of drug therapy used. Nonetheless, renin-angiotensin-aldosterone system inhibitors (RAASIs) and beta-blockers (BBs) have been somewhat unusual in this regard, and they have caused great controversy over whether they should be continued or discontinued preoperatively. More recently, the continuation of BBs has been recommended for chronic usage [4]. Abrupt cessation of BBs may lead to withdrawal syndrome, sympathetic overactivity, and acute hypertension [10]. In recent days, it remains controversial whether RAASIs should be continued preoperatively. Discontinuation of RAASIs is claimed to reduce the risk of intraoperative hypertension and vasoplegia [11,12] and is associated with a significant reduction in cardiovascular events and mortality 30 days after the intervention [13].

In the present observational study, we aimed to determine the effect of antihypertensive drug treatment strategies on pre-anesthesia operating room blood pressure and to investigate the effects of the adjustments made in patients using RAASI on pre-anesthesia blood pressure.

### MATERIALS AND METHODS

A total of 717 adult patients were included in this prospective, cross-sectional, observational study in a tertiary hospital in Ankara, Turkey. We collected data on patients’ demographic features during the preanesthetic examination, including past diagnosis and treatment of hypertension, comorbidities, and chronic medications. During the preoperative preparation, which is usually performed 2 weeks to 1 month before surgery at the hospital’s outpatient clinics; SBP, DBP, and heart rate (HR) were taken as basal measurements. Blood pressure was measured using automatic blood pressure measurement machines (GE Healthcare B40 Patient Monitors, GE Healthcare, UK), from the upper arm, by cuffs according to body characteristics, after resting for 15 min. The patients were under routine antihypertensive therapy. In the operating room, pre-anesthesia measurements were taken before anesthesia induction (GE Healthcare B650 Carescape Monitors, GE Healthcare). Patients with non-hypertensive basal measurements without antihypertensive therapy were evaluated in our previous study [14]. Patients with SBP ≥ 140 and/or DBP ≥ 90 mmHg at basal measurements and/or patients receiving antihypertensive therapy were included in the study. These patients were divided into six groups according to antihypertensive drug treatments: group none, group RAAS inhibitors (RAASI), group beta blockers (BB), group calcium channel blockers (CCB), group diuretics (D), and group combined (Co) (Fig. 1). Patients without antihypertensive therapy, although basal measurements were SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg, were referred to as group none. Each measurement consisted of three separate measurements taken over a 15-min pe-
period with 5-min intervals, after which the highest values were recorded. Blood pressure measurements were measured using automatic blood pressure measurement machines from the upper arm, by cuffs according to body characteristics. Patients were not premedicated with an anxiolytic or analgesic agent. After the measurements, the operation was started with the appropriate anesthetic method for the patient. Intraoperative and postoperative data were not included in this study, and blood pressure data obtained from the basal and operating room measurements were analyzed. Elective surgeries were postponed in patients with pre-anesthesia SBP $\geq 180$ and/or DBP $\geq 110$ mmHg, as recommended by the latest guidelines [4,6].

Patients undergoing emergency surgery and patients under the age of 18, patients whose basal measurements were normotensive while not under antihypertensive therapy, and patients who received antihypertensive therapy but did not comply with the treatment protocol, and whose treatment protocol was changed after the basal measurements were excluded from the study. As required by the routine practice of our clinic, patients took non-RAASI antihypertensive drugs until the morning of the operation, and patients using RAASI discontinued using RAASI 10–12 h before the operation.

This study complied with the Declaration of Helsinki, and ethical approval was granted by the local institutional ethical board (no. 13226/19.12.2017). Informed consent was obtained from all patients.

### Statistical methods

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Co., NY, USA). In order to describe the basic features of patients, mean, standard deviation (SD), minimum and maximum values for normally distributed continuous variables, median, 1st quartile (1Q), and 3rd quartiles (3Q) for non-normally distributed continuous variables; the number of patients and their proportions for categorical variables were calculated as descriptive statistics. The Shapiro–Wilk test or the Kolmogorov–Smirnov test was used to investigate whether data were normally distributed. Comparisons among groups were performed using one-way analysis of variance (ANOVA) or Kruskal–Wallis test. The Games–Howell or least significant difference post hoc test was used for pairwise comparisons of groups, when the assumption of homogeneity of variance was violated or not for one-way ANOVA. Significance was set at $P < 0.05$, using two-sided comparisons.

### RESULTS

A total of 717 adult non-cardiac elective surgery patients participated in this cross-sectional study. Among them, 383 patients who were normotensive based on baseline measurements (SBP $\leq 140$ and/or DBP $\leq 90$ mmHg) and not under any antihypertensive therapy were excluded from the analysis. The remaining 334 patients were divided into six groups ac-

![Fig. 1. Flow diagram. RAASI: renin-angiotensin-aldosterone system inhibitors, BB: beta blockers, CCB: calcium channel blockers, D: diuretics, Co: combined.](image-url)

### Table 1. Patients disposition and analysis sample

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>n</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Patients with no antihypertensive treatment</td>
<td>72</td>
<td>21.6%</td>
</tr>
<tr>
<td>RAASI</td>
<td>Patients on chronic treatment with RAAS inhibitors</td>
<td>119</td>
<td>35.6%</td>
</tr>
<tr>
<td>BB</td>
<td>Patients on chronic treatment with beta blockers</td>
<td>48</td>
<td>8.1%</td>
</tr>
<tr>
<td>CCB</td>
<td>Patients on chronic treatment with calcium channel blockers</td>
<td>27</td>
<td>8.1%</td>
</tr>
<tr>
<td>D</td>
<td>Patients on chronic treatment with diuretics</td>
<td>12</td>
<td>3.6%</td>
</tr>
<tr>
<td>Co</td>
<td>Patients on chronic treatment with combined drugs</td>
<td>56</td>
<td>16.8%</td>
</tr>
</tbody>
</table>

Fig. 1. Flow diagram. RAASI: renin-angiotensin-aldosterone system inhibitors, BB: beta blockers, CCB: calcium channel blockers, D: diuretics, Co: combined.
According to the antihypertensive drug treatment (Fig. 1). Table 2 presents the demographic data of the entire study population (Table 2). When the whole study population was evaluated in general, pre-anesthetic blood pressure measurements were SBP 163.58 ± 24.43 mmHg, DBP 88.10 ± 12.41 mmHg, and mean blood pressure (MBP) 113.25 ± 14.63 mmHg.

Pre-anesthesia SBP, DBP, MBP, and HR measurements were significantly higher than preoperative measurements in all groups (P < 0.001); however, DBP was not significantly different in group D (Table 3). There was a significant difference in preoperative SBP, DBP, MBP, and HR measurements between the groups (P < 0.001, P < 0.001, P = 0.001, and P = 0.032, respectively). In group none, the preoperative measurements of SBP and DBP were significantly higher than those in the RAASI, BB, CCB, and Co groups, and the preoperative measurements of MBP were significantly higher than all other groups.

There was a significant difference in terms of pre-anesthesia SBP, DBP, MBP, and HR measurements between the groups (P = 0.046, 0.006, 0.004, and 0.023, respectively). In group none and group RAASI, pre-anesthesia measurements of SBP, DBP, and MBP were significantly higher than those in group BB (P = 0.006, 0.004, and 0.023, respectively). Group BB had the lowest pre-anesthesia SBP, DBP, and MBP.

Table 3 also presents the pre-anesthesia blood pressure measurements in terms of the ESC/ESH 2018 classification in all groups (Table 3). A statistically significant difference was found between the groups when pre-anesthesia measurements were classified (χ² = 26.72, P = 0.031). For the majority of patients in the RAASI group (31.9%), the pre-anesthesia blood pressure measurements were grade 3. From another point of view, the majority of the 80 patients (47.5%) with pre-anesthesia measurement grade 3 belong to group RAASI. Operations were deferred in patients with grade 3 pre-anesthesia blood pressure.

**DISCUSSION**

Hypertension can cause perioperative hemodynamic changes, which may be associated with perioperative morbidity and mortality [1]. As the number of patients undergoing surgery increases, management of perioperative hypertension has become a leading topic in clinical practice. We evaluated the effects of antihypertensive drugs on pre-anesthesia induction blood pressure measurements. As a general result of the study, it was observed that pre-anesthesia blood pressures of the patients were not at normotensive levels, and patients using RAASI had higher pre-anesthesia SBP and MBP than patients using other antihypertensive drugs. Patients with BB were also observed to have the lowest pre-anesthesia SBP, DBP, and MBP values. Antihypertensive drugs were chosen according to the patients’ comorbidities. However, it also differs between guidelines. In this study, we evaluated antihypertensive drug therapies that were previously managed by cardiologists. Thirty-five percent of our study participants used angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) as monotherapy, while 16.8% of participants used combined drugs.

### Table 2. Demographical Data of Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group None (n = 72)</th>
<th>Group RAASI (n = 119)</th>
<th>Group BB (n = 48)</th>
<th>Group CCB (n = 27)</th>
<th>Group D (n = 12)</th>
<th>Group Co (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>48 (66.7)</td>
<td>78 (65.5)</td>
<td>38 (79.2)</td>
<td>15 (55.6)</td>
<td>12 (100)</td>
<td>41 (73.2)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>57.33 ± 13.34 (21–93)</td>
<td>64.77 ± 9.88 (37–92)</td>
<td>61.81 ± 9.76 (45–84)</td>
<td>60.85 ± 15.45 (33–85)</td>
<td>66.00 ± 5.34 (53–72)</td>
<td>67.11 ± 10.03 (40–87)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>0.28 ± 0.06 (0.16–0.57)</td>
<td>0.29 ± 0.05 (0.18–0.49)</td>
<td>0.27 ± 0.04 (0.15–0.37)</td>
<td>0.27 ± 0.04 (0.21–0.36)</td>
<td>0.31 ± 0.05 (0.24–0.40)</td>
<td>0.28 ± 0.04 (0.20–0.37)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>7 (9.7)</td>
<td>32 (26.9)</td>
<td>13 (27.1)</td>
<td>7 (25.9)</td>
<td>5 (41.7)</td>
<td>19 (33.9)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1 (1.4)</td>
<td>23 (19.3)</td>
<td>26 (54.2)</td>
<td>6 (22.2)</td>
<td>4 (33.3)</td>
<td>31 (55.4)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td></td>
<td>4 (3.4)</td>
<td>1 (2.1)</td>
<td>1 (3.7)</td>
<td>1 (8.3)</td>
<td>1 (1.8)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>8 (11.1)</td>
<td>14 (11.8)</td>
<td>5 (10.4)</td>
<td>2 (7.4)</td>
<td>4 (33.3)</td>
<td>5 (8.9)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>1 (1.4)</td>
<td>3 (2.5)</td>
<td>-</td>
<td>2 (7.4)</td>
<td>-</td>
<td>4 (7.1)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td></td>
<td>2 (1.7)</td>
<td>7 (14.6)</td>
<td>2 (7.4)</td>
<td>1 (8.3)</td>
<td>6 (10.7)</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>8 (11.1)</td>
<td>2 (1.7)</td>
<td>3 (6.3)</td>
<td>2 (7.4)</td>
<td>1 (8.3)</td>
<td>3 (5.4)</td>
</tr>
<tr>
<td>Renal disease</td>
<td></td>
<td>2 (1.7)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5 (8.9)</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean ± SD (min-max). RAASI: renin-angiotensin-aldosterone system inhibitors, BB: beta blockers, CCB: calcium channel blockers, D: diuretics, Co: combined antihypertensives, -: not available.
RAASIs are commonly used to treat hypertension. They act by inhibiting the renin-angiotensin-aldosterone system and include ACEi, ARBs, and direct renin inhibitors. ACEi is recommended as a first- or second-line therapy for the treatment of hypertension [4,6]. They are particularly important in blood pressure regulation in diabetic patients, as they prevent the development of diabetic nephropathy and are cardioprotective in patients recovering from myocardial infarction [15]. However, whether RAASI should be continued preoperatively remains controversial. Some studies suggest that RAASI may cause relative hypovolemia, which may predispose intraoperative hypotension [16,17] and worsen mortality [18,19], although others did not observe an association between the use of ACEi and intraoperative hypotension, complications, or increased 30-day mortality [15,17]. A review of Rosenman et al. [20] revealed that patients who received the immediate preoperative ACEi or ARB may be at increased risk for the development of perioperative hypotension; however, it is also claimed that there is inadequate evidence to determine whether hypotension leads to patient-important adverse outcomes. The 2018 ESC/ESH guidelines for the management of arterial hypertension suggest that “transient preoperative discontinuation of RAASI should be considered in patients with hypertension undergoing noncardiac surgery” as class IIa recommendation [4], and the 2017 ACC/AHA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults suggests that “in patients with hypertension undergoing major surgery, discontinuation of ACEi or ARBs perioperatively may be considered” as class IIb recommendation [6],
while the 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing non-cardiac surgery suggests that “continuation of RAASI is reasonable perioperatively” as class IIa recommendation [21]. The ESC/ESH recommendation is consistent with a large prospective cohort study which suggested that withholding RAASI before major non-cardiac surgery was associated with a lower risk of death and postoperative vascular events [16]. We discontinued the RAASIs preoperatively in the morning 12 h before the operation as a routine hospital protocol even though the guidelines do not suggest any discontinuation duration before surgery. Our study results showed significantly higher pre-anesthesia SBP and MBP values in patients who used RAASI chronically before surgery and discontinued preoperatively. In our study population, 47% of the 80 patients whose operation was delayed due to grade 3 pre-anesthesia blood pressure were patients who discontinued the RAASI regimen preoperatively. Although the operation was not postponed, the majority of patients with grade 2 pre-anesthesia blood pressure (30.3%) discontinued the RAASI regimen preoperatively. From another point of view, the majority (31.9%) of pre-anesthesia blood pressure measurements of patients who discontinued RAASI was grade 3.

BBs inhibit catecholamines at G protein-coupled β-adrenoceptors and reduce blood pressure. This β-1 receptor blockade in the heart causes a reduction in HR and myocardial contractility. Blockade of the juxtaglomerular apparatus causes a reduction in renin secretion and salt and water retention [22]. The discontinuation of BBs prior to an operation has been a long debate, but recently, it has been suggested as a class IIb recommendation by the 2014 ACC/AHA and the 2018 ESC/ESH guidelines that patients who are currently under chronic BB treatment should continue their medication preoperatively [4,21]. This recommendation is based on the results of several studies which suggest that abrupt discontinuation of BBs is associated with higher rates of mortality and cardiac complications [9,23]. Our study showed that patients who were under chronic treatment with BBs had the lowest pre-anesthesia SBP, DBP, and MBP values. Moreover, their pre-anesthesia blood pressure values were mostly grade 1 (33.3%). These results show that chronic BB treatment provides optimal pre-anesthesia blood pressure values. BBs are not generally used as first-line agents unless the patient needs secondary prevention following myocardial infarction [22]. In this regard, these results are valuable because patients with coronary artery disease tend to be more vulnerable to intraoperative blood pressure fluctuations caused by pre-anesthesia hypertension.

Why is an optimal pre-anesthesia blood pressure important? Preoperative hypertension can cause perioperative hemodynamic changes associated with perioperative morbidity and mortality, such as intraoperative hypotension and tachycardia [24,25]. It has been claimed that hypertensive patients may have greater cardiovascular lability and exaggerated hemodynamic stress response, particularly at the induction of anesthesia, due to increased catecholamine levels and increased sensitivity of peripheral vessels to catecholamines [26]. These blood pressure fluctuations may cause perioperative myocardial ischemia [27] and renal and cognitive impairment [28]. As a limitation of the present study, we did not analyze any intra- or postoperative data.

The above-mentioned issues predispose clinicians to avoid anesthetizing patients who are hypertensive before the induction of anesthesia. It is recommended to cancel elective surgery if SBP is 180 mmHg or higher, or if the DBP is 110 mmHg or higher [2,4]. Anesthesiologists are responsible for referring patients with elevated blood pressure to appropriate treatment during preassessment. However, in some cases, patients may be out of order, and blood pressure which was controlled during preassessment may be unexpectedly elevated before anesthesia induction and put both the patient and the anesthetist in difficulty. Besides hemodynamic problems, this unexpected hypertension may lead to the postponement of surgery and an increase in labor costs and hospital expenses.

Frequently, antihypertensive drugs are administered in the morning to reduce daytime blood pressure surges. However, the confirmed 24-h blood pressure patterns show a morning surge, which is a complex neurohormonal phenomenon that is especially related to the activation of the sympathetic nervous system upon awakening [29]. In our study group, emotional stress against the operation may be an additional factor for morning surges. Recently, several studies had a special interest in this subject because morning hours have the highest rate of major cardiovascular events [29,30].

Chronotherapy involves moving one or more antihypertensives from morning to nighttime dosing to prevent a morning surge in blood pressure. It is claimed that nighttime dosing promotes 24-h blood pressure profiles and does not cause an additional risk; therefore, it is recommended in the general population [30]. In our opinion, to reduce the additional risk of surgery-related stress and blood pressure elevations, the morning doses may be moved to nighttime dos-
es adequate time before the operation.

The limitations of the present study include the fact that we analyzed pre-anesthetic data only and did not collect intraoperative or postoperative data. In addition, there were relatively small-sized groups; however, we did not exclude them and presented all patients’ data.

In conclusion, it was found that pre-anesthesia SBP and MBP were higher in patients using RAASI than in patients using other antihypertensive drugs, and the lowest pre-anesthesia SBP, DBP, and MBP values were found in patients using BB. RAASI discontinuation 10–12 h before the operation does not provide optimal pre-anesthesia blood pressure and may not be replaced by another medicine after its discontinuation before the operation leads to an elevation in blood pressure, that is, an increase in the number of postponed surgeries. In this context, we propose that another medicine should be given as replacement after cessation of RAASI, or the antihypertensives that patients used chronically may be administered as nighttime doses in accordance with the chronotherapy principle. This issue should be re-evaluated in future studies.

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

11. Kristensen SD, Knuts J, Saraste A, Anker S, Bøtker HE, Hert SD.


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- The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.
- Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.
- All data generated or analyzed during this study are includ-
...ed in this published article [and its supplementary information files].

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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.

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4. Protection of human and animal rights

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

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

5. Registration of the clinical research

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

6. Reporting guidelines

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

7. Author and authorship

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

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

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

8. Plagiarism and duplicate publication

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

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

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

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

IV. Manuscript Preparation

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

- 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)
- GLOBAL ADVANCES in Health and Medicine for reporting of clinical cases (http://www.gahmj.com)

1. Word processors and format of manuscripts

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

2. Abbreviation of terminology

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

Ex) target controlled infusion (TCI)

After that, “TCI” can be used instead of “target controlled infusion.” Common abbreviations may be used, however, such as DNA. Abbreviations can be used if they are listed as a MeSH subject heading (https://www.ncbi.nlm.nih.gov/mesh).

3. Word spacing

1) Leave 1 space on each side when using arithmetic marks
such as +, -, ×, etc.
Ex) 24 ± 2.5
Leave no space when using hyphen between words.
Ex) intra-operative
2) When using parentheses, leave 1 space on each side in English, and leave no space in the Korean manuscript.
3) When using brackets in parentheses, apply square brackets.
Ex) ([ ])
4) Manuscripts in Korean should obey the rules of Korean spelling (www.korean.go.kr).

4. Citations

1) If a citation has 2 authors, write as “Hirota and Lambert.” If there are more than 3 authors, apply “et al.” at the end of the first author’s surname.
Ex) Kim et al. [1]
2) Citations should be applied after the last word.
Ex) It is said that hypertension can be induced [1] and the way to injure the brain [2] is...
Ex) Choi and Kim [1] reported...
3) Apply citations before a comma or period.
Ex) ...is reported [1],
4) Several or coupled superscripts can be written as [1–5] or [1,3,5].

5. Arrangement of manuscript

The manuscript should be organized in the order of title, abstract, introduction, materials and methods, results, discussion, acknowledgments, references, tables, figures, and figure legends. Figures should be uploaded as separate files. The title of each new section should begin on a new page. The conclusion should be included in the discussion section. Number pages consecutively, beginning with the first page of the manuscript. Page numbers should be placed at the middle of the bottom of the page. For survey-based clinical studies, the original survey document does not need to be included in the body of the manuscript but may be included as a supplement in an appendix.

6. Organization of manuscript

1) Clinical or experimental research
   (1) 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 of no more than 40 characters, including letters and spaces in Korean, or 10 words in English, should be provided. If this title is inappropriate, the Editorial Board may revise it.
3) Author information
   First name, middle initial, and last name of each author, with their highest academic degree(s) (M.D., Ph.D., etc.), and institutional affiliations; make sure the names of and the order of authors as they appear on the Title Page and entered in the system match exactly.
4) Previous presentation in conferences
   Title of the conference, date of presentation, and the location of the conference may be described.
5) Funding statement
   Disclosure of all financial support for the work, including departmental or institutional funding/support.
6) Conflicts of interest
   Any conflicts of interest for any or all authors within the 36 months of submission. If no competing interests, please add the following statement: “The authors declare no competing interests.” If any of these elements are not applicable to your submission, write “not applicable” after the number and topic; for example, “Prior Presentations: Not applicable.”

2) Manuscript
   ① Title and Running title (without author information)
      It should be the same as the Cover page.
   ② Abstract
      All manuscripts should contain a structured abstract that is written only in English. Authors should provide an abstract of no more than 250 words. It should contain 4 subsections: Background, Methods, Results, and Conclusions. Citation of references is not permitted in the abstract. A list of key words at least 4,
with a maximum of 10 items, should be included at
the end of the abstract. Key words should be selected
from MeSH (https://www.ncbi.nlm.nih.gov/mesh),
and these should be written in small letters with the
first letter capitalized. Separate each word with a
semicolon (;), and include a period (.) at the end of
the last word. Ex) Keywords: Carbon dioxide; Cere-
bral vessels; Oxygen; Spinal analgesia.

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

4 Materials and Methods
The materials and methods section should include
sufficient details regarding the design, subjects, and
methods of the research in order, as well as methods
used for data analysis and control of bias in the study.
Sufficient details must be provided in the methodol-
ogy section of an experimental study so that it can be
further replicated by others.
Institute and author names should be avoided.
When reporting experiments with human or animal
subjects, the authors should indicate whether they
received approval from the Institutional Review
Board for the study. When reporting experiments
with animal subjects, the authors should indicate
whether the handling of the animals was supervised
by the Institutional Board for the Care and Use of
Laboratory Animals. Demographic data should be
included in the materials and methods section if ap-
licable. As a rule, subsection titles are not recom-
wended. If several study designs were used, then
subtitles can be used without assigning numbers.
Ensure correct use of the terms sex (when reporting bi-
ological factors) and gender (identity, psychosocial or
cultural factors), and, unless inappropriate, report the
sex and/or gender of study participants, the sex of ani-
mals or cells, and describe the methods used to deter-
mine sex and gender. If the study was done involving an
exclusive population, for example in only one sex, au-
thors should justify why, except in obvious cases (e.g.,
prostate cancer). Authors should define how they deter-
mined 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

5 Results
Results should be presented in a logical sequence in
the text, tables, and figures, giving the main or most
important findings first. Do not repeat all of the data
provided in the tables or figures in the text; empha-
size or summarize only the most important observa-
tions. Results can be sectioned by subsection titles
but should not be numbered. Citation of tables and
figures should be provided as Table 1 and Fig. 1.
Type or print each table on a separate page. Figures
should be uploaded as separate tif, jpg, pdf, gif, ppt
files.

6 Statistics
Precisely describe the methods of statistical analysis
and computer programs used. Mean and standard
deviation should be described as mean ± SD, and mean and standard error should be written as mean ± SEM. Median and interquartile should be described as median (IQR, 3Q). When displaying P values, use a capital P and do not put a “.” between “P” and “value”.

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

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

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

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

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

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

G. A priori sample size calculation should be described in detail. Sample size calculation must aim at preventing false negative results pertaining to the primary, instead of secondary, endpoint. Usually, the mean difference and standard deviation (SD) are typical parameters in estimating the effect size. The power must be equal to or greater than 80 percent. In the case of multiple comparisons, an adjusted level of significance is acceptable.

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

I. Results must be written in significant figures. The measured and derived numbers should be rounded off to reflect the original degree of precision. Calculated or estimated numbers (such as mean and SD) should be expressed in no more than one significant digit beyond the measured accuracy. Therefore, the mean (SD) of cardiac indices in patients measured on a scale that is accurate to 0.1 L/min/m² should be expressed as 2.42 (0.31) L/min/m².

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

Discussion

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

Funding

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

Acknowledgments

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

References

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

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

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


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

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

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

• Description format
  A. Regular journal
  Author name. Title of article. Name of journal published year; volume: start page-final page.


  Journal article volume with supplement


  Journal article issue with supplement


B. Monographs


- If reference page is only 1 page, mark ‘p’.

- Note if it is beyond the 2nd edition.


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

C. Chapter

Any separate author of a chapter should be provided.


D. Electronic documents


E. Online journal article


F. Advance access article


Tables

• Only one table is to be drawn per page in the order cited in the text.

• The title of the table is to be in English and written
at the top of the table in the form of a phrase.

- Words in the table excluding the title should use capital letters for the first word, and the following words are to be written in small letters.
- For demographic data, gender is recorded as M/F, age as yr (if necessary, use days or months in children) without decimal point. The “±” sign within the table is to be aligned with the rows above and below.
- Footnotes are to be written in the following order: “Values are mean ± SD (or SEM) or median (1Q, 3Q)” the explanations for the groups and the abbreviations in order of appearance, and statistics. Abbreviations apart from internationally recognized abbreviations are to be explained with their full spellings at the bottom of the table. Full spellings are to be presented even for repeated abbreviations for each table in order of appearance.
- Significance marks are to conform to the Vancouver style (Uniform Requirements for Manuscripts Submitted to Biomedical Journals. JAMA 1997; 227: 927-34). In other words, these must be in the order of *, †, ‡, §, ∥, ¶, **, ††, ‡‡ and written as superscripts.

⑫ Legends for figures and photographs
- All of the figures and photographs should be described in the text separately.
- The description order is the same as in the footnotes in tables and should be in recognizable sentences.
- Define all abbreviations every time they are repeated.

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

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

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

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

2) Case Reports
A case report is almost never a suitable means to describe the efficacy of a treatment or a drug; instead, an adequately powered and well-controlled clinical trial should be performed to demonstrate such efficacy. The only context in which a case report can be used to describe efficacy is in a clinical scenario, or population, that is so unusual that a clinical trial is not feasible. Case reports of humans must state in the text that informed consent to publication was obtained from the patient or guardian. Copies of written informed consents should be kept. If necessary, the editor or reviewers may request copies of these documents. If these steps are impossible, Institutional Review Board approval should be obtained prior to submission. Rarity of a disease condition is itself not an acceptable justification for a case report.

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

(2) Abstract: All case reports should contain a structured abstract that is written only in English. Provide an abstract of no more than 150 words. It should contain 3 subsections: Background, Case, and Conclusions. A list of keywords, with a minimum of 3 and maximum of 10 items, should be included at the end of the abstract.

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

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

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

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

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

3) Reviews
Review articles synthesize previously published material into an integrated presentation of our current understanding of a topic. Review articles should describe aspects of a topic in which scientific consensus exists, as well as aspects that remain controversial and are the subject of ongoing scientific disagreement and research. Review articles should include unstructured abstracts written in English equal to or less than 250 words. The organization should be in order of abstract, introduction, text following each title, conclusion and references. Figures and tables should be provided in English. Body text should not exceed 30 A4-sized pages, and the number of figures and tables should each be less than 6. However, if necessary, the number of pages, number of figures and tables can be added in accordance with the decision of the editorial committee.

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

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

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

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

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

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

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

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

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

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