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

APM aims to improve the safety and care of patients receiving anesthesia and the quality of anesthesiologists’ clinical practice by publishing articles on anesthesia, including perioperative management, critical care, and pain medicine.

The scope of APM includes the following:

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

The journal’s regional focus is mainly Korea, but it welcomes submissions from researchers all over the world. This work was supported by the Korean Federation of Science and Technology Societies (KOFST) grant funded by the Korean government.

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2. The mean time to recovery of the vastus lateralis muscle was significantly faster with sugammadex compared with the placebo group (P < 0.001).
3. The mean time to recovery of the vastus lateralis muscle was significantly faster with sugammadex compared with the placebo group (P < 0.001).
4. The mean time to recovery of the vastus lateralis muscle was significantly faster with sugammadex compared with the placebo group (P < 0.001).

Conclusion:
Suggamex is recommended for NMB reversal in major guidelines.

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Introduction

Preprints are preliminary research reports that have not yet been peer-reviewed. They have been widely adopted to promote the timely dissemination of research across many scientific fields [1,2]. However, because preprints have not been certified by peer review, they should not be relied on to guide clinical practice or health-related behavior nor should they be reported in the news media as established information [3]. Nonetheless, the launch of preprint servers has led to the increasing use of preprints in the clinical and health science research community [4]. Although the COVID-19 pandemic highlighted the benefits of preprints, including the rapid and open communication of research findings [5-7], concerns remain that early and open public access to preliminary medical research may harm patients or public health practices, by possibly expediting a misleading finding or faulty research that has been conducted or interpreted in error [8]. In this review, the history, current status, strengths, and weaknesses of preprints as well as ongoing concerns regarding journal articles with preprints are discussed. An optimal approach to preprints is suggested for editorial board members, authors, and researchers.

Keywords: medRxiv; Peer review; Preprint; Research report.
HISTORY OF PREPRINTS

In 1961, the Information Exchange Groups was introduced by the USA’s National Institutes of Health (NIH) to facilitate the distribution of preprints in the biological sciences. Until 1966, this system attracted many researchers and produced more than 1.5 million copies of preprints, but it was then restricted because journals refused to publish articles that had been made available as a preprint \[9,10\].

In August 1991, Paul Ginsparg launched an electronic bulletin board intended to serve a few hundred colleagues working in a subfield of theoretical high-energy physics. Its range of topics later expanded to include physics, mathematics, computer science, quantitative biology, quantitative finance, statistics, electrical engineering, systems science, and economics. It began at Los Alamos National Labs, but as its popularity grew it was relaunched as the ‘arXiv’ (www.arxiv.org) server, hosted by Cornell University. arXiv is considered the first and largest preprint platform [2]. Additional preprint servers followed for different academic fields, such as BioRxiv (2013, Biology, www.biorxiv.org) and medRxiv (2019, Health Science, www.medrxiv.org). A list of preprint servers and their policies and practices across platforms can be found at www.asapbio.org/preprint-servers.

Currently available preprint platforms are divided into 1) profit (such as PeerJ Preprints, Nature Precedings and F1000Research) and non-profit (such as arXiv, BioRxiv and medRxiv), 2) general (posting nearly all preprints from a wide range of disciplines, such as Authorea, Preprints, Academia, and ResearchGate) and field-specific (such as bioRxiv, medRxiv ChemRxiv and EarthArXiv), and 3) regional (such as INA-Rxiv, Frenxiv, AfricArxiv, Arabxiv).

The introduction of the overlay journal, which does not produce its own content but selects from articles on preprint servers, contributed to the growth of preprint servers both quantitatively and qualitatively \[11\].

CURRENT STATUS OF PREPRINTS

The number of preprint submissions has increased over the years and reached a peak in 2019 (Fig. 1). The cumulative numbers of preprint submissions are 2,185,334 at arXiv, 180,133 at bioRxiv, 100,805 at Research Square, and 48,849 at medRxiv. The cumulative numbers of preprint downloads continue to increase and, in 2019, reached 2,641,473,782 at arXiv, 144,168,644 at bioRxiv, and 63,895,520 at medRxiv (Fig. 2).

The National Library of Medicine launched ‘NIH Preprint Pilot’ in June 2020 with the goal of making preprints stemming from NIH-supported research accessible via PubMed Central (PMC) and PubMed. NIH Preprint Pilot consists of two phases. Phase 1, which ran from June 2020 to December 2022, focused on improving the discoverability of preprints related to SARS-CoV-2 and COVID-19 research carried out.

Fig. 1. Number of preprint submissions categorized by individual preprint platforms.
2.5e+6
2.0e+6
1.5e+6
1.0e+6
5.0e+5
0

Cumulative number of submissions
Year

Fig. 2. Cumulative number of preprint submissions categorized by individual preprint platforms.

with NIH support. Phase 2, which began in January 2023, covers all preprints, whether stemming from research with direct NIH support or involving an NIH-affiliated author, posted to an eligible preprint server (bioRxiv, medRxiv, arXiv, and Research Square) on or after January 1, 2023. Further information on NIH Preprint Pilot is available at NIH Preprint Pilot - PMC.

As of January 31, 2023, 49,792 preprints had been released on medRxiv. This is a significant increase compared to the server’s first complete month, July 2019, in which only 129 preprints were released, and ~40 times more preprints than available in January 2020 (1,289 preprints). The number of preprint submissions to medRxiv reached a high point in 2019, followed by a peak in the number of downloads in 2020 (Fig. 3). These increases can be attributed largely to research focused on the COVID-19 pandemic.

The scientific response to the COVID-19 pandemic coincided with and promoted an unprecedented approach to research communication, one based on rapid, open-platform reporting of research results and considerable developments within preprint research literature. Both are considered essential to guide timely, evidence-based public health responses during infectious disease outbreaks and other public health emergencies [6,12].

STRENGTHS AND WEAKNESSES OF PREPRINTS

Preprint posting of non-peer-reviewed work enables rapid access to information by circumventing possible drawn-out journal submission or publication procedures. Preprint platforms have become increasingly prevalent and have also bridged the gap between academic and non-academic audiences by providing public access to research on a wide range of topics [13]. However preprints are not peer-reviewed, which has both advantages and disadvantages. In several notable cases, this has allowed the dissemination of unsupported, faulty conclusions across several media channels. In these cases, preprints have received harsh criticism and several have since been rescinded.

CURRENT CONCERNS OF PREPRINTS

The rapid propagation of preprints has raised several issues. These are discussed in the following sections, from the positions of editorial board members, peer reviewers, and authors.

Does a journal allow a manuscript with preprints to be submitted for formal publication?

Due to the exponential expansion of preprints throughout
the COVID-19 pandemic, submitting a manuscript with a preprint has become commonplace [5], which has forced journals to establish policies for those submissions. Due to limitations in its capacity for editorial service and/or a preference for avoiding chaotic preliminary situations, a journal may choose not to allow the submission of a manuscript with a preprint. Alternatively, a journal may accept the submission of manuscript with a preprint by requiring the author to report the existence of the preprint and its DOI. The preprint policies of publishing companies vary and include “can share,” “should allow,” and “encourage.”

In terms of the number of preprint DOIs, an editorial board may choose to accept preprints with only one DOI, in the case that a preprint has been posted to multiple preprint platforms. Tracking a preprint with two DOIs doubles the load of editorial services and may lead to substantial confounding situations.

**Is a preprint citable as a reference in the manuscript?**

Among the preprints in medRxiv, 77.0% (1,077 out of 1,399) were published in peer-reviewed journals within a median of 6 months after posting [14]. In a journal article that assessed how COVID-19 evidence presented in preprints changed after review, point estimate values were found to have changed by an average of 6%, with a strong correlation (0.99) between estimate values before and after review [15]. Although a substantial portion of preprints were later published as peer-reviewed journal articles, and the robustness of the evidence reported in preprints was found to be high, a preprint is preferably cited as a reference after the corresponding peer-reviewed journal article has been published, because the peer review process reduces uncertainty and substantiates the evidence reported in the preprint. It is also crucial that preprint authors disclose the preliminary nature of the reported findings to the reader and refrain from overstating the outcomes of any study that has not undergone peer review. If a journal accepts preprint citations in journal submissions, the reference format should make clear that a preprint has been cited and the non-peer reviewed status of the source [16].

**Is a double-blind review process necessary in the review of manuscripts with preprints?**

In a double-blind review process, neither authors nor reviewers are aware of one another’s identity. This system is used to minimize review biases, whether toward authors in the reviewer’s own co-author networks or those against competing corresponding authors. For these reasons, double-blind review is a crucial component of the peer review process for publications and disciplines.

However, because many decisions are made by editors, double-blind peer review cannot completely eliminate bias. In addition, many reviewers who seek to identify the authors
are often successful. Preprints in particular may make it more challenging to maintain blinding because a manuscript with a preprint discloses the identities of the authors to peer reviewers. Committee on Publication Ethics (COPE) prohibits posting pseudonymous preprints, but there are other information sources that can jeopardize blindness. For instance, randomized clinical trials registered at clinical trial registries can be accessed by peer reviewers and will reveal the authors’ names. Likewise, seminar announcements, conference programs or papers, or social media posts are all searchable online [17]. These issues are not specific to preprints, but they do further complicate their management.

When a manuscript has a preprint, reviewers are also given the opportunity to comment and to provide input on it. Remarks about the study’s merits and faults as well as any unrecognized research controversies may assist the reviewer in his or her task but they may also harm the review process. As a result, it is crucial that reviewers carefully and critically consider the obtained information and strive to avoid pre-judging the work described in the manuscript.

**How to handle changes in the evidence reported between the original preprint and the peer reviewed manuscript?**

A peer reviewed, published journal article should be considered a cornerstone of evidence, even if controversies remain. Further discussion and review may lead to additional evidence and a subsequent peer-reviewed article. Therefore, after the research in the preprint is formally published in a journal, the original preprint should be hyperlinked to the published article to reflect the change in content.

In addition, as the publisher has the copyright on a journal article published after peer review, it is better to cite a peer-reviewed journal article than a preprint.

**Is it acceptable that the authors of a manuscript are different from those of a preprint?**

Authorship should be limited to researchers with significant intellectual, social, and financial contributions. It should also imply responsibility and accountability for published work.

Many preprint platforms do not yet define the authorship criteria for preprints. However, some preprint platforms, including Preprint.org, define authorship in accordance with the International Committee of Medical Journal Editors (ICMJE) recommendation. Several preprint platforms also address reporting and ethical considerations, such as clinical trial registration, competing interest statement, patient/participant permission, and ethics committee approvals.

If the authors of a submitted article differ from those of the preprint, the authors must justify the change in authorship and demonstrate that it complies with ICMJE recommendations.

**Is the submission of a manuscript with unintentional ‘scoop’ issues allowed?**

A ‘scoop’ occurs when researchers publish their findings before a competing team working on the same issue has published theirs, or when an idea or set of results are referred to in a publication without proper attribution.

In a field that is competitive and moves quickly, a research team (team A) may choose to publish its results in preprints rather than in reputable publications because being first is more important to the team than being thorough. If another research team (team B) later submits equivalent data to a journal, what should the journal’s acceptance policy be? The implementation of most research projects is time-consuming. If the work of team B is released shortly after that of team A, it is impossible for team B to have begun and completed a completely new research project within the short time span. In such cases, team A may have unintentionally scooped team B and manuscript submission by the latter may be allowed.

Being scooped is one of the worst things that can happen to a researcher. If he or she intended to submit work to a journal after posting a preprint but the results and conclusions are almost the same as those already submitted, the manuscript may be rejected by the journal editor or no longer qualify for publication in a better journal. Journals should therefore always consider potential scoop issues during the publication review process and look for and assess papers published on related topics.

**How to enforce the review process for a submitted manuscript with a preprint?**

Enormous interest among scholars following the posting of a preprint on a platform could result in information overload and disorderly circumstances. In addition to an experienced peer review of a submitted manuscript, its preprint history needs to be tracked and summarized by an addition-
al, independent editor focused on the posting procedure and format rather than on the academic considerations. The findings should then be shared with peer reviewers and the journal editor.

Journals should also decide whether to consider comments posted on preprint platforms before and/or during the peer review process; if so, standard formats and mechanisms should be established as to how these will be considered.

**INFLUENCE OF SOCIAL MEDIA AND PUBLICATION ETHICS**

In 2020, a report on the use of hydroxychloroquine to treat COVID-19 was posted on medRxiv and simultaneously accepted for publication in an open-access journal. On the same day, the president of the USA publicly stated his belief in this treatment. Prescriptions of hydroxychloroquine surged 2000% within 2 months, and US stockpiles of hydroxychloroquine reached 63 million doses within 4 months. This preprint was discussed 1027 times on Twitter and posted 75 times on an internet portal blog. Academic societies debated the effectiveness of hydroxychloroquine, and the therapeutic efficacy was eventually shown to be extremely poor. Nonetheless, the article was cited 3024 times according to the Web of Science, and the publishing journal’s impact factor increased from 5.283 in 2020 to 15.250 in 2021, which was largely attributable to the article [18].

The resulting waste of medical resources was not due solely to the released preprint, as the improper media coverage of a scientific finding without adequate peer review also played a major role. This case also demonstrates that editors and authors should not use journal articles and preprints for ethically questionable purposes.

In conclusion, the policy regarding preprints is still evolving. Journals may allow the submission of a manuscript that was posted on a preprint platform. Preprints can be cited as references after peer-reviewed journal articles are published but they should only be cited alone in exceptional circumstances, without overstating the work reported in the preprint. Special considerations for dealing with scoops, authorship, publication ethics, and social influence should be provided.

**FUNDING**

None.

**CONFLICTS OF INTEREST**

Hyun Kang is the current Editor-in-Chief of *Anesthesia and Pain Medicine*, and Hyoung-Chul Oh is the current Editor-in-Chief of *Korean Journal of Internal Medicine*. However, they were not involved in the peer reviewer selection, evaluation, or decision process of this article. This manuscript is published simultaneously in the *Korean Journal of Internal Medicine* and *Anesthesia and Pain Medicine*.

**DATA AVAILABILITY STATEMENT**

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

**AUTHOR CONTRIBUTIONS**


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**REFERENCES**

7. Watson C. Rise of the preprint: how rapid data sharing during


INTRODUCTION

Traumatic brain injury (TBI) is defined as an alteration in brain function or any other evidence of brain pathology as a result of an external force. Alteration in brain function here implies loss of consciousness or a decreased level of consciousness, loss of memory, neurologic deficits, or alteration in mental state at the time of the injury [1]. TBI has traditionally been classified using clinical severity scores, and the Glasgow Coma Scale [2] is a universally-accepted tool for TBI classification; however, severity will not be described separately in this article. Only the management of anesthesia in patients with TBI who undergo surgery other than neurosurgery is discussed here. The most common situation is when multiple-trauma patients require surgical treatment for body parts other than the head; therefore, the main focus of this article is the intraoperative management for trauma surgery. Considerations may differ depending on whether the non-neurosurgery is performed before or after primary treatment for brain injury. In addition, neurosurgical consultation may be necessary for intracranial pressure (ICP) monitoring and management.

When a patient with TBI needs to undergo non-neurosurgery, proper attention should be given to the prevention of secondary brain injury while performing the surgery and administering anesthesia. Understanding the systemic physiological changes caused by trauma and preparing for the resulting cerebral hemodynamic changes are the main starting points for safe anesthesia management, with the ultimate goal being an improved outcome wherein the patient’s brain function is restored and preserved. Clinical choices and decisions based on current clinical guidelines and evidence will be reviewed in this article.

PRIMARY AND SECONDARY BRAIN INJURY

Primary brain injury refers to damage that occurs directly...
at the time of the initial trauma and includes the mechanical impact to the head and resulting epidural/subdural/intracranial hematomas, skull fractures, and diffuse axonal injuries [3]. Secondary brain injury is a consequence of these physiological insults and develops over time after the onset of the initial injury, causing further damage to the cerebral physiology and worsening outcomes in TBI patients [4]. The major initiating factors of secondary injury are hypotension and hypoxemia; other factors include hyperthermia, hyperglycemia/ hyperglycemia, and hyponatremia/hyponatraemia [4,5]. Prevention of secondary brain injury should be included among the goals of anesthesia for TBI patients undergoing non-neurosurgery [4].

**GUIDELINES**

The Brain Trauma Foundation has published evidence-based clinical guidelines describing the management of severe TBI (Guidelines for the Management of Severe Traumatic Brain Injury, 4th edition, 2016) [6]. The contents related to anesthesia management are summarized in Table 1. Details regarding the topics listed in the table are described, as and when required, in the following sections.

**INTRAOPERATIVE MANAGEMENT**

Systemic blood pressure and ICP management: threshold

In TBI, the increased intracranial volume caused by bleeding or tissue edema is initially compensated for by a decrease in cerebrospinal fluid (CSF) volume. However, there is a limit to this compensation, with further increases in space-occupying lesions increasing the ICP excessively, which restricts blood flow to the skull, resulting in tissue ischemia [7]. Elevated ICP is also transmitted to the brain parenchyma and can lead to uncal herniation [7].

Cerebral perfusion pressure (CPP) = Mean arterial pressure (MAP) – ICP

In order to maintain adequate CPP, monitoring and management of both systemic blood pressure and ICP is required. Both a decrease in MAP or an elevation in ICP will deleteriously alter the effective perfusion pressure.

Management of TBI includes maintaining adequate cerebral blood flow and oxygenation to avoid secondary brain injury. Previously, this therapy was directed at managing ICP, but there has recently been a shift towards strategies aimed at maintaining adequate CPP. Maintaining systolic blood pressure at ≥ 100 mmHg for patients 50–69 years old and at ≥ 110 mm Hg or above for patients 15–49 or over 70 years old may be considered to decrease mortality and improve outcomes (level III) [6]. ICP monitoring remains a level IIB recommendation in the latest Brain Trauma Foundation guidelines [6]. Using information obtained by ICP monitoring for the management of patients with severe TBI is recommended to reduce in-hospital and 2-week post-injury mortality [8].

According to The Brain Trauma Foundation, ICP > 22 mmHg is associated with increased mortality (level IIB). There are no Class I study data that indicate an optimal CPP threshold or any specific optimal CPP in patients with TBI. It has been found that maintaining the CPP below 50 mmHg produces signs of ischemia and raising it above 60 mmHg avoids cerebral oxygen desaturation in the injured brain [9,10]; that is, it is suggested that the critical threshold for CPP lies between 50 and 60 mmHg and that CPP below 50 mmHg should be avoided. One study that proposed a critical CPP threshold of 60 mmHg suggested that the treatment goal should be to maintain the CPP at 70 mmHg to remain above the threshold [11]. Current guidelines recommend maintaining CPP at 60–70 mmHg and acknowledge that optimal CPP may vary depending on cerebral blood flow auto-regulation [6].

**How to estimate ICP**

Both invasive and non-invasive methods can be used to evaluate ICP [12,13]. Invasive methods generally involve the use of either external ventricular drains (EVDs) or intraparenchymal monitors. The EVD method serves the dual purposes of CSF diversion and continuous ICP measurement and is considered the gold standard [12]. Non-invasive methods for monitoring ICP include pupillometry, optic nerve sheath diameter measurement, and transcranial Doppler; however, these have various limitations with regard to intraoperative use. Although ICP monitoring in patients with TBI is a level IIB recommendation according to the Brain Trauma Foundation guidelines [6], ICP monitoring during extracranial surgery requires the patient to be equipped with a device, such as an EVD, that can be connected to pressure monitors used in the operating room. If there is no attached device, cooperation with a neurosurgeon is required, which

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Table 1. Summary of the Recommendations Related to Anesthetic Management from the Brain Trauma Foundation Guidelines for the Management of Severe TBI, 4th Edition

<table>
<thead>
<tr>
<th>Prophylactic hypothermia</th>
<th>Early (within 2.5 h) or short-term (48 h post-injury) prophylactic hypothermia is not recommended to improve outcomes in patients with diffuse injury.</th>
<th>Level IIB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperosmolar therapy</td>
<td>Insufficient evidence.</td>
<td>Level III</td>
</tr>
<tr>
<td>CSF drainage</td>
<td>An EVD system centered at the midbrain with continuous drainage of CSF may be considered to lower ICP burden more effectively than intermittent drainage. Use of CSF drainage to lower ICP in patients with an initial Glasgow Coma Scale score &lt; 6 during the first 12 h after injury may be considered.</td>
<td>Level III</td>
</tr>
<tr>
<td>Ventilation therapies</td>
<td>Prolonged prophylactic hyperventilation with PaCO₂ of 25 mmHg or less is not recommended.</td>
<td>Level IIB</td>
</tr>
<tr>
<td>Anesthetics, analgesics, and sedatives</td>
<td>Administration of barbiturates to induce burst suppression measured by EEG as prophylaxis against the development of intracranial hypertension is not recommended. High-dose barbiturate administration is recommended to control elevated ICP refractory to maximum standard medical and surgical treatment. Hemodynamic stability is essential before and during barbiturate therapy. Although propofol is recommended for the control of ICP, it is not recommended for improvement in mortality or 6-month outcomes. Caution is required, as high-dose propofol administration can result in significant morbidity.</td>
<td>Level IIB</td>
</tr>
<tr>
<td>Steroids</td>
<td>The use of steroids is not recommended for improving outcomes or reducing ICP. In patients with severe TBI, high-dose methylprednisolone is associated with increased mortality and is contraindicated.</td>
<td>Level I</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>Early tracheostomy is recommended to reduce mechanical ventilation days when the overall benefit is assessed to outweigh the risk of complications associated with such a procedure. However, there is no evidence that early tracheostomy reduces mortality or the rate of nosocomial pneumonia.</td>
<td>Level IIA</td>
</tr>
<tr>
<td>ICP monitoring</td>
<td>Management of severe TBI patients using information from ICP monitoring is recommended to reduce in-hospital and 2-week post-injury mortality.</td>
<td>Level IIB</td>
</tr>
<tr>
<td>CPP monitoring</td>
<td>Management of severe TBI patients using guidelines-based recommendations for CPP monitoring is recommended to reduce 2-week mortality.</td>
<td>Level IIB</td>
</tr>
<tr>
<td>Advanced cerebral Monitoring</td>
<td>Jugular bulb monitoring of arteriovenous oxygen content difference may be considered to reduce mortality and improve outcomes at 3 and 6 months post-injury.</td>
<td>Level III</td>
</tr>
<tr>
<td>Blood pressure thresholds</td>
<td>Maintaining systolic blood pressure at ≥ 100 mmHg for patients 50 to 69 years old and at ≥ 110 mmHg for patients 15 to 49 or over 70 years old may be considered to reduce mortality and improve outcomes.</td>
<td>Level III</td>
</tr>
<tr>
<td>ICP thresholds</td>
<td>Treatment for ICP above 22 mmHg is recommended, because values above this level are associated with increased mortality.</td>
<td>Level II B</td>
</tr>
<tr>
<td>CPP thresholds</td>
<td>The recommended target CPP value for survival and favorable outcomes is between 60 and 70 mmHg. Whether the minimum optimal CPP threshold is 60 or 70 mmHg is unclear and may depend upon the patient’s autoregulatory status. Avoiding aggressive attempts to maintain CPP above 70 mm/Hg by using fluids and vasopressors may be considered because of the risk of adult respiratory failure.</td>
<td>Level IIB</td>
</tr>
<tr>
<td>Advanced cerebral monitoring thresholds</td>
<td>Jugular venous saturation &lt; 50% may be a threshold to avoid in order to reduce mortality and improve outcomes.</td>
<td>Level III</td>
</tr>
</tbody>
</table>


will depend on the clinical environment at each institution.

Methods to maintain CPP: reducing ICP

The fastest way to decrease ICP is to allow CSF drainage, if possible. Another simple alternative to promote cerebral venous drainage is head-of-bed elevation to 30° (the reverse Trendelenburg position) while maintaining the patient’s neck in a neutral position. Hyperosmolar medications can lower ICP by allowing osmotic mobilization of water across the intact blood-brain barrier (BBB) into the intravascular space, thus reducing cerebral water content; commonly used agents include mannitol and hypertonic saline. If the patient is stable, 0.25–1 gm/kg of mannitol can be carefully administered slowly over 15 min to avoid intravascular volume depletion and hypotension due to urinary losses. Currently, there is not sufficient data to reach a definitive conclusion—although hypertonic saline showed a trend towards lower mortality and a more beneficial effect on CPP compared to mannitol, there were no statistically significant
differences in mortality and neurological outcomes between hypertonic saline and mannitol administration [14].

Although the ideal serum sodium concentration is not well established, close monitoring of blood sodium levels is imperative to prevent hyponatremia, as rapid changes in serum sodium levels may be a causative factor for central pontine myelinolysis. A serum sodium concentration greater than 155 mmol/L has been suggested to be an independent predictor of acute kidney injury [15]. It should also be considered that the effects of administering a hyperosmolar agent will be altered in case of BBB rupture, which is common in patients with TBI [7].

**Methods to maintain CPP: increasing systemic blood pressure**

Although decreasing ICP is the first-line therapy, increasing MAP to maintain CPP should also be considered. Patients with TBI who need to undergo non-neurosurgery may be in an acute state, in which systemic hemodynamics are unstable due to trauma, or a subacute state, in which patients are recovering from the trauma. Accordingly, blood pressure must be appropriately managed to maintain CPP even before the induction of anesthesia, and special attention is required to avoid exacerbating hypotension due to anesthetics or bleeding during surgery. If there is a modifiable cause of hypotension, its management should be prioritized, and vasopressor administration must always be considered. Selecting which vasopressor to use is less straightforward. A retrospective analysis showed that phenylephrine was the preferred vasopressor, with a greater increase in MAP and CPP after the start of infusion compared to norepinephrine or dopamine [16]. At equal MAP, using ephedrine resulted in better brain microcirculation and oxygen delivery than with the use of phenylephrine [17]. However, clear clinical evidence regarding the different effects of vasopressors in conditions with BBB disruption is still lacking and needs further investigation [18]. Given the ample evidence that autoregulation of cerebral blood flow in response to changes in CPP is impaired in both severe and mild TBI [19-21], careful attention to blood pressure management is necessary, because low blood pressure can be directly linked to reduced cerebral blood flow.

**Airway management**

The incidence of cervical spine injury in trauma patients is reported to range from 3.5 to 6.2% [22,23]. Notably, cervical spine injury must always be suspected in patients with TBI, and caution should be exercised during endotracheal intubation and while repositioning patients. Video-guided laryngoscope with cervical immobilization was reported to reduce the upper cervical spine motion than Macintosh laryngoscope [24,25] and facilitated a more rapid tracheal intubation compared with the flexible bronchoscope [26]. Awake tracheal intubation using a flexible bronchoscope can minimize cervical spine movement [27], but requires sufficient procedural experience and may be difficult to perform depending on the level of consciousness of patients with brain trauma. In anesthetized patients without cervical immobilization, tracheal intubation using a video-guided laryngoscope resulted in greater cervical spine movement than a flexible bronchoscope, and jaw thrust during flexible bronchoscopy also causes movement of the cervical spine [28]. Therefore, an awake bronchoscopic approach is expected to be more effective for experienced clinicians when the situation, including the patient’s condition, allows, whereas using a flexible bronchoscope, lightwand, or video-guided laryngoscope with cervical immobilization may be a better option for inexperienced clinicians. Nasotracheal intubation is better to be avoided in case of patients with skull base fractures; in such cases, there is a risk that the tube may pass through the cribiform plate and enter the frontal brain region as it advances [29].

Tracheostomy is commonly performed on patients with TBI in the intensive care unit—in approximately 32% of cases—and is most frequently performed after the first week in the intensive care unit [30]. A recent systematic meta-analysis reported that early tracheostomy in patients with severe TBI contributes to reducing mechanical ventilation duration, intensive care unit and hospital stay duration, as well as the incidence of ventilator-associated pneumonia [31]. The Brain Trauma Foundation guidelines also recommend early tracheostomy when the overall benefits appear to outweigh the risk of complications [6].

**Choice of induction agents for anesthesia**

 Intravenous anesthetics, which are mainly used for the induction of general anesthesia, have various effects on cerebral blood flow and the cerebral metabolic rate of oxygen (CMRO₂). Propofol, thiopental, midazolam, and etomidate reduce CMRO₂, resulting in decreased cerebral blood flow and ICP. However, thiopental and propofol can cause hypo-
tension and reduce CPP; therefore, caution must be exercised with regard to dose titration. Etomidate has a limited effect on MAP and is advantageous for managing CPP. Unfortunately, a single dose of etomidate is sufficient to cause adrenal insufficiency, and there are concerns that its use may be associated with mortality in patients with sepsis [32].

Even though a recent meta-analysis supports its use [33], the evidence is insufficient to guarantee the safety of etomidate use under septic conditions [34]. Ketamine has historically not been indicated for patients with brain trauma, based on the belief that it has detrimental effects on ICP. However, recent clinical data support the neuroprotective effects of ketamine via reducing glutamate levels and inhibiting cortical spreading depolarization [35,36]. A systematic review concluded that there was no evidence of harm due to ketamine use in patients with acute brain injury [37]. When inducing anesthesia in a patient with TBI, etomidate can be considered preferentially in patients with unstable hemodynamics, whereas ketamine can be an alternative option if septic shock is the cause of unstable hemodynamics.

**Anesthetics for maintenance**

There is no evidence to indicate that TBI outcomes can be improved based on the type of anesthetic agent used. Maintenance of anesthesia may be accomplished using inhaled or intravenous anesthetics, with careful consideration of the hemodynamic management goals. Total intravenous anesthesia using propofol and opioids is advantageous for cerebral hemodynamic management and neurophysiological monitoring and is frequently used in neurosurgery. As a highly selective alpha-2-adrenergic agonist, dexmedetomidine, which is expected to reduce ICP by reducing cerebral blood flow, has been reported to reduce anesthetic and opioid requirement and postoperative nausea and vomiting when used as an adjunct to general anesthetics [38], but evidence regarding its optimal dose as an adjuvant and its comparative effects versus other anesthetics is lacking [39]. Low concentrations of isoflurane and sevoflurane suppress brain metabolism and constrict cerebral blood vessels [40]. At higher concentrations, the direct vasodilatory effects of volatile anesthetics dominate, increasing both cerebral blood flow and ICP. Nitrous oxide is another cerebral vasodilator that increases cerebral blood flow and ICP; therefore, it should ideally be avoided [41]. When a volatile anesthetic is selected for general anesthesia, a minimum alveolar concentration of < 1 seems to be appropriate for patients with TBI [40].

**Oxygenation and ventilation**

Hypoxemia (generally defined as PaO\(_2\) < 60 mmHg) is a major factor in the development of secondary brain injury and should be avoided [4,42]. Despite the evidence being insufficient to conclude whether it affects clinical outcomes, hyperoxia after TBI has been suggested to be associated with higher mortality [43]. Therefore, a balanced approach that avoids the higher and lower extremes is suggested for oxygenation management.

PaCO\(_2\) is a potent mediator of cerebrovascular reactivity. Hypercapnia causes cerebral vasodilation via CSF acidosis; therefore, even a small increase in PaCO\(_2\) may have deleterious effects on ICP in TBI patients with low intracranial compliance [44,45]. Hypocapnia causes cerebral vasoconstriction via an increase in CSF pH, and sustained reduction in PaCO\(_2\) can lead to cerebral ischemia [44]. The Brain Trauma Foundation recommends avoiding hypocapnia [6] and hyperventilation in patients at risk of herniation, for short-term control of ICP, should be cautious. According to a recent meta-analysis, approximately 20% of TBI patients have acute respiratory distress syndrome (ARDS), which leads to worse neurological outcomes and higher mortality [46]; this indicates the need to use lung-protective ventilation during general anesthesia, especially in TBI patients with multiple-trauma, although concerns regarding resulting hypercapnia remain. Given the risks and benefits of lung-protective ventilation, the consensus when applying mechanical ventilation to patients with brain injury strongly recommends lung-protective ventilation in the presence of ARDS and no elevated ICP, and weakly recommends lung-protective ventilation in the absence of ARDS or elevated ICP [47].

Positive end-expiratory pressure (PEEP) can promote improved oxygenation and reduced intrapulmonary shunting; however, increased PEEP can lead to hypotension and alveolar overdistension with increased dead space, resulting in a higher PaCO\(_2\) [48]. Furthermore, the increased intrathoracic pressure following elevated PEEP may reduce the pressure gradient of cerebral venous outflow and lead to an increase in ICP [49]. Therefore, as a practical strategy for safe PEEP titration in patients with ARDS and elevated ICP, it was suggested that the level of PEEP should be adjusted by monitoring the response of blood pressure and ICP such that increasing the PEEP does not increase ICP [50].
Coagulation monitoring

At the time of admission to the emergency department, coagulopathy is present in up to 25–35% of trauma patients [51]. During the initial hours of trauma-induced coagulopathy development, hypocoagulability is typically present, resulting in bleeding; later, coagulopathy is characterized by a hypercoagulable state associated with venous thromboembolism and multiple organ failure [52]. Coagulopathy is an integral component of a vicious cycle when combined with acidosis and hypothermia [53].

Ongoing intracranial bleeding can lead to increased ICP, brain herniation, and death. Tranexamic acid reduces bleeding by inhibiting the enzymatic breakdown of fibrinogen, and fibrin blood clots [54]. The role of tranexamic acid in the management of TBI remains unclear—a recent randomized controlled study showed that tranexamic acid administration within 3 h of injury reduced all-cause 24-h mortality in cases of mild to moderate injury, but had no effect on 28-day all-cause mortality [55], while a recent meta-analysis showing that tranexamic acid has no effect on mortality or neurological recovery, although its use probably does not increase the risk of adverse events [56].

Current approaches to trauma resuscitation focus on controlling bleeding and managing trauma-induced coagulopathy through the timely administration of hemostatic therapy [57]. Conventional coagulation tests include platelet counting and fibrinogen level and PT and aPTT measurement; however, they are relatively slow and do not provide a measure of platelet function or fibrinolysis [58,59]. Due to these shortcomings, anesthesiologists and trauma critical-care surgeons often prefer viscoelastic hemostatic assay-guided blood component therapy for evaluating bleeding patients in whom coagulopathy is common [58]. The two most commonly used viscoelastic hemostatic assays are thromboelastography and rotational thromboelastometry. Viscoelastic hemostatic assays provide clinicians with real-time data and a complete view of the coagulation process, from clot initiation and formation to clot stability and fibrinolysis measurements [57]. Although recent studies and reviews have described no differences in clinical outcomes between resuscitation guided by viscoelastic hemostatic assays and those guided by conventional coagulation tests [59,60], clinicians can use both methods to monitor hemostasis across heterogeneous groups of patients.

Glycemic control

Trauma triggers an increase in stress hormone and cytokine levels, resulting in enhanced glucose production, reduced insulin production, and insulin resistance in peripheral tissues [61]. In the context of acute illness or injury, this has been termed stress-induced hyperglycemia and is defined as a transient plasma glucose level > 200 mg/dl in patients who are normally euglycemic [62]. There is no consensus on the best approach for glycemic control in patients with TBI. Studies on the association between stress-induced hyperglycemia and patient outcomes have consistently reported higher morbidity and mortality rates [63,64]. However, it remains unclear whether stress-induced hyperglycemia has a direct causative effect on worsening outcomes or is simply a marker of more severe disease [62]. The prospective, multicenter Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation study reported a higher 90-day mortality with strict glucose control than with standard care, without any effect on organ failure or length of stay, suggesting that the target of glycemic control can be abandoned [65]. In a study that evaluated outcomes before and after strict glucose control therapy with a target glucose level of < 140 mg/dl in critically ill trauma patients, mortality, length of hospital stay and intensive care unit stay, and number of ventilator days did not differ between comparison periods [66]. These trial results do not allow for conclusive conclusions to be drawn regarding the exact glucose level that should be maintained. Tight glycemic control to maintain blood glucose levels below 110 mg/dl is likely not required and may even be detrimental to patient outcomes [62], including causing hypoglycemia [67]. A moderate level of glycemic control aimed at stabilizing glucose levels while reducing hyperglycemic and hypoglycemic events appears to be safe [68].

Temperature management

A systematic review published in 2003 showed that clinically induced hypothermia could reduce the risks of mortality and poor neurological outcomes in adults with TBI [69]. It has been hypothesized that hypothermia has a neuroprotective effect in TBI by disrupting post-injury biochemical and inflammatory cascades [70]. However, a multicenter randomized trial demonstrated that early prophylactic hypothermia did not improve neurological outcomes at 6 months compared to normothermia in patients with severe
TBI [71]. Similarly, the results of another recent meta-analysis do not support the use of early prophylactic hypothermia (within 6 h after injury) as a neuroprotective strategy in adult patients with TBI, although they indicate that hypothermia could effectively reduce refractory high ICP [72]. Meanwhile, the incidence of central or neurogenic fever is considerably high in patients with severe TBI, especially in those with diffuse axonal or frontal lobe injury [73]; fever due to infection is also common in patients with severe trauma [74]. The detrimental effects of fever on the neurological recovery of patients with acute brain injury have been increasingly recognized [75-77]. Evidence supports the maintenance of normothermia in patients with TBI [78], and the Brain Trauma Foundation guidelines do not recommend prophylactic hypothermia [6]. Additionally, core body temperature is not a reliable indicator of brain temperature [79], and direct measurement remains the best way to monitor brain temperature in patients with brain injury, although brain temperature monitoring is currently not routinely applicable.

**TIMING OF SURGERY**

There is no evidence to specify the exact and safe time following TBI for elective surgery. Some studies recommend elective non-neurosurgery 6 months after recovery from TBI [80], based on the fact that patient symptoms generally do not improve or worsen 6 months after severe TBI [81]. However, in a meta-analysis comparing the effects of early and late fracture fixation on the prognosis of patients with limb fractures and concomitant TBI, late fixation (performed > 14 days after trauma) was associated with nonunion or malunion, and early fixation (within 24 h) did not affect the incidence of mortality, pneumonia, ARDS, or neurologic adverse events [82]. A retrospective cohort study reported that early orthopedic and facial fracture fixation (≤ 24 h after injury) under general anesthesia was not associated with worse neuropsychological or functional outcome than late surgery in multisystem trauma patients with TBI [83]. Currently, there are no contraindications to anesthesia in TBI, and once the decision to proceed with surgery has been made, steps should be taken to reduce the risks associated with surgery based on an understanding of the pathophysiology of TBI and the interactions between surgery and application of anesthesia [84].

**FUTURE RESEARCH AND CHALLENGES**

Due to the clinical characteristics of trauma patients, it is difficult to conduct randomized controlled studies on trauma cases. In TBI, the most important aspect is to recover the patient’s cognitive function. To improve this outcome, it is necessary to pursue the best medical practices by accumulating and analyzing a large amount of clinical evidence. Further research is expected to focus on the recovery of patient neurological function and improving their quality of life.

**CONCLUSION**

The overall strategy for anesthesia management in non-neurosurgery for patients with TBI is similar to that in neurosurgery for TBI. However, especially when ICP is elevated following trauma and decompressive craniectomy is not performed, there is a risk of secondary brain injury during non-neurosurgery, because the brain still has impaired autoregulation. Thus, related indicators, including blood pressure, oxygen saturation, ICP, temperature, and coagulation status, should be properly monitored and controlled to prevent secondary brain injury while administering anesthesia for non-neurosurgery.

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**CONFLICTS OF INTEREST**

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

**DATA AVAILABILITY STATEMENT**

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

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INTRODUCTION

Sugammadex is a chemically modified γ-cyclodextrin that is used as a selective reversal agent for steroidal neuromuscular blockade. The use of sugammadex has greatly increased globally; however, little is known about its potential adverse effects in pregnant and lactating women or those using hormonal contraceptives. There are three important theoretical assumptions. Firstly, pregnancy-related physiological changes involve most organs and affect the pharmacokinetic profiles of medications. Considering the physiological changes in pregnant women and the pharmacokinetic properties of sugammadex, alterations in the dosage and safety profiles of sugammadex may occur during pregnancy. Secondly, very large and polarized sugammadex molecules are expected to have limited placental transfer to the fetus and excretion into breast milk. Finally, sugammadex can bind to steroidal neuromuscular blocking agents as well as other substances with similar structures, such as progesterone. As a result of using sugammadex, progesterone levels can be reduced, causing adverse effects such as early pregnancy cessation and failure of hormonal contraceptives. This narrative review aims to demonstrate the correlations between sugammadex and pregnancy, lactation, and reproductive potential based on previously published preclinical and clinical studies. This will bridge the gap between theoretical assumptions and currently unknown clinical facts. Moreover, this review highlights what anesthesia providers should be aware of and what actions to take while administering sugammadex to such patients.

Keywords: Contraceptive agents, hormonal; Lactation; Pregnancy; Sugammadex.
concerned about adverse events (7.8%). Sugammadex use is estimated to increase substantially globally, alleviating economic concerns as sugammadex patents have already expired or are about to expire soon [4,5].

Can sugammadex replace acetylcholinesterase inhibitors in patients undergoing surgery and receiving rocuronium? Pregnant and lactating women are generally excluded from most clinical trials; therefore, no efficacy or safety studies have been conducted on these patients. It is not surprising that there are insufficient data on the Pregnancy and Lactation Labeling Rule for sugammadex. Only theoretical assumptions are made (Table 1). Pregnancy-related physiological changes involve most organs and affect the pharmacokinetic profiles of medications. Considering the physiological changes in pregnant women and pharmacokinetic properties of sugammadex, there may be alterations in its dosage and safety profile during pregnancy. Very large polarized sugammadex molecules are expected to have limited placental transfer to the fetus and excretion into breast milk [6]. Finally, sugammadex binds to steroidal NMBA and other substances with similar structures, such as progesterone [7,8]. The use of sugammadex can reduce progesterone levels, which may cause adverse effects such as early cessation of pregnancy and failure of hormonal contraceptives. However, there is no clinical evidence supporting this assumption.

The purpose of this narrative review is twofold. The first is the scientific aspect, including preclinical and clinical studies of previously published correlations between sugammadex and pregnancy, lactation, and reproductive potential, thereby bridging the gap between theoretical assumptions and currently unknown clinical facts. The second is the practical clinical aspect, which discusses what anesthesia providers and patients should be aware of, and what hospitals need to be institutionalized to use sugammadex for these patients.

**THEORETICAL ASSUMPTIONS AND PRECLINICAL EVIDENCE**

**Pregnancy-related physiologic and pharmacokinetic changes**

During pregnancy, significant physiological changes occur owing to increased estrogen and progesterone levels, beginning in the first trimester, peaking at term and labor,

| Table 1. Gaps Between Theoretical Assumptions/preclinical Studies and Clinical Evidence |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| Clinical situations | Theoretical assumptions/preclinical studies | Clinical evidences |
| Cesarean section | Increased volume of distribution and clearance: different dosing may be needed. | May be effective and safe with adult dosing. 16 mg/kg administration has never been reported but Difficult Airway Society guideline recommend to use high-dose of sugammadex when CICV occurred. |
| Non-obstetric surgery | | |
| Fetal development | Large and polarized molecule: limited placental transfer Conflicting results in preclinical studies: incomplete ossification, neuronal apoptosis. | Small clinical studies: no evidence of fetal developmental abnormalities. |
| Maintenance of pregnancy | Capturing and eliminating progesterone: failure to maintain pregnancy | Small clinical studies: no evidence of preterm labor, miscarriage or stillbirth. |
| Hormonal contraceptives | Capturing and eliminating progesterone: failure of hormonal contraceptives conflicting results in preclinical studies. | Small clinical studies: steroidal hormonal changes in human are insignificant and temporal. No clinical studies to confirm the causal relationship between unintended pregnancy and sugammadex. |
| Lactation | Large and polarized molecule: limited breast milk transfer Preclinical study showed peak concentration in breast milk 30 min after sugammadex administration. Early in the postpartum period, gaps between the mammary alveolar cells increased and peak concentration of sugammadex may pass through breast milk. | No clinical studies of the presence of sugammadex in human breast milk. Drug and Lactation Database says it may be safe. SOAP statement recommends to avoid it at term or near term pregnancy. |

and gradually reversing a few weeks postpartum [9]. Pregnancy-related physiological changes involve most organs and affect the pharmacokinetic profile of medications [10,11]. Decreased gastrointestinal motility and increased gastric pH affect drug absorption. Increased total body water, plasma volume, and capillary hydrostatic pressure lead to a significantly increased volume of distribution. Decreased concentrations of drug-binding proteins increase the bioactivity of certain drugs. Increased cardiac output induces greater hepatic and renal blood flow, resulting in the increased clearance of some medications.

However, information regarding pharmacokinetic changes or dosage requirements is lacking for most drugs used during pregnancy [12]. Moreover, it is often unclear whether altered pharmacokinetics lead to changes in drug efficacy or to adverse effects. Unfortunately, the use of sugammadex during pregnancy is not exempt. As sugammadex has no affinity for plasma proteins when administered intravenously, it immediately encapsulates rocuronium in a 1:1 molar ratio [13,14]. This leads to a concentration gradient that shifts rocuronium from the peripheral compartment (neuromuscular junction) to the central compartment (plasma), where it is encapsulated by sugammadex [15]. The sugammadex-rocuronium complex is highly soluble, and urinary excretion is the major route for its elimination without being metabolized by the liver [13].

Considering the physiological changes in pregnant women and pharmacokinetic properties of sugammadex, several analogies can be made. First, an increase in total body water increases the volume of distribution of the hydrophilic drug, which lowers the plasma concentration. The glomerular filtration rate (GFR) increases during pregnancy, and for drugs excreted by glomerular filtration, renal clearance parallels the changes in GFR during pregnancy [16]. However, the extent to which volume distribution increases and whether the dose of hydrophilic drugs should be increased remain unclear. Unlike the uniform increase in the GFR during pregnancy, the effect of renal tubular transport on renal clearance varies among drugs. Therefore, there are limitations in theoretically estimating the efficacy and safety of sugammadex during pregnancy.

Maternal-fetal transfer and fetal development

Sugammadex is a modified γ-cyclodextrin with a lipophilic core and hydrophilic periphery and a molecular weight of 2,178 daltons. The addition of eight side chains extended the cavity size to achieve a better fit for steroidal NMBA [17]. In addition, negatively charged carboxyl groups were added at the ends of the eight side chains to maintain structural integrity and enhance electrostatic binding to the positively charged quaternary nitrogen of rocuronium [6]. Theoretically, it is difficult for sugammadex to pass through the placenta owing to its large molecular size and negatively charged characteristics [18].

Preclinical studies by Merck have reported conflicting results [19]. In an embryo-fetal development study, pregnant rats received daily intravenous administration of sugammadex up to six times the maximum recommended human dose (MRHD). No treatment-related maternal or embryo-fetal changes were observed. In another embryo-fetal development study, pregnant New Zealand white rabbits received daily intravenous administration of sugammadex up to eight times the MRHD. A decrease in fetal body weight was observed in the offspring at maternal doses of 65 and 200 mg/kg. Moreover, incomplete ossification of the sternum and an unossified first metacarpal were found in the offspring at a maternal dose of 200 mg/kg/day. Furthermore, maternal toxicity was observed at 200 mg/kg. Considering that bone retention of sugammadex occurred in rats after intravenous injection with a mean half-life of 172 days, these findings may be attributed to the drug [19]. No evidence of malformation was observed at any dose. In a prenatal and postnatal development study, pregnant rats were intravenously administered sugammadex at concentrations up to six times the MRHD dose. There were no drug-related effects on rat parturition during prenatal or postnatal development. However, there was postnatal loss due to pup cannibalization. Therefore, effects of sugammadex on steroidal hormones and pheromones should not be excluded.

The effect of drugs on fetal neuronal development is an emerging issue. Palanca et al. [20] reported that sugammadex alone promoted neural apoptosis in primary cultures. Neural apoptosis was further promoted when sugammadex was used alone rather than in combination with steroidal NMBA in primary cultures [21]. It was concluded that sugammadex caused depletion of neuronal cell cholesterol, resulting in oxidative stress and neuronal apoptosis. However, this does not occur in vivo because the mature blood-brain barrier (BBB) prevents the passage of sugammadex. Thus, sugammadex may pass through a compromised BBB, such as an immature or damaged one. The potential of anesthetics to cause neuroapoptosis and other neurodegenerative changes in the developing brain has become evident in
animal studies over the past 20 years [22,23]. One study postulated that the co-administration of sugammadex with neonatal sevoflurane may exacerbate neuronal apoptosis due to changes in BBB integrity [24]. Neonatal mice exposed to 2% sevoflurane for 6 h developed BBB ultrastructural abnormalities. The co-administration of sugammadex with sevoflurane in neonatal mice further increased neuroapoptosis in the brain compared to 2% sevoflurane alone, whereas sugammadex alone did not induce apoptosis. This possibility should be considered when administering sugammadex with inhaled anesthetics in pregnant women. However, further studies are required to confirm these findings.

Interaction with progesterone

As sugammadex encapsulates steroidal NMBA, it may also bind to other appropriately sized steroidal substances. Progesterone is such a substance and in vitro binding studies suggest that progesterone levels may decrease by approximately 34% when exposed to sugammadex [19]. Decreased progesterone levels can lead to two serious adverse effects. One is failure to maintain early pregnancy, and the other is hormonal contraceptive failure.

Two animal studies that investigated the effect of sugammadex on progesterone levels in pregnant animals have been conducted [25,26]. Pregnant rats were randomly assigned to three groups and injected under sedation on the 7th day of gestation: control, sugammadex 30 mg/kg, and rocuronium 3.5 mg/kg + sugammadex 30 mg/kg [25]. Blood samples were obtained 35 min after injection to determine progesterone levels. Progesterone levels were not significantly different between the groups, and successful completion of pregnancy and absence of stillbirths or miscarriages were reported.

Pregnant rabbits were randomly divided into three groups: control, rocuronium administered at the onset of general anesthesia (GI group), and rocuronium + sugammadex administered 60 min after general anesthesia (GII group) [26]. In the GI group, progesterone levels at 60 and 90 min after general anesthesia were significantly lower than the baseline progesterone levels. In addition, the progesterone levels at 60 and 90 min after general anesthesia were significantly lower in the GII group than those in the GI group. However, all pregnancies were successful without early birth or stillbirth. Because studies are still lacking and the results are inconclusive, it cannot definitely be concluded that sugammadex affects pregnancy by lowering progesterone levels.

Lactation

Generally, low plasma protein binding, low molecular weight, and highly lipophilic and cationic drugs favor increased drug excretion into breast milk [27]. In contrast, sugammadex is large, hydrophilic, and has a half-life of 2 h and pKa of 2.82 [6]. Therefore, it is appropriate to predict minimal excretion of sugammadex into breast milk. Moreover, the oral absorption of sugammadex is thought to be low; therefore, it can be assumed that the amount of sugammadex delivered to breastfed infants is negligible. In a milk excretion study in rats, 20 mg/kg sugammadex was injected intravenously on postnatal day 9 and the maximum drug level was achieved at approximately 30 min [19]. The oral administration of sugammadex via milk did not induce adverse effects on survival, body weight, or physical or behavioral development in rats. However, there is no published evidence to support this.

CLINICAL EVIDENCE

Cesarean section

In cesarean sections, neuraxial anesthesia is preferred over general anesthesia; however, general anesthesia is still administered under some conditions [28]. Because pregnancy-related physiological changes peak at term and delivery, the efficacy and safety profiles are of primary concern when using sugammadex after fetus delivery. A randomized controlled noninferiority trial was conducted to show that a high-dose of rocuronium can achieve intubation conditions comparable to those of succinylcholine for cesarean delivery [29]. In the rocuronium group, 2 mg/kg sugammadex was administered if the train of four (TOF) count was ≥ 1 and 4 mg/kg sugammadex was used if the post-tetanic count was ≥ 1. Among the 120 patients, the time from neuromuscular blockade reversal to TOF ratio > 0.9 was 104 ± 63 (mean ± SD) s. In addition, no signs of residual blockade or side effects were observed. These findings are similar to those reported in other clinical studies [30,31].

The sugammadex doses required for the routine reversal of moderate or deep blocks during cesarean section appear to be sufficiently effective and safe at doses equivalent to adult doses (2–4 mg/kg). In emergencies, such as cannot intubate and cannot ventilate (CICV), a high-dose of sugammadex (16 mg/kg) must be administered for immediate reversal before fetal birth; however, these cases have not yet
been reported. Recent large multicenter studies showed difficult intubation rates of 2.0–5.4% which is similar to the general surgical population (4.4%) [32-34]. In contrast, failed intubation rate is higher in pregnant women (0.12–0.53%) compared with that in the general surgical population (0.06%) [32,33,35]. In 2015, the Obstetric Anesthetists’ Association and Difficult Airway Society developed the first national obstetric guidelines for difficult airway management [36]. The guidelines recommend considering high-dose sugammadex administration for immediate reversal of CICV. Although there is no evidence for the efficacy and safety of high-dose sugammadex in pregnant women and fetuses, it is reasonable to consider sugammadex administration because the risks of exposure to severe hypoxia could be more harmful than the potential risk of using high doses of sugammadex.

**Non-obstetric surgery**

Unlike cesarean sections, pregnant women undergoing non-obstetric surgery do not deliver a fetus and must continue their pregnancy. Therefore, few clinical studies have reported the use of sugammadex in such cases, and these have only recently been published in the form of case series [18,37-40]. Theoretically, the passage through the placenta or BBB is limited; however, animal experiments have shown worrisome results [19,24]. In 2019, an interesting case of sugammadex placental transfer was reported [37]. A woman at 29 weeks of gestation required an intrauterine transfusion for Rh (D) alloimmunization. During the intrauterine transfusion procedure, maternal respiratory distress occurred because of the intramyometrial injection of rocuronium, which was intended to be administered intramuscularly to the fetus. After the administration of sugammadex (100 mg), the patient’s respiratory distress resolved. After the patient had stabilized, additional rocuronium was administered to the fetal buttocks. Interestingly, adequate paralysis was achieved in the fetus without sustained paralysis induced by the maternal sugammadex injection, suggesting limited maternal-fetal placental transfer of sugammadex.

Recently, several case series and a multicenter retrospective study on maternal and fetal outcomes after sugammadex use in pregnant women have been published [18,38-40] (Table 2). In two case series, patients were at 4–26 gestational age and received 0.7–4.3 mg/kg sugammadex. Although preterm premature rupture of membranes (N = 8/25) and preterm labor (N = 12/25) occurred, none of these episodes

### Table 2. Summary of Obstetric and Fetal Outcomes after Sugammadex Administration in Non-obstetric Procedure

| Study | Number of patients | Dose of SGX (mg/kg) | GA at SGX administration (wk) | GA at delivery (wk) | Unplanned CD/total delivery | Abortion or still birth | PPRM or placental abruption | CD/total | GA at SGX administration (wk) | GA at delivery (wk) | Unplanned CD/total delivery | Abortion or still birth | PPRM or placental abruption | CD/total | GA at SGX administration (wk) | GA at delivery (wk) | Unplanned CD/total delivery | Abortion or still birth | PPRM or placental abruption | CD/total |
|-------|-------------------|--------------------|-----------------------------|--------------------|---------------------------|---------------------------|-------------------------|------------------------|-----------------------------|-----------------------------|----------------------|---------------------------|-------------------------|-------------------------|------------------------|-----------------------------|-----------------------------|----------------------|---------------------------|-------------------------|-------------------------|------------------------|
occurred within 2 weeks of receiving sugammadex [18]. In another case series, only one patient experienced preterm labor; however, it was induced by severe preeclampsia and developed 12 weeks after sugammadex administration [38]. In a multicenter retrospective observational study with 73 patients who received sugammadex and 51 patients who did not [39], the gestational age was 15.0 ± 5.1 (mean ± SD) weeks and the median total dose of sugammadex was 200 mg. Miscarriages and preterm births within 4 weeks of sugammadex administration were not significantly different between the patients with and those without sugammadex exposure. In one study, a larger dose of sugammadex (8 mg/kg) was administered to 15 patients who underwent electroconvulsive therapy [40]. Spontaneous abortion occurred in one patient and one infant developed neonatal respiratory distress. Moreover, no patients experienced preterm delivery or labor induced by sugammadex administration. Although these studies did not show obvious detrimental effects of sugammadex on maternal and fetal outcomes, their retrospective nature and small sample size cannot confirm the safety concerns.

**Levels of progesterone and unintended pregnancy**

Few clinical studies have examined steroidal hormone levels after sugammadex injection [41,42]. One study investigated the hormonal profiles of 50 young male patients randomly divided into N (neostigmine) and S (sugammadex 4 mg/kg) groups [42]. Sugammadex showed no adverse effects on progesterone and cortisol levels, while it was associated with a temporary increase in aldosterone and testosterone levels. They explained that sugammadex has no effect on progesterone levels because of its relatively low affinity (120 to 700 times lower than that of rocuronium) and tight binding to plasma proteins. A more recent prospective observational study was conducted to investigate the effects of sugammadex on perioperative estrogen and progesterone levels in premenopausal women aged 18–50 years [41]. After 240 min of sugammadex administration, progesterone in patients taking oral contraceptives tended to decrease; however, it was non-significantly decreased within 20% below baseline, far less than the 34% expected pharmacokinetically. Nonetheless, they did not consider the menstrual cycle or surgical stress, which significantly affect hormonal levels. In addition, because endogenous progesterone is suppressed by oral contraceptives (exogenous progesterone), a small change in progesterone exaggerates the percentage change. Both authors suggested that statistically significant changes in hormonal levels were borderline or temporary and would be clinically insignificant.

However, investigating the association between unexpected pregnancies and sugammadex use is difficult. Lazorwitz et al. [43] reported a single case (0.7%; 95% confidence intervals: 0–4.1%) of unexpected pregnancy after sugammadex administration in 134 patients using hormonal contraceptives. Based on the ultrasound measurements, the estimated date of conception was 19 days after sugammadex administration. Although there are no clinical reports of unintended pregnancy due to sugammadex-progesterone interaction, the manufacturer advises seriously considering this interaction. They recommended that if an oral contraceptive is taken on the same day that sugammadex is administered or non-oral hormonal contraceptives are used, the patient must use an additional non-hormonal contraceptive method or a backup method of contraception for the next 7 days [19]. Unintended pregnancy can be personally, socially, and economically burdensome; therefore, patients should be informed and educated even if there is a slight possibility. However, several studies show that 78–94% of anesthesia providers are aware of the risk of oral contraceptive failure with sugammadex, whereas only 20 to 33% of anesthesia providers discuss this with their patients [44,45]. Appropriate education and policies are required to overcome discrepancies between knowledge and practice. Anesthesia providers must assess the risk of oral contraceptive failure induced by sugammadex preoperatively and screen women of childbearing age for oral contraceptive administration. If women are at risk of oral contraceptive failure, anesthesia providers should counsel about sugammadex and its alternatives (acetylcholinesterase inhibitors) and make decisions regarding the choice of NMB antagonists. After surgery, information should be provided through a take-home leaflet or letter to improve postoperative recall [46,47]. Along with these perioperative processes, education of relevant medical staff and feedback from audits are necessary.

**Lactation**

Currently, there is no clinical evidence regarding the use of sugammadex during breastfeeding [48]. However, owing to the biochemical and pharmacokinetic characteristics of sugammadex and preclinical evidence, sugammadex is acceptable for use during breastfeeding [49]. In contrast, a
statement published by the Society for Obstetric Anesthesia and Perinatology (SOAP) disagrees with immediate breastfeeding [8]. According to the World Health Organization recommendations, breastfeeding should be initiated within the first hour of birth [50]. If a mother who received sugammadex after cesarean section began breastfeeding within 1 h after delivery, she may have breastfed at the peak concentration of sugammadex. Moreover, in the early postpartum period, large gaps between mammary alveolar cells enhance the delivery of maternal proteins to breast milk and may allow sugammadex to pass through breast milk [51]. Immature metabolism and renal function delay sugammadex clearance in infants. Therefore, SOAP recommends the use of acetylcholine esterase inhibitors and, if not, pumping and discarding breast milk for the first 12–14 h after surgery [8].

CONCLUSION

The use of sugammadex in pregnant and lactating women and in those of childbearing age taking oral contraceptives shows a large gap between theoretical estimation and clinical practice. Scientific and clinical evidence is increasingly being published to fill this gap; however, it remains insufficient. Therefore, it seems that now is the time to practice “Do not harm” rather than practicing “Doing good”. Premature birth and miscarriage owing to failure to maintain pregnancy, fetal deformities, developmental disorders, and unexpected pregnancies are completely different from the acute and temporary side effects of drugs. These are permanent afflictions and catastrophes for both individuals and the society. Therefore, it should be approached with more caution than other issues. However, although there is a lack of clear evidence, it is most likely that sugammadex is already playing the role of “Doing good” in some clinical situations such as cesarean section and CICV. Thus, what we need to know are theoretical knowledge and accumulated scientific data. What we have to do is establish a perioperative process of sugammadex use in pregnant and lactating patients and those on oral contraceptives. In addition, we must conduct related research and share our data worldwide. If we accomplish what we need to know and do, we will be able to move forward from “Do not harm” to “Doing good”.

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CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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Sugammadex use during pregnancy

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INTRODUCTION

Despite the concept deeming far from new, tubeless anesthesia has recently been witnessed more often during operations. With the ongoing trend of minimally invasive surgery backed by technological advances, it seems inevitable that anesthetic management should embrace these advancements as well. Beyond the early concept of apneic oxygenation, the advent of high-flow nasal oxygenation (HFNO) has recently been used as a key technique for tubeless anesthesia. HFNO provides humidified, heated oxygen up to 70 L/min, which promises improved oxygenation and ventilation, allowing for prolonged apneic oxygenation. In previous physiological and clinical studies, HFNO has been demonstrated that tubeless anesthesia safely provide an uninterrupted surgical field during laryngeal surgeries. Although tubeless anesthesia remains uncommon, it can be a good alternative to conventional anesthesia if anesthesiologist and a surgeon select appropriate patients together with sufficient experience. A safe strategy for tubeless anesthesia, along with appropriate backup plans, including endotracheal intubation and high-frequency jet ventilation, should be considered for upper airway surgery.

THE CONVENTIONAL ANESTHESIA FOR UPPER AIRWAY SURGERY

Endotracheal intubation with a narrow tube has been considered the conventional method for laryngeal microsurgery (LMS) under general anesthesia and neuromuscular blockade. Under general anesthesia with endotracheal intubation, most anesthesiologists feel relieved that patient safety is established by securing the airway and controlling the ventilation. However, there are still potential risks of inad-
vertent airway injury during intubation and higher airway pressure due to the narrow endotracheal tube. In addition, intubated anesthesia may contribute to inadequate surgical exposure of posterior laryngeal lesions and a narrow working space in upper airway surgery.

For sufficient exposure of the periglottic area, the endotracheal tube must be extubated and reintubated intermittently during the procedure, when necessary. This inevitable apneic period can cause desaturation and hypercarbia, which can be fatal, particularly in patients with poorly compensated cardiopulmonary function. Furthermore, the durations of surgery and anesthesia are usually prolonged.

To improve the surgical conditions of the upper airway, high-frequency jet ventilation (HFJV) has been used since the 1980s, where high-capacity humidified oxygen-mixed air is regularly injected into a thin plastic cannula [15,16]. Compared to endotracheal intubation, the HFJV provides the surgeon with superior accessibility to the posterior part of the larynx with a wider view [17]. However, the technique has several disadvantages. Inappropriate airway pressure monitoring or insufficient expiratory airflow increases the risk of pulmonary barotrauma, manifesting as pneumothorax, hypoxemia, or hypercapnia. Moreover, because small tidal volumes are applied at a high physiological rate through a cannula, continuous adjustment is required to appropriately position the airflow during the entire surgical procedure [18]. Because of these disadvantages, HFJV is not widely used in upper airway surgery, despite its benefits as an alternative ventilatory support.

THE RATIONALE OF TUBELESS ANESTHESIA FOR UPPER AIRWAY SURGERY

Before the concept of HFNO, conventional anesthetic management was considered optimal for upper airway surgery, although anesthesiologists were discontent with manipulating the endotracheal tubes following the inevitable apneic periods. Apneic oxygenation is the administration of oxygen with a nasal prong or nasopharyngeal catheter during the apneic period and has been evaluated in patients undergoing general anesthesia since the early 20th century [19,20]. It revealed prolongation of the time to desaturation and lower the incidence of hypoxemia during endotracheal intubation and short laryngeal surgeries [1,21,22]. However, it is not an alternative to conventional anesthesia because of the rapid increase in carbon dioxide (CO₂) and the subsequent decrease in pH [23].

Introduction of HFNO

Transnasal humidified rapid-insufflation ventilatory exchange is a physiological term that implements HFNO using a nasal cannula. HFNO can provide efficient and safe apnea oxygenation. The most commonly used commercial device is the Optiflow™ system (Fisher & Paykel Healthcare), and it consists of an air/oxygen blender and flow meter, a heated humidifier, and wide-bore nasal prongs (Fig. 1) [24]. An air/oxygen blender connected to the circuit enables the anesthesiologist to precisely titrate the fractional inspired oxygen (FiO₂) up to 1.0 at a high flow rate of up to 70 L/min. Despite the high flow rate, HFNO prevents dryness in the nasal cavity or discomfort by providing adequately heated (37°C) and humidified (44 mgH₂O/L) gas [25].

Physiologic effects of HFNO

HFNO offers distinct advantages over other oxygenation methods because of its prominent positive effects on respiratory physiology. First, the continuous high flow of 100% oxygen causes denitrogenation and washout of the anatomical dead space [26,27]. During apnea, alveolar oxygen absorption exceeds CO₂ production because of relative differences in blood solubility, generating a negative pressure gra-
dient that favors the bulk flow of gas from the anatomical dead space into the alveoli, a phenomenon called ventilatory mass flow [28]. Increased alveolar ventilation flushes out expired CO$_2$, thereby reducing the rate of CO$_2$ accumulation and dead space rebreathing. Thus, HFNO therapy reduces the risk of hypercapnia in an apneic patient [29]. Secondly, HFNO generates a low level of continuous positive airway pressure (PEEP) of 2.7–7.4 cmH$_2$O. The degree of PEEP depends on the flow rate, geometry of the upper airway, and breathing through the nose or mouth [8]. PEEP generated through HFNO assists in alveolar recruitment, preventing atelectasis and reducing shunting, thereby improving oxygenation. Furthermore, a heated and humidified air supply reduces breathing work, thereby reducing the energy requirements associated with gas conditioning. It also prevents against drying of the nasopharyngeal and tracheobronchial mucosa and improves mucociliary clearance with improving patient comfort [3,8,30].

**HFNO in upper airway surgery**

Owing to these physiological effects, HFNO has generated interest as a tubeless anesthetic for upper airway surgeries. A number of prospective observational studies and case reports demonstrated the feasibility of HFNO as an alternative to conventional ventilation during laryngoscopic surgery [4,8-14,31-34]. Table 1 shows the characteristics and outcomes of the main reports on tubeless anesthesia in adult patients undergoing upper airway surgeries. In 2015, Patel and Nouraei [10] reported the benefits of tubeless anesthesia using HFNO in 25 patients with difficult airways who underwent hypopharyngeal or laryngotracheal surgery for the first time. All patients showed an extended median apneic time of 14 min without arterial desaturation < 90%. Notably, one patient showed an apneic time of 65 min, which allowed pharyngolaryngeal surgery to be completed without complications. Lyons and Callaghan [9] and Maupue et al. [31] reported on the effects of tubeless laryngeal or tracheal surgery under apneic conditions with HFNO for sufficient gas exchange. The median apneic times were 19 and 27 min, respectively, ensuring adequate oxygenation and ventilation. Even still not common, emerging evidence has suggested that tubeless anesthesia with HFNO is effective in oxygenation and ventilation in most patients undergoing upper airway surgery.

**IMPACT OF TUBELESS ANESTHESIA ON PATIENT OUTCOME**

The most prominent benefits of tubeless anesthesia are improved operative outcomes and reduced time to laryngoscopic suspension and surgery by providing a better view of an uninterrupted surgical field (Fig. 2) [6,7,14,32]. Furthermore, postoperative patient comfort, as assessed by nausea, vomiting, and agitation, was acceptable because tubeless anesthesia is maintained only by total intravenous anesthesia [7,30,32]. These advantages allow tubeless anesthesia to be frequently used in the field of otolaryngology for various upper airway surgeries ranging from microlaryngeal excision to surgery for subglottic stenosis. Among the favorable surgery-related and patient-related outcomes of HFNO, the most noteworthy are the excellent oxygenation and ventilation by CO$_2$ clearance.

**Oxygenation**

Through the mass flow of oxygen, HFNO increases gas transfer and lung volume, which improves oxygenation during the procedure. Several studies reported comparable oxygenation on tubeless anesthesia using HFNO [8,10-12,30,34-36]. Min et al. [11] conducted a randomized controlled clinical study to compare the efficacy of HFNO and endotracheal intubation during LMS. This study revealed comparable oxygenation with HFNO and endotracheal intubation, demonstrating the feasibility of HFNO in upper airway surgery. In addition, the apnea time was up to 55 min in the HFNO group without complications. In addition, To et al. [12] reported the successful use of HFNO in 17 patients with subglottic stenosis who underwent balloon dilatation. The median apnea time to preserve appropriate oxygenation was 18 min. A retrospective study revealed excellent oxygenation with HFNO, which showed a low rate of oxygen desaturation, requiring jet ventilation rescue in patients with subglottic stenosis [37]. In this study, the median apnea time was > 40 min.

**CO$_2$ clearance**

According to previous case reports and clinical studies, the rate of CO$_2$ accumulation, rather than the oxygenation level, can limit the application of HFNO. Although HFNO reduces the rate of CO$_2$ accumulation compared to apneic oxygenation [8,38], tubeless anesthesia is acceptable only for
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of cases</th>
<th>Patient characteristics</th>
<th>Anesthetic management</th>
<th>Outcomes related to tubeless anesthesia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Age (yr)</td>
<td>BMI (kg/m²)</td>
<td>Anesthetics</td>
</tr>
<tr>
<td>Patel and Nouraei [10]</td>
<td>25</td>
<td>49 ± 15</td>
<td>30 (23, 36)</td>
<td>Propofol, fentanyl</td>
</tr>
<tr>
<td>Lyons and Callaghan [9]</td>
<td>28</td>
<td>56.6 ± 18</td>
<td>24.8 ± 4.5</td>
<td>Propofol, remifentanil</td>
</tr>
<tr>
<td>To et al. [12]</td>
<td>17</td>
<td>52 (20, 27)</td>
<td>27 (20, 36)</td>
<td>Propofol, opioid</td>
</tr>
<tr>
<td>Gustafsson et al. [8]</td>
<td>30</td>
<td>51 ± 12.7</td>
<td>25.1 ± 3.5</td>
<td>Propofol, remifentanil</td>
</tr>
<tr>
<td>Tam et al. [33]</td>
<td>1</td>
<td>55</td>
<td>-</td>
<td>Propofol, remifentanil</td>
</tr>
<tr>
<td>Yang et al. [34]</td>
<td>23</td>
<td>52 (39, 25, 67)</td>
<td>25.8 (22.5, 27.3)</td>
<td>Propofol, alfentanil, midazolam</td>
</tr>
<tr>
<td>Maupeu et al. [31]</td>
<td>22</td>
<td>49 (26, 76)</td>
<td>25 (18, 35)</td>
<td>Propofol, remifentanil</td>
</tr>
<tr>
<td>Lee and Quek [4]</td>
<td>1</td>
<td>50</td>
<td>40</td>
<td>Propofol, remifentanil</td>
</tr>
<tr>
<td>Waters et al. [13]</td>
<td>105</td>
<td>53.3 ± 17.49</td>
<td>27.04 ± 5.04</td>
<td>Propofol, opioid</td>
</tr>
<tr>
<td>Nekhendzy et al. [32]</td>
<td>10</td>
<td>50.0 ± 12.4</td>
<td>25.8 ± 4.8</td>
<td>Propofol, remifentanil</td>
</tr>
<tr>
<td>Min et al. [11]</td>
<td>56</td>
<td>59 (20, 84)</td>
<td>23.8 ± 3.5</td>
<td>Propofol, remifentanil</td>
</tr>
<tr>
<td>Huh et al. [14]</td>
<td>44</td>
<td>52.7 ± 20.9</td>
<td>23.2 ± 3.03</td>
<td>Propofol, remifentanil</td>
</tr>
</tbody>
</table>

Values are presented as number only, mean ± SD, or median (1Q, 3Q). BMI: body mass index, SpO₂: pulse oxygen saturation, EtCO₂: end-tidal carbon dioxide, TcCO₂: transcutaneous carbon dioxide.
short laryngeal operations. The rate of CO₂ increase during tubeless anesthesia using HFNO remains to be elucidated, as it is related to anesthetic techniques and methods of analysis. An experimental study using laboratory airway models demonstrated CO₂ clearance differences according to the oxygen flow rate [39]. The mean CO₂ clearance increased from 0.29 ml/min to 1.13 ml/min as the flow rate increased from 20 to 70 L/min. In clinical studies, EtCO₂ was reported to increase 1.1 mmHg/min in patients with spontaneous ventilation, while peripheral venous CO₂ being 1.6 mmHg/min and PaCO₂ being 1.8 mmHg/min in apneic patients [9,10]. Although CO₂ accumulation was non-linear and leveled off over time, the most critical factor for discontinuing tubeless anesthesia is hypercarbia, which results in acidosis. Min et al. [11] demonstrated the best cutoff point for a safe apneic period of 28 min using HFNO, which may cause significant respiratory acidosis beyond this period, which is consistent with the results of other clinical studies. However, respiratory acidosis was resolved quickly by rescue endotracheal intubation or jet ventilation in previous studies, which supports the use of HFNO during short upper airway surgery with cautious monitoring and standby rescue methods. Among the reports and articles so far, no significant complications of tubeless anesthesia using HFNO have been reported in upper airway surgery. Potential complications can be prevented by closely monitoring oxygenation and ventilation.

**STRATEGY OF TUBELESS ANESTHESIA FOR UPPER AIRWAY SURGERY**

**Patient selection**

Surgical concerns regarding adequate access and visualization, as well as anesthetic concerns regarding oxygenation and ventilation, should be balanced when applying HFNO in upper airway surgery. In addition to the indications (patent airway and short laryngeal surgery) and contraindications (skull base defect, increased intracranial pressure, and unstable hemodynamics) for HFNO, anesthesiologists should consider risk factors when determining the duration of tubeless anesthesia maintenance. In previous studies, elevated body mass index (BMI) was the only significant predictor of oxygen desaturation during HFNO [4,13,30,37,40]. BMI > 30 kg/m² was associated with a greater risk of requiring rescue ventilation, similar to alterations in respiratory physiology in obesity. Fat deposition primarily reduces pulmonary compliance by decreasing chest wall compliance [41]. In addition, airway resistance and airway pressure increase proportionally with the degree of obesity, which makes the propensity to overcome atelectasis and subsequent desaturation in obesity less likely [41,42]. These results demonstrate that tubeless anesthesia is safe and feasible for upper airway surgery in nonobese patients.

**Surgical factors to consider**

The effectiveness of HFNO depends on whether the patient has a patent upper airway. Therefore, patient disease characteristics are important factors affecting the applicabil-
ity of tubeless anesthesia. Tubeless anesthesia is very helpful for posterior lesions because the endotracheal tube may hinder the surgical field [10,33]. Tubeless anesthesia can be a good option for supraglottic and glottic tumors because endotracheal intubation is challenging. Despite providing tubeless anesthesia and partial obstruction from surgical instruments, especially when the lesion is located in the glottis, transcutaneous CO₂ levels are increasing more rapidly [7].

Although several advantages associated with surgery have been advocated, fire safety should be considered in LMS using lasers. Ignition can occur in the presence of an oxygen-rich environment, an oxidizer (tissue or plastic), or an energy source (CO₂-laser). Therefore, airway surgeries using lasers under HFNO have the potential risk of airway fires. However, successful case reports of orolaryngeal surgeries using laser and electrocautery with HFNO have been published [30,33,35,40]. They revealed that there was no risk of airway fire despite delivering 100% oxygen at up to 70 L/min because there were no combustible materials such as polyvinyl chloride endotracheal tubes or gauze. It has been concluded that the risk of flammability does not increase with HFNO in laryngeal surgery using a laser unless there is a flammable foreign object. In contrast, animal simulation studies using electrocautery and lasers have revealed airway fires in HFNO [43,44]. According to these reports, removing combustible materials from the surgical field could greatly increase safety, but a high FiO₂ of over 80% with interrupted laser strikes is highly likely to cause a sustained flame because human tissue and smoke can still serve as fuel and ignite under HFNO. Because there are limited clinical reports supporting the use of HFNO with pure oxygen and laser, the use of low FiO₂ before the use of laser or electrocautery is recommended to minimize energy application and achieve safe airway surgery with HFNO.

A strategy for tubeless anesthesia

A secure protocol for tubeless anesthesia during upper airway surgery should be established and implemented. Before general anesthesia is induced, preparation for rescue endotracheal intubation or jet ventilation should be confirmed. For preoxygenation, the patients should be positioned supine with their heads elevated at 10–20°. HFNO with an oxygen concentration of 100% at 30–40 L/min is recommended for at least 3 min. Pre-oxygenation can be performed with the mouth open or closed. After preoxygenation, intravenous induction should be performed, usually with propofol and remifentanil in a target-controlled infusion, which should be titrated to the patient’s hemodynamics and a bispectral index (BIS) target of 40–60. Upper airway patency should be maintained with jaw thrust after loss of consciousness until surgical laryngoscopy is performed. Rocuronium (0.6 mg/kg) can be administered as a repeat bolus according to the TOF during surgery. Tubeless anesthesia without neuromuscular blockade has been explored; however, it has not been generally accepted because of the surgical difficulties caused by involuntary movement. Immediately after inducing general anesthesia, HFNO should be maintained at 100% oxygen at a flow rate of 70 L/min during non-laser upper airway surgery. At the end of the surgery, a supraglottic airway or endotracheal tube can be inserted for ventilation during recovery from general anesthesia.

Instruments for monitoring tubeless anesthesia

In addition to routine monitoring of blood pressure, electrocardiography, oxygen saturation, and BIS for general anesthesia, there are some helpful and noninvasive instruments for monitoring patient safety during tubeless anesthesia. Arterial blood gas analysis is the gold standard for measuring the partial pressure of arterial CO₂. However, this method is invasive. End-tidal CO₂ (EtCO₂) concentration monitoring is a noninvasive method for predicting PaCO₂ which is routinely used in intubated patients, but is not possible in tubeless anesthesia. Transcutaneous partial pressure of CO₂ (TcCO₂) monitoring is a new noninvasive method that can continuously and reliably measure PaO₂ in a patient without endotracheal intubation during surgery [45-48]. Even TcCO₂ is found to reflect PaCO₂ more accurately than EtCO₂. Therefore, TcCO₂ monitoring is mandatory during tubeless anesthesia to predict the respiratory status of patients, as hypercarbia is the most critical factor that anesthesiologists should manage with caution.

Another useful instrument for tubeless anesthesia is oxygen reserve index (ORI™, Masimo Co.). ORI is a new parameter that noninvasively indicates real-time oxygenation reserve status [49]. In range of PaO₂ 100–200 mmHg, ORI varies between 0.00 and 1.0, which reflects the patient’s mild hypoxemic status. Considering the ventilatory status, tubeless anesthesia should be accompanied by monitoring of these specific instruments to prevent complications associated with apnea.
CONCLUSION

Tubeless anesthesia via HFNO is not new, but is an early adoption for anesthesiologists in upper airway surgery. If anesthesiologists and surgeons select appropriate patients and apply tubeless anesthesia based on sufficient experience, it could be a good alternative to conventional anesthesia. To establish a safe surgical environment with tubeless anesthesia, meticulous patient monitoring along with appropriate backup plans, including endotracheal intubation and HFJV, should be supported.

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None.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS

Conceptualization: Se-Hee Min, Jeong Hwa Seo. Formal analysis: Se-Hee Min. Writing - original draft: Se-Hee Min. Writing -review & editing: Se-Hee Min, Jeong Hwa Seo. Supervision: Se-Hee Min, Jeong Hwa Seo.

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Computed tomography-guided Gasserian ganglion interventions for cancer-related facial pain in patients with complex anatomy: insights and recommendations

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Background: The Gasserian ganglion is a well-known target for facial pain management, and patients with cancer present an anatomical challenge owing to tumor progression or treatment itself. Computed tomography (CT) is an alternative method for guiding these procedures.

Methods: This was an observational retrospective analysis of patients with cancer-related facial pain who underwent CT-guided Gasserian ganglion interventions using local anesthetics, local anesthetics with steroids, phenol, and radiofrequency. Demographic, clinical, and procedure-related variables were collected from January 1, 2015, to December 30, 2018, at the National Cancer Institute. Data distribution was determined using the Kolmogorov–Smirnov test. A paired sample t-test (with a cut-off of P < 0.05 for statistical significance) was used for comparing outcome.

Results: We observed a significant reduction in numerical rating scale and douleur neuropathique 4 scores from 7.6 ± 1.4 and 4.4 ± 1.4 to 3.2 ± 2.0 and 2.2 ± 1.4 points, respectively (P < 0.001). After the procedure, 70.8% of the patients were satisfied; 16.7% were very satisfied, and 12.5% were unsatisfied. No intra-or postoperative complications were observed. The most common neoplasms were head and neck tumors (83.3%).

Conclusions: Our data suggest that CT guidance is an effective and safe option for managing cancer-related facial pain in patients with complex anatomy, resulting in a significant reduction in pain, high satisfaction rates, and no mechanical complications. Future research should aim to refine the role of CT guidance in multimodal pain management in this population.

Keywords: Cancer pain; Facial pain; Neoplasm; Trigeminal ganglion.
INTRODUCTION

Eighty percent of patients with head and neck cancer complain of facial pain [1]. Pain in these settings may result directly from the tumor or as a side effect of oncological treatment in the form of radiotherapy, surgery, or even chemotherapy. Additionally, cancer progression and treatment can sometimes lead to anatomical deformations that complicate interventional therapy (Fig. 1).

Although oncological facial pain is mainly related to head and neck tumors, intracranial and, rarely, distal tumors may present with similar symptoms. These include headache, trigeminal neuralgia, trigeminal autonomic cephalalgia, and orofacial pain. Additionally, distal tumors may present with neuropathies [2]. Most of the time, these patients present with trigeminal-like pain; therefore, the Gasserian ganglion is an instrumental target for interventional pain management in this population.

For trigeminal neuralgia pain, evidence recommends microvascular decompression (very weak), stereotactic radiosurgery (weak), radiofrequency treatment of the Gasserian ganglion (weak), and pulsed radiofrequency (very weak) [3–5]; the common sequence includes a previous diagnostic block. For patients with cancer, the literature supports the use of neurolytic agents [6]. Furthermore, some studies have included peripheral approaches to distal branches [7].

The foramen ovale approach can be a difficult and time-consuming interventional procedure for physicians, requiring precision to place the needle. Moreover, suboptimal needle positioning can lead to treatment failure, recurrence, and potential complications, including nonspecific block, intracranial hemorrhage, subarachnoid injection, and infections [8,9].

Some authors have reported a successful stereotactic approach combined with a three-dimensional computed tomographic reconstruction model to improve accuracy, safety, and efficiency [10]. We share our experience with computed tomography (CT) guidance Gasserian ganglion interventions and their role in treating cancer-related facial pain in patients with complex anatomy.

MATERIALS AND METHODS

Study design

This observational, retrospective study was conducted at the National Cancer Institute of Mexico City. Approval was obtained from the institutional review board (2019/0097). The requirement for written informed consent was waived owing to the retrospective nature of the study.

Data collection

A review of the electronic medical records at the Instituto Nacional de Cancerología pain clinic was conducted from January 1, 2015, to December 30, 2018, at the National Cancer Institute. We included patients over 18 years of age diagnosed with cancer-related facial pain confirmed by magnetic resonance imaging, refractory to medical treatment, with a numerical rating scale (NRS) over 5 points, and who underwent a CT-guided Gasserian ganglion intervention. Patients with mental disorders, poor documentation, or other causes of pain were excluded.

Variables

The following data were collected from the patient charts: age; sex; tumor type; side (left, right, or bilateral); affected

Fig. 1. Computed tomography of head and neck tumors showing complex anatomy.
branch (V1, V2, V3, or combination); drugs used for the intervention (local, steroids, phenol); and time of radiofrequency. We monitored intra- and postoperative complications including corneal anesthesia or loss of corneal reflex, blindness, facial dysesthesia, masseter weakness, cerebrospinal fluid leakage, carotid-cavernous fistula, and perioperative death. Patient satisfaction was evaluated on a Likert scale (unsatisfied to very satisfied).

We collected outcome data regarding pre- and post-procedural status, NRS 0–10, and the douleur neuropathique 4 (DN4) questionnaire. Satisfactory pain relief was defined as a reduction of 3 points in the NRS and DN4 scores for at least 7 days.

Gasserian ganglion intervention technique

All procedures were performed by experienced pain physicians in CT rooms in the supine position under standard sedation (2 µg/kg fentanyl and 0.075 mg/kg midazolam). The puncture was performed according to the Hartel anatomical landmarks for percutaneous procedures. The head was positioned supine and rotated slightly away from the puncture side. The entry point was 2.5 cm lateral to the mouth angle (Fig. 2). After skin preparation and local anesthesia, a 22-G (32 mm) needle was introduced into the foramen ovale, and a 128-slice spiral CT Siemens Flash scan was used to confirm the needle position. After verification, medical treatment was administered to each patient as follows: radiofrequency, 10% phenol, bupivacaine, or steroids (dexamethasone). All patients were closely-monitored for 2 h and

Fig. 2. Three-dimensional reconstruction showing the computed tomography-guided bilateral approach.
reevaluated 7 days later.

**Statistical analysis**

Data distribution was determined using the Kolmogorov–Smirnov test. Categorical data were described as percentages and continuous data as medians and standard deviations. A paired sample t-test (with a cut-off of $P < 0.05$ for statistical significance) was used for outcome comparison. All statistical analyses were performed using SPSS Version 25.0 (IBM Co.).

**RESULTS**

A total of 32 patients were initially screened, and 24 were included in the final analysis: 70% female and 30% male, respectively. The mean age was 56.6 ± 13.5 years. The right side was affected in 58.3% of the cases, and a combination of branches, specifically V2 + V3, was the most common presentation (75%). More than 8% of interventions were performed bilaterally. The most common neoplasms were head and neck tumors (83.3%) (Table 1). Neurolysis was performed with phenol in 37.5% of patients, and radiofrequency was performed in 33.3%, with a median time of 180 (120, 360) s (Table 2).

Most patients (95.8%) had favorable clinical outcomes. After the procedure, 70.8% of the patients were satisfied, 16.7% were very satisfied, and 12.5% were unsatisfied. Facial dysesthesia was the only complication reported by 8.3% of patients (Table 3). We observed a significant reduction in NRS and DN4 scores from 7.6 ± 1.4 and 4.4 ± 1.4 to 3.2 ± 2.0 and 2.2 ± 1.4 points, respectively ($P < 0.001$) (Table 4). when looking at complications separated by intervention; this was observed in the phenol plus radiofrequency group (Table 5).

**DISCUSSION**

Hartel first described the treatment of trigeminal neuralgia with absolute alcohol through a percutaneous foramen ovale approach to the Gasserian ganglion in 1912 [11]. However, the efficacy and safety of percutaneous interventions depend mainly on the precision of the target. When using

<table>
<thead>
<tr>
<th>Table 1. Patient Characteristics</th>
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</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Age (yr)</td>
</tr>
<tr>
<td>Causes of trigeminal neuralgia</td>
</tr>
<tr>
<td>Hematopoietic tumors</td>
</tr>
<tr>
<td>Breast cancer</td>
</tr>
<tr>
<td>Head and neck tumors</td>
</tr>
<tr>
<td>Affected branch</td>
</tr>
<tr>
<td>V1 + V2</td>
</tr>
<tr>
<td>V2 + V3</td>
</tr>
<tr>
<td>V1 + V2 + V3</td>
</tr>
<tr>
<td>Affected side</td>
</tr>
<tr>
<td>Left</td>
</tr>
<tr>
<td>Right</td>
</tr>
<tr>
<td>Bilateral</td>
</tr>
<tr>
<td>Pain assessment</td>
</tr>
<tr>
<td>NRS</td>
</tr>
<tr>
<td>DN4</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean ± SD. NRS: numerical rating scale, DN4: douleur neuropathique 4.

<table>
<thead>
<tr>
<th>Table 2. Treatment Modalities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Management</strong></td>
</tr>
<tr>
<td>Steroids</td>
</tr>
<tr>
<td>Steroids + bupivacaine</td>
</tr>
<tr>
<td>Phenol 10%</td>
</tr>
<tr>
<td>Radiofrequency</td>
</tr>
<tr>
<td>Radiofrequency time median (s)</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or median (1Q, 3Q).

<table>
<thead>
<tr>
<th>Table 3. Evaluation After Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical outcomes</strong></td>
</tr>
<tr>
<td>Favorable clinical outcomes</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Satisfaction after procedure</td>
</tr>
<tr>
<td>Not satisfied</td>
</tr>
<tr>
<td>Satisfied</td>
</tr>
<tr>
<td>Very satisfied</td>
</tr>
<tr>
<td>Complications</td>
</tr>
<tr>
<td>Corneal anesthesia</td>
</tr>
<tr>
<td>Blindness</td>
</tr>
<tr>
<td>Facial dysesthesia</td>
</tr>
<tr>
<td>Masseter weakness</td>
</tr>
<tr>
<td>CSF leakage</td>
</tr>
<tr>
<td>CCF</td>
</tr>
<tr>
<td>Death</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or number only. CSF leakage: cerebrospinal fluid leakage, CCF: carotid-cavernous fistula.
fluoroscopy, it may be challenging to visualize the foramen ovale, as soft tissues and blood vessels cannot be visualized. This is especially relevant for patients with cancer, as the anatomy is often disturbed by tumor progression, radiation, chemotherapy, or surgery. CT is a useful tool for identifying the optimal position and predicting intraoperative difficulties. Although previous studies on CT reconstruction for difficult-to-access foramen ovale interventions have been published [10], no study has been performed in an oncological population with complex anatomy, including bilateral approaches.

The present study showed a significant reduction in NRS (7.6–3.2; P < 0.001) and DN4 (4.4–2.2; P < 0.001) scores and most patients reported being satisfied. Our results are consistent with those of previous studies [10–14]. Regarding clinical presentation, we obtained similar results, with the right branch being the most affected, specifically V2 + V3 [15,16]. We also agree with previous studies on the etiology of pain, where head and neck tumors were the most frequent [1,2].

Regarding treatment options, we opted for phenol, not glycerol, because of accessibility in our hospital; nevertheless, phenol 10% has been described as a valuable option, especially in patients with cancer [17]. There is still controversy regarding the optimal administration of radiofrequency therapy. However, most studies suggest lesions at a maximum of 0.5 V, 75 cycles/s at 55 to 80°C for 120 s; we presented a median time of 180 s [17,18].

Unlike previous studies, we included patients with bilateral pain treated with chemical neurolysis, which demands a higher anatomic understanding and skills. Nevertheless, similar to these studies, we reproduced an effective and safe CT-guided technique [12–14]. We achieved 100% technical success with appropriate needle positioning with a significant reduction in pain. In contrast, Telischak et al. [14] reported minor complications, such as throat numbness, which can be explained by the combined approach of the Gasserian and glossopharyngeal nerves. Zheng et al. [12] reported that facial dysesthesia was the most common complication. This was the only complication reported in our patients. There are two explanations for this: a short follow-up time and a more precise location with 3D reconstruction, which was presented in patients with significant anatomical deformations.

Two previous meta-analyses [19,20] concluded that puncture guidance technology has an absolute advantage in puncturing the foramen ovale, can improve the one-puncture success rate, learning curve, and safety, and can reduce the incidence of complications and operation times. We reproduced this in an oncological population with complex anatomy using CT guidance.

**Limitations**

The present study had certain limitations inherent to a retrospective, single-center investigation. The survival of pa-

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**Table 4. Comparison Before and After Intervention**

<table>
<thead>
<tr>
<th>Pain assessment</th>
<th>Before</th>
<th>After</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRS score</td>
<td>7.6 ± 1.4</td>
<td>3.2 ± 2.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>DN4 score</td>
<td>4.4 ± 1.4</td>
<td>2.2 ± 1.4</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. NRS: numerical rating scale, DN4: douleur neuropathique 4.

**Table 5. Complications Separated by Intervention**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Steroid</th>
<th>Pulsed RF + conventional RF</th>
<th>Phenol 10%</th>
<th>Conventional RF</th>
<th>Pulsed RF</th>
<th>Conventional RF + phenol 10%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corneal anesthesia (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Blindness (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Facial dysesthesia (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>8.3</td>
</tr>
<tr>
<td>Masseter weakness (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CSF leakage (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CCF (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Death (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Patients with cancer can explain our limited sample size; in addition, only patients with complex anatomy were included. We did not evaluate the results in terms of quality of life, and associated or secondary symptoms, such as anxiety or depression, were not investigated. Additionally, the follow-up was very short; therefore, we could not monitor late complications.

Conclusions

To the best of our knowledge, this is the first study performed on a cancer patient population using bilateral approaches. Our data suggest that CT guidance is a safe tool for interventional physicians treating facial pain in cancer patients with complex anatomy. Therefore, we do not recommend using only fluoroscopic guidance techniques in patients with head and neck cancer who have previously undergone surgery or have other causes of intricate anatomy. Accordingly, our algorithm includes a recent CT and magnetic resonance imaging and the use of local anesthetic as an initial treatment. If pain relief is significant but short-lived, chemodenervation (short survival time) or radiofrequency (long survival time) therapy is considered. Larger prospective, randomized, multicenter clinical trials are necessary to validate our outcomes and refine the role of CT guidance in multimodal pain management in this specific population.

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

REFERENCES


The effect of 6% hydroxyethyl starch 130/0.4 preloading on the blood glucose levels in diabetic patients undergoing orthopedic surgery with spinal anesthesia: a randomized pilot study

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¹Department of Anesthesiology and Pain Medicine, Chosun University Hospital, ²Department of Anesthesiology and Pain Medicine, College of Medicine and Medical School, Chosun University, Gwangju, ³Department of Anesthesiology and Pain Medicine, Yonsei Bon Hospital, Seoul, Korea

Background: Perioperative hyperglycemia can occur in surgical patients and may increase postoperative morbidity and mortality, especially in patients with diabetes. Therefore, we conducted the present study to evaluate whether the administration of 6% hydroxyethyl starch (HES)-130/0.4 increases blood glucose levels in patients with diabetes.

Methods: Forty patients undergoing lower limb surgery under spinal anesthesia were randomly allocated into two groups according to the fluids administered 20 min before spinal anesthesia (Group L, lactated Ringer’s solution; Group H, 6% HES-130/0.4). Patient characteristics, intraoperative variables, blood glucose levels, mean blood pressure (MBP), and heart rate (HR) were recorded at five time-points (0, 20, 60, 120, and 240 min).

Results: A total of 39 patients were analyzed (Group L, n = 20; Group H, n = 19). The amount of intraoperative fluid was significantly higher in Group L than in Group H (718.2 ml vs. 530.0 ml, P = 0.010). There were no significant differences in the changes in blood glucose levels, HR, or MBP between the two groups (P = 0.737, P = 0.896, and P = 0.141, respectively). Serial changes in mean blood glucose levels from baseline also showed no significant differences between the groups (P = 0.764).

Conclusions: There were no significant changes in blood glucose levels when lactated Ringer’s solution or 6% HES-130 was used. When compared to the lactated Ringer’s solution, no evidence that 6% HES-130/0.4 produces hyperglycemia in diabetic patients could be found. Further evaluation of larger populations is needed.

Keywords: Blood glucose; Colloids; Diabetes mellitus; Hydroxyethyl starch derivative; Hyperglycemia; Ringer’s lactate.

INTRODUCTION

Surgical patients often show high blood glucose levels, which are known to be caused by a hypermetabolic response to various surgical or anesthetic stresses [¹,²]. The catabolic nature of human homeostasis results in the activation of endocrine systems, such as the hypothalamic-pituitary-adrenocortical pathway, which leads to changes in the
regulation of hormones [1-3]. Increased secretion of counterregulatory hormones, such as catecholamines, cortisol, glucagon, or growth hormone, promotes gluconeogenesis and hepatic glucose production, all while inhibiting insulin release by pancreatic β-cells [1]. These changes in hormone levels and metabolism lead to increased blood glucose levels and interrupt glucose control during surgery.

Perioperative hyperglycemia is significantly related to adverse clinical outcomes and is thought to be an independent risk factor for postoperative morbidity and mortality [1,4,5]. Perioperative hyperglycemia can occur regardless of whether a patient has diabetes, and its incidence in patients undergoing general surgery ranges between 20 and 40% [1]. However, patients with diabetes may require more frequent surgical interventions and hospitalizations [6]. Moreover, diabetic patients can have worse surgical outcomes, including acute diabetic complications, as well as show increased infection rates, delayed wound healing, longer hospital stays, and worse perioperative mortality rates than non-diabetic patients [6]. Therefore, diabetic patients undergoing surgery should be carefully considered to avoid the risk of hyperglycemia during surgical procedures [4].

Although there are concerns regarding side effects in some clinical situations [7], hydroxyethyl starch (HES), a synthetic carbohydrate polymer, is still used for fluid resuscitation, as colloids still have advantages for intravascular volume expansion in clinical hypovolemia [7-9]. HES can also be used to prevent hypotension after spinal anesthesia [10]. HES is a derivative of amylopectin and may have the potential to increase blood glucose levels, as amylopectin is a highly branched compound of starch that resembles glycogen in structure, is rapidly hydrolyzed by amylase, and has a half-life of approximately 20 min [7,11]. Several studies have reported that 6% HES-130/0.4 does not increase blood glucose levels or cause slight increases within physiological limits in surgical patients without diabetes [11-13]. However, there are objections that HES (6% HES-450 or 6% Pentastarch-200) significantly increases blood glucose levels [14,15]. Moreover, controversy remains regarding whether 6% HES-130/0.42 causes a significant increase in blood glucose levels in surgical patients with diabetes [16].

In consideration of the above, we conducted the present study to evaluate whether preloading of 6% HES-130/0.4 increases blood glucose levels compared to control lactated Ringer’s solution in patients with diabetes undergoing lower limb surgery under spinal anesthesia.

**MATERIALS AND METHODS**

After approval from Institutional Review Board of Chosun University Hospital (2014-10-003), we carefully explained the study and obtained written informed consent from the patients. We conducted this randomized, double-blind, controlled study in accordance with the Ethical Principles for Medical Research Involving Human Subjects outlined in the Helsinki Declaration of 1975 (revised 2013).

A total of 40 patients with type 2 diabetes mellitus who were undergoing spinal anesthesia for elective surgery of the lower limb (American Society of Anesthesiologists physical status classification II and aged between 30 and 80 years) in our hospital were enrolled in the study. The inclusion criteria were as follows: body weight within 40 to 75 kg, taking only oral medications for glucose control, and well-controlled glucose levels that did not require hospitalization (hemoglobin A1c, HbA1c < 7.0%) [12,14]. The exclusion criteria were as follows: uncontrolled diabetes; diabetic patients treated with insulin; taking of drugs such as acetaminophen, steroids, or ascorbic acid, which can cause hyperglycemia continuously; history of allergy to corn or other experimental drugs; dysfunction of the kidney, liver, or heart; coagulation disorders; and hypovolemia or hypervolemia, including pulmonary edema.

All recruited patients agreed to participate in the study and were allocated in a 1:1 ratio according to computer-generated random numbers. An independent anesthesiologist prepared the sealed envelopes, and patients were allocated into two groups according to the number of sealed envelopes in sequential order. Group I (n = 20) was administered lactated Ringer’s solution (15 ml/kg; JW Pharmaceutical, Korea). Group H (n = 20) was administered 6% HES 130/0.4 (Volulyte; Fresenius Kabi; 7.5 ml/kg).

Diabetes was managed following the guidelines of the consultant to the Department of Medicine [17,18]. On the morning of surgery, the patients were advised not to take any oral diabetes medications. After overnight fasting, blood glucose levels were measured in the ward. Hyperglycemia with blood glucose > 200 mg/dl was treated with small doses of short-acting insulin (0.1 U/kg). Hypoglycemia < 70 mg/dl was treated with dextrose 50% solution. Eventually, the patients’ blood glucose levels were maintained within the target range (80–180 mg/dl) before surgery [19]. Any patient with poor glycemic control before the surgery dropped out of the study. During the study, the patients fasted.

After obtaining intravenous access with an 18-gauge intra-
HES in diabetic patients

The primary outcome of this study was to compare changes in blood glucose levels according to the preloading of the designated fluids. Blood glucose levels were measured by blinded anesthesiologists and nurses according to the following time intervals: T0, baseline before administration of the designated fluid; T1, 30 min after administration of the designated fluid; T2, 1 h after administration of the designated fluid; T3, 2 h after administration of the designated fluid; and T4, 3 h after administration of the designated fluid. The means and differences from the baseline glucose levels were calculated and compared at each time point. Secondary outcomes such as mean blood pressure (MBP) and heart rate (HR) were measured simultaneously when blood glucose levels were assessed. Patient characteristics and perioperative variables such as age, sex, height, weight, body mass index (BMI), comorbidity, preoperative HbA1c, blood glucose level on the morning of surgery, fasting time, type and duration of surgery, duration of tourniquet use, amount of administered bupivacaine, block level, number of patients requiring phenylephrine use, total administered dose of phenylephrine, amount of intraoperative fluid, and estimated blood loss were recorded.

Statistical analysis

The sample size was calculated using G*Power3 free software (Franz Faul, University of Kiel). First, the effect size was calculated based on a previous study that compared blood glucose levels after administration of lactated Ringer’s solution and 6% HES [12]. However, according to the data from a previous study (effect size: 1.75, variance explained by special effects: 8.54, variance within groups: 9), the calculated sample size was too small [20]. Therefore, we assumed the effect size to be 0.3 according to Cohen’s guidelines for social science [21]. Based on the results of a previous study that compared blood glucose levels between baseline and 1 h after administration [12], the correlation among the repeated measures was calculated to be 0.25. The total sample size was 38 for the repeated-measures two-way ANOVA test; this was performed with five consecutive measurements of blood glucose levels, with α = 0.05, and with a power of 80%. A dropout rate of 5% was considered, and 20 patients were allocated to each group.

Statistical analyses were performed using SPSS software (version 21.0, IBM Co.). Normality tests were performed using the Shapiro–Wilk test. Normally distributed data (age, height, weight, BMI, preoperative HbA1c, blood glucose level on the morning of surgery, fasting time, duration of surgery, duration of tourniquet use, and amount of intraoperative fluid) were analyzed using Student’s t-test. Non-normally distributed data, such as the administered dose of bupivacaine, total administered dose of phenylephrine, and estimated blood loss, were analyzed using the Mann–Whitney U test. Categorical variables were analyzed using the Chi-square test (sex and number of patients requiring the use of phenylephrine) or Fisher’s exact test (comorbidity, type of surgery, and block level). Values were expressed as mean ± SD, median (1Q, 3Q), or number of patients (%) with exact P values. A repeated measures two-way ANOVA was performed to compare the differences in MBP, HR, and blood glucose levels between the groups. The changes in blood glucose levels according to the time sequence were also analyzed using repeated-measures two-way ANOVA. A Greenhouse–Geisser correction was applied to the data, as it did not satisfy the sphericity assumption after Mauchly’s test of sphericity. Post-hoc tests were performed using the Mann–Whitney U test. After Bonferroni correction, adjusted P values < 0.05 were considered statistically significant.
RESULTS

Forty patients were assessed for eligibility and enrolled. Patients’ blood glucose levels were maintained within the target range (80–180 mg/dl) on the morning of surgery and did not require further management with insulin or dextrose solution administration. One patient was excluded owing to the need to convert from spinal anesthesia to general anesthesia due to inadequate blockade. Finally, data from 39 patients (Group L, n = 20; Group H, n = 19) were analyzed (Fig. 1).

There were no significant differences in the patient characteristics or preoperative variables between the groups (Table 1). The perioperative outcomes also showed no significant differences, except for the amount of intraoperative fluid. The amount of intraoperative fluid was significantly higher in Group L than in Group H (718.2 ml vs. 530.0 ml, P = 0.011, Table 2).

The changes in mean blood glucose levels according to the time sequence did not show significant differences between the two groups (P = 0.737 with Greenhouse–Geisser correction). There were also no significant differences in the mean blood glucose levels at any of the five time points (Fig. 2). Serial changes in the mean blood glucose levels from the baseline values also showed no significant differences between the groups (P = 0.764 with Greenhouse–Geisser correction, Fig. 2).

Changes in MBP and HR did not show any significant differences between the groups (MBP, P = 0.896 with Greenhouse–Geisser correction; HR, P = 0.141). There were also no significant differences in MBP and HR at any of the five time points (Fig. 3).

DISCUSSION

In this study, the preloading of 6% HES-130/0.4 before spinal anesthesia showed no significant increase in blood glucose levels compared to the control lactated Ringer’s solution during lower limb surgery in patients with diabetes. Therefore, compared to lactated Ringer’s solution, we could not find evidence that 6% HES-130/0.4 produces hyperglycemia in diabetic patients.

The molar substitution of hydroxyl residues into hydroxyethyl residues of HES increases water solubility and delays amylase hydrolysis by amylase [7,9]. The average number of hydroxyethyl residues of 6% HES-130/0.4 is 4/10 glucose molecules [7]. Therefore, 6% HES-130/0.4 has six parts that have not been substituted for hydroxyethyl resi-
Table 1. Patient Characteristics and Preoperative Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group L (n = 20)</th>
<th>Group H (n = 19)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>62.6 ± 10.5</td>
<td>63.2 ± 12.2</td>
<td>0.719</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>10/10</td>
<td>10/9</td>
<td>0.869</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>181.8 ± 8.5</td>
<td>163.5 ± 7.0</td>
<td>0.582</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62.0 ± 10.1</td>
<td>63.8 ± 8.2</td>
<td>0.269</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.7 ± 3.2</td>
<td>23.8 ± 2.2</td>
<td>0.152</td>
</tr>
<tr>
<td>Comorbidity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes only</td>
<td>5 (25.0)</td>
<td>4 (21.1)</td>
<td></td>
</tr>
<tr>
<td>Diabetes with hypertension</td>
<td>15 (75.0)</td>
<td>15 (78.9)</td>
<td></td>
</tr>
<tr>
<td>Preoperative hemoglobin A1c (%)</td>
<td>5.8 ± 0.6</td>
<td>5.9 ± 0.7</td>
<td>0.829</td>
</tr>
<tr>
<td>Blood glucose level on the morning of surgery (mg/dl)</td>
<td>112.5 ± 16.8</td>
<td>120.6 ± 21.5</td>
<td>0.192</td>
</tr>
<tr>
<td>Fasting time (h)</td>
<td>13.7 ± 2.6</td>
<td>13.7 ± 2.4</td>
<td>0.929</td>
</tr>
<tr>
<td>Type of surgery</td>
<td></td>
<td></td>
<td>0.389</td>
</tr>
<tr>
<td>Arthroscopic knee operation</td>
<td>2 (10.0)</td>
<td>5 (26.3)</td>
<td></td>
</tr>
<tr>
<td>Fracture reduction and fixation</td>
<td>9 (45.0)</td>
<td>10 (52.6)</td>
<td></td>
</tr>
<tr>
<td>Implant removal</td>
<td>6 (30.0)</td>
<td>3 (15.8)</td>
<td></td>
</tr>
<tr>
<td>Simple excision</td>
<td>3 (15.0)</td>
<td>1 (5.3)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, number only, or number (%). Group L: preloading with lactated Ringer’s solution (15 ml/kg) as the control group, Group H: preloading with 6% hydroxyethyl starch 130/0.4 (7.5 ml/kg).

Table 2. Perioperative Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group L (n = 20)</th>
<th>Group H (n = 19)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of surgery (min)</td>
<td>83.8 ± 30.9</td>
<td>85.3 ± 29.6</td>
<td>0.892</td>
</tr>
<tr>
<td>Duration of tourniquet use (min)</td>
<td>63.8 ± 30.9</td>
<td>65.8 ± 28.6</td>
<td>0.789</td>
</tr>
<tr>
<td>Administered dose of bupivacaine (mg)</td>
<td>8.0 (8, 10)</td>
<td>8.0 (8, 10)</td>
<td>0.939</td>
</tr>
<tr>
<td>Block level</td>
<td></td>
<td></td>
<td>0.904</td>
</tr>
<tr>
<td>T8</td>
<td>3 (15.0)</td>
<td>4 (21.1)</td>
<td></td>
</tr>
<tr>
<td>T10</td>
<td>13 (65.0)</td>
<td>11 (57.9)</td>
<td></td>
</tr>
<tr>
<td>T12</td>
<td>4 (20.0)</td>
<td>4 (21.1)</td>
<td></td>
</tr>
<tr>
<td>A number of patients requiring the use of phenylephrine</td>
<td>6 (30.0)</td>
<td>5 (26.3)</td>
<td>0.798</td>
</tr>
<tr>
<td>Total administered dose of phenylephrine (μg)</td>
<td>0 (0, 50)</td>
<td>0 (0, 25)</td>
<td>0.951</td>
</tr>
<tr>
<td>Amount of intraoperative fluid (ml)</td>
<td>718.2 ± 189.3</td>
<td>530.0 ± 226.9</td>
<td>0.011</td>
</tr>
<tr>
<td>Estimated blood loss (ml)</td>
<td>47.5 (30, 100)</td>
<td>60 (30,100)</td>
<td>0.419</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, median (1Q, 3Q), or number (%). Group L: preloaded with lactated Ringer’s solution (15 ml/kg) as the control group, Group H: preloaded with 6% hydroxyethyl starch 130/0.4 (7.5 ml/kg).

dues, which are easily hydrolyzed by amylase to raise blood glucose levels [7]. Previous studies have shown significant increases in blood glucose after using HES (6% HES-450 or 6% Pentastarch-200/0.5) in non-diabetic surgical patients [14,15]. However, other reports that studied changes in blood glucose levels after using 6% HES-130/0.4 showed no significant increase or a slight increase within physiological limits in non-diabetic surgical patients [11-13]. This difference is thought to be caused by the difference in the number of hydroxyethyl residue substitutions and the C2/C6 ratio according to the type of HES, which could affect the hydrolysis rate of HES by amylase [7,9]. In particular, the attachment of hydroxyethyl residues to the C2 molecules of glucose molecules strongly inhibits the hydrolysis of starch by amylase [7,9]. Therefore, HES with a higher C2/C6 ratio is hydrolyzed more slowly. Notably, the C2/C6 ratio of 6% HES-450 or 6% Pentastarch-200 is 5:1, whereas the C2/C6 ratio of 6% HES-130/0.4 is 9:1 [7].

Patients with diabetes who are undergoing surgery might be more susceptible to surgical stress, which changes the regulation of metabolism and hormones, leading to hyperglycemia easily [1-4]. Therefore, careful consideration of the
Fig. 2. Changes in the mean blood glucose levels (mean ± SD). The numbers represent the changes in mean blood glucose levels from the baseline values (T0) at certain time points (mean ± SD). Group L was preloaded with lactated Ringer’s solution (15 ml/kg) as the control group, whereas Group H was preloaded with 6% hydroxyethyl starch 130/0.4 (7.5 ml/kg). T0: baseline before administration of the designated fluid, T1: 30 minutes after administration of the designated fluid, T2: 1 hour after administration of the designated fluid, T3: 2 hours after administration of the designated fluid, T4: 3 hours after administration of the designated fluid.

Fig. 3. Changes in mean blood pressure and heart rate (mean ± SD). (A) Mean blood pressure and (B) heart rate. Group L was preloaded with lactated Ringer’s solution (15 ml/kg) as the control group, whereas Group H was preloaded with 6% hydroxyethyl starch 130/0.4 (7.5 ml/kg). T0: baseline before administration of the designated fluid, T1: 30 minutes after administration of the designated fluid, T2: 1 hour after administration of the designated fluid, T3: 2 hours after administration of the designated fluid, T4: 3 hours after administration of the designated fluid.
selection of perioperative fluids is required for patients with diabetes. Recently, one study showed that preloading of 6% HES-130/0.4 30 min prior to general anesthesia in diabetic patients significantly increased blood glucose levels within the first hour of initial administration [16]. Moreover, the increase in blood glucose levels after preloading with 6% HES-130/0.4 was much greater in patients with diabetes than in those without diabetes [16]. However, our study showed no significant changes in the blood glucose levels of diabetic patients over 3 h, regardless of the type of fluid administered. It is thought that this discrepancy resulted from differences in the anesthetic methods, as this study employed spinal anesthesia instead of general anesthesia. A previous study comparing perioperative blood glucose levels in patients undergoing hip arthroplasty showed a significant increase in glucose levels in patients undergoing general anesthesia versus spinal anesthesia [22]. The glucose levels of the patients who received spinal anesthesia remained stable and required no additional glycemic control during surgery by attenuating the hyperglycemic response to surgical stimuli. In addition to the above results, the blood glucose levels of the patients in the current study remained stable despite the use of HES, and the patients also did not require any glycemic control during the observational period. The following hypothesis can be considered as the cause of these results: First, the characteristics of 6% HES-130/0.4, including its high molecular weight, molar substitution, and high C2/C6 ratio, inhibit hydrolysis by amylase, which is likely the primary mechanism for the conversion of HES into glucose [7]. Second, degraded molecules from HES are small enough (molecular weight of approximately 40–50 kDa) to be excreted in the urine rapidly before amylase-dependent breakdown occurs [23]. Third, HES metabolism requires amylase and increases serum amylase to levels as high as twice the basal value [24]. However, serum amylase activity is significantly decreased in patients with type 2 diabetes mellitus [25]. Therefore, the conversion of HES to glucose may be delayed. Additionally, in the patients in this study, preloading of 6% HES-130/0.4 decreased the requirements for intraoperative fluids compared to lactated Ringer’s solution (718.2 ml vs. 530.0 ml, P = 0.011). In addition, as there were no significant differences in the administered doses of bupivacaine, block levels after spinal anesthesia, use of phenylephrine, or vital signs such as MBP and HR, the amounts of loading fluids after spinal anesthesia for the maintenance of vital signs were reduced in patients administered 6% HES-130/0.4 compared to those administered lactated Ringer’s solution.

The general incidence of spinal anesthesia-induced hypotension ranges from 25–75% [26]. It is well known that preloading colloids before spinal anesthesia significantly reduces the incidence of hypotension and related side effects compared to crystalloids. Thus, colloids are a better fluid for pre-hydration than crystalloids [27]. Although we did not analyze patient hemodynamics such as spinal anesthesia-induced hypotension or hypotension during the surgery as a secondary outcome, we believe that the result of this study in which preloading of 6% HES-130/0.4 decreased the amount of intraoperative fluid is worth referring to in the future. This study had several limitations. First, we included only patients with well-controlled diabetes (HbA1c < 7.0%) who took oral medications. Postoperative hyperglycemia in patients with diabetes is significantly associated with preoperative fasting glucose levels and HbA1c [28]. Therefore, diabetic patients with poor glycemic control are vulnerable to surgical stress and may be at a risk of increased postoperative morbidity and mortality [6]. Therefore, the results may differ if the experiment were to be conducted in patients with poor glycemic control. Furthermore, additional research that includes patients with glycemic control using insulin is required. Second, although it is known that the use of lactate Ringer’s solution leads to transient hyperglycemia via the conversion of lactate to glucose in diabetic patients [29], Ringer’s lactate solution was used as the control fluid in this study. However, according to a theoretical analysis, one liter of lactated Ringer’s solution contains 29 mmol of lactate, which can create a maximum increase in glucose concentration by about 18.02 mg/dl in a patient weighing 70 kg and that has 100% gluconeogenesis efficiency [30]. Moreover, lactate alone cannot induce significant hyperglycemia in actual clinical practice because the efficiency of gluconeogenic pathways is not 100% and the loss of lactate is due to oxidative metabolism [30]. Therefore, the use of lactated Ringer’s solution as a control fluid seems to have a limited effect on glycemic control in fasting diabetic patients under spinal anesthesia. Finally, the sample size of the current study was relatively small, despite it being deemed as appropriate based on the calculations for the pilot study. In addition, we only observed glucose levels 4 h after the administration of fluids. As approximately half of the administered HES remains after 24 h [7,9], a long-term follow-up study with a larger sample size is needed.

In conclusion, the preloading of 6% HES-130/0.4 in patients with diabetes under spinal anesthesia did not increase
blood glucose levels compared to lactate Ringer’s solution. There were also no significant differences in the serial changes in mean blood glucose levels after administration of fluids between 6% HES-130/0.4 and lactate Ringer’s solution. Therefore, evidence that 6% HES-130/0.4 produces hyperglycemia in diabetic patients could not be found; however, further evaluation with long-term follow-up is required.

FUNDING

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CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS


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Effect of sevoflurane-remifentanil and propofol-remifentanil anesthesia on glycocalyx shedding during deep inferior epigastric perforator flap breast reconstruction: a prospective randomized, controlled trial

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Background: The endothelial glycocalyx (EG) is an important structure that regulates vascular homeostasis. Deep inferior epigastric perforator (DIEP) flap is expected to cause substantial EG breakdown owing to the long procedural duration and ischemia–reperfusion injury. This prospective, randomized, controlled study aimed to compare syndecan-1 levels during sevoflurane-remifentanil and propofol-remifentanil anesthesia in patients who underwent DIEP flap breast reconstruction.

Methods: Fifty-one patients were randomized to either sevoflurane (n = 26) or propofol (n = 25) groups. Anesthesia was maintained with remifentanil in combination with either sevoflurane or propofol. The primary endpoint was the concentration of serum syndecan-1 measured at 1 h after surgery.

Results: Fifty patients (98.0%) completed the study. Patients in the propofol group had significantly lower levels of syndecan-1 than patients in the sevoflurane group at 1 h after operation (23.8 ± 1.6 vs. 30.9 ± 1.7 ng/ml, respectively; Bonferroni corrected P = 0.012). There were no significant differences between groups in postoperative complications. The postoperative hospital stay was 8.4 ± 2.5 days in the sevoflurane group and 7.4 ± 1.0 days in the propofol group (P = 0.077).

Conclusions: Propofol-remifentanil anesthesia resulted in lesser increases in syndecan-1 levels compared to increases with sevoflurane-remifentanil anesthesia in patients who underwent DIEP flap reconstruction. Our results suggest that propofol-remifentanil anesthesia shows protective effects against EG damage during DIEP flap breast reconstruction in contrast to sevoflurane-remifentanil anesthesia.

Keywords: Anesthesia, inhalation; Anesthesia, intravenous; Breast cancer; Breast reconstruction; Glycocalyx; Syndecan-1.
INTRODUCTION

The endothelial glycocalyx (EG) is a gel-like layer coating the luminal surface of the vascular endothelium that functions to regulate vascular homeostasis. EG is vulnerable to degradation by various insults, including ischemia–reperfusion injury [1]. Because EG functions to regulate vascular permeability and leukocytes transmigration, damage to the EG can lead to increased vascular permeability and interstitial edema. Exaggerated inflammatory responses can also occur by upregulation of interactions between leukocytes and the endothelium [2,3]. Various surgical procedures, as well as disease states such as sepsis and major trauma, can cause degradation (also called shedding) of the EG layer, as evidenced by the increased levels of syndecan-1, a component of the core protein structure of the EG [4-6].

Deep inferior epigastric perforator (DIEP) flap reconstruction is one of the most advanced procedures for breast reconstruction following mastectomy for breast cancer [7-9]. It has gained popularity owing to its more aesthetically natural results, lower complication rates, and reduction of additional operations required [10]. However, the procedure is technically challenging and complex, and involves a lengthy duration of surgery during which meticulous adjustment of blood pressure and fluid management is required [10]. Moreover, because the flap is completely detached and blood supply is later re-established, ischemia–reperfusion injury may occur that can influence the viability of the flap [10].

Although sevoflurane anesthesia reportedly exerts some protective effects against EG degradation from ischemia–reperfusion injury in experimental studies [11,12], clinical results demonstrating a protective effect against EG of inhalation anesthetics have been inconsistent [13-15]. In one clinical study, the anesthetic agent chosen in patients undergoing minimally invasive gastrectomy has been shown to influence the degree of EG layer degradation [16]. However, to our knowledge, no studies have evaluated the influence of the anesthetic agents on the occurrence and degree of severity of glycocalyx shedding during DIEP flap breast reconstruction surgery.

Therefore, we hypothesized that sevoflurane-remifentanil and propofol-remifentanil anesthesia would have different effects on EG shedding during mastectomy with immediate DIEP flap breast reconstruction. This prospective, randomized, controlled trial aimed to compare EG shedding during sevoflurane-remifentanil and propofol-remifentanil anesthesia by comparing syndecan-1 levels in patients with breast cancer who underwent mastectomy with immediate DIEP flap breast reconstruction.

MATERIALS AND METHODS

This prospective, randomized, controlled study was approved by the Institutional Review Board (IRB) and Hospital Research Ethics Committee (Yonsei University Health System, Seoul, Korea; IRB protocol no. 4-2021-0401), and registered at http://clinicaltrials.gov (ClinicalTrials.gov identifier: NCT05136508). It was conducted in accordance with the ethical principles of the Helsinki Declaration-2013, following good clinical practice guidelines. Patients aged ≥ 20 years with American Society of Anesthesiologists physical status of I to III who were scheduled to undergo total mastectomy with immediate DIEP flap reconstruction between May and November 2021 were included after obtaining informed written consent. Exclusion criteria were the need for a bilateral DIEP flap reconstruction, the inability to read or comprehend the informed consent forms, contraindications to the administration of sevoflurane or propofol, a history of thromboembolic disease, current contraceptive or thrombotic administration, renal dysfunction (estimated glomerular filtration rate < 60 ml/min/1.73 m²), pregnancy, breast feeding, or any kind of neuropsychiatric disease.

The included patients were randomly assigned to either the sevoflurane group (n = 26) or the propofol group (n = 25) according to a randomized assignment table, which was prepared by applying the block randomization method with a block size of 4. In the sevoflurane group, anesthesia induction was initiated using a bolus dose of propofol (1.0–1.5 mg/kg) and a target-controlled infusion (TCI) of remifentanil (effect-site concentration [Ce] set to 4.0 ng/ml). In the propofol group, a commercial TIVA pump (Orchestra® Base Primea, Fresenius-Kabi) was used for both propofol and remifentanil administration, and anesthesia induction was started with a TCI of propofol (Ce of 4.0–4.5 μg/ml) and remifentanil (Ce of 4.0 ng/ml). In the sevoflurane group, anesthesia was maintained using an age-adjusted end-tidal minimal alveolar sevoflurane concentration of 0.8–1.0 and TCI of remifentanil. In the propofol group, anesthesia maintenance was performed via TCIs of propofol and remifentanil to maintain patient state index values within the range of 25–50 [17,18].

Upon entering the operating room, all patients were continuously monitored by electrocardiogram, non-invasive blood pressure, peripheral oxygen saturation, patient state...
The sample size was calculated based on a previous study using PASS software version 15.0.2 [16]. The calculation was performed to detect a difference of 5.9 ng/ml in the postoperative concentration of syndecan-1 between the propofol and sevoflurane groups with a significance level of 5% and a statistical power of 80%. This resulted in a total of 69 patients per group, allowing an interim analysis using Pocock’s alpha-spending function. Considering a potential dropout rate of 5%, this study was designed with 73 patients in each group. An interim analysis was performed when 25 patients had completed the study in each group. Based on the results of the interim analysis, the study was discontinued, and 50 patients were included in the final analysis.

Continuous variables are expressed as mean ± standard
deviation and categorical variables are shown as the number of patients (percentage). Group differences with regards to continuous variables were determined using the student’s t-test and Chi-square test (if the portion of cells with an expected cell frequency of less than 5 was less than 20% of all the cells) or the Fisher’s exact test (otherwise) were applied for those in categorical variables. A linear mixed model analysis was employed for repeated-measure variables such as MAP, HR, PPV, remifentanil Ce, Syndecan-1 concentration, white blood cell count, hemoglobin levels, and neutrophil, lymphocyte, and platelet counts, which determined the group and time effects. When the interaction of group, time, and group-by-time showed statistical significance, post-hoc analyses with Bonferroni correction were performed to adjust for multiple comparisons. Statistical significance was defined as a P value < 0.05. All statistical analyses were performed using SAS® version 9.4 (SAS Institute Inc.).

RESULTS

Demographic and intraoperative characteristics

Of the 56 patients assessed for eligibility, 51 patients were randomly allocated into the sevoflurane or the propofol group, of which 50 completed the study (98.0%). One patient in the sevoflurane group who underwent only partial mastectomy was excluded from the final analysis. A summary of the progress through the phases of the trial can be found in the Consolidated Standards of Reporting Trials flow diagram (Fig. 1).

The patients’ characteristics are demonstrated in Table 1. None of the variables showed significant differences between the two groups. Table 2 presents the operative variables. Patients in the propofol group were administered with significantly higher doses of remifentanil and propofol and with significantly lower doses of norepinephrine compared to patients in the in the sevoflurane group (All P < 0.001). There were no significant differences in other operative variables between the two groups.

The perioperative changes in the MAP, HR, PPV, and remifentanil Ce are shown in Fig. 2. No statistical differences in MAP and PPV were found between the two groups (Fig. 2A and C, respectively). However, patients in the propofol group had significantly lower HRs beginning 30 min after microscopic reanastomosis until the end of operation than those of patients in the sevoflurane group (Bonferroni correct P = 0.009, 0.017, 0.034, and 0.047 at Micro30min, Microend, Situp10min, and OPend, respectively; Fig. 2B). The remifentanil Ce was significantly higher in the propofol group than in the sevoflurane group at all-time points (Bonferroni correct P = 0.016 at intu10min; Bonferroni correct P < 0.001 at all other time points; Fig. 2D).

Fig. 1. Consolidated Standards of Reporting Trials diagram of the study.
Table 1. Patients’ Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sevoflurane group (n = 25)</th>
<th>Propofol group (n = 25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>49 ± 7</td>
<td>48 ± 9</td>
<td>0.776</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.95 ± 4.42</td>
<td>23.82 ± 3.62</td>
<td>0.328</td>
</tr>
<tr>
<td>ASA physical status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>25 (100)</td>
<td>25 (100)</td>
<td></td>
</tr>
<tr>
<td>Co-morbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (8)</td>
<td>3 (12)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td>0.235</td>
</tr>
<tr>
<td>Non-smoker</td>
<td>25 (100)</td>
<td>22 (88)</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>0 (0)</td>
<td>3 (12)</td>
<td></td>
</tr>
<tr>
<td>Postmenopausal status</td>
<td>10 (40)</td>
<td>7 (28)</td>
<td>0.371</td>
</tr>
<tr>
<td>Preoperative chemotherapy</td>
<td>7 (28)</td>
<td>6 (24)</td>
<td>0.747</td>
</tr>
<tr>
<td>Preoperative CEA (ng/ml)</td>
<td>2.2 ± 1.5</td>
<td>2.1 ± 1.9</td>
<td>0.800</td>
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<tr>
<td>Preoperative CA15-3 (U/ml)</td>
<td>11.0 ± 5.5</td>
<td>11.4 ± 4.7</td>
<td>0.788</td>
</tr>
<tr>
<td>Receptor group</td>
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<td></td>
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<tr>
<td>Estrogen receptor positive</td>
<td>17 (68)</td>
<td>20 (80)</td>
<td>0.333</td>
</tr>
<tr>
<td>Progesterone receptor positive</td>
<td>13 (52)</td>
<td>15 (60)</td>
<td>0.569</td>
</tr>
<tr>
<td>HER 2 positive</td>
<td>8 (32)</td>
<td>7 (28)</td>
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</tr>
<tr>
<td>Tumor pathology</td>
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<td>0.117</td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>6 (24)</td>
<td>8 (32)</td>
<td></td>
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<tr>
<td>Invasive ductal carcinoma</td>
<td>14 (56)</td>
<td>7 (28)</td>
<td></td>
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<tr>
<td>Infiltrating other</td>
<td>5 (20)</td>
<td>10 (40)</td>
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<tr>
<td>Histopathologic grade</td>
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<tr>
<td>Low</td>
<td>11 (44)</td>
<td>11 (44)</td>
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</tr>
<tr>
<td>Intermediate</td>
<td>9 (36)</td>
<td>8 (32)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>5 (20)</td>
<td>6 (24)</td>
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</tr>
<tr>
<td>Stage</td>
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</tr>
<tr>
<td>0</td>
<td>6 (24)</td>
<td>9 (36)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7 (28)</td>
<td>4 (16)</td>
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<tr>
<td>2</td>
<td>10 (40)</td>
<td>12 (48)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2 (8)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number (%). ASA: American Society of Anesthesiologists, CEA: carcinoembryonic antigen, CA 15-3: cancer antigen 15-3, HER: human epidermal growth factor receptor type 2.

Syndecan-1 serum concentration

Serum concentrations of syndecan-1 significantly increased compared with baseline values over the sampled time points in both groups. When comparing syndecan-1 levels between groups, the propofol group showed significantly lower levels of syndecan-1 compared to the sevoflurane group at Situp<sub>10min</sub> (20.1 ± 1.4 vs. 25.2 ± 1.5 ng/ml; Bonferroni corrected P = 0.049), and at PO<sub>1h</sub> (23.8 ± 1.6 vs. 30.9 ± 1.7 ng/ml; Bonferroni corrected P = 0.012). In both groups, significantly elevated serum concentration of syndecan-1 was noted at Situp<sub>10min</sub> compared to the value at baseline (Intu<sub>10min</sub>), and this increase from baseline was also seen with syndecan-1 levels at PO<sub>1h</sub> (Fig. 3).

Postoperative recovery variables and complications

There was no significant difference in postoperative recovery variables and complications in two groups (Table 3). Four patients in the sevoflurane group (3 cases for hematoma evacuation and 1 for venous congestion and anastomosis re-exploration) and 1 patient in the propofol group (for hematoma evacuation) underwent re-operation (P = 0.349).
Postoperative hospital stay was 8.4 ± 2.5 days in the sevoflurane group and 7.4 ± 1.0 days in the propofol group (P = 0.077).

**Laboratory values**

Table 4 indicates the perioperative laboratory values. Patients in the propofol group showed significantly lower WBC and neutrophil count at 1 h after operation than those in the sevoflurane group (P = 0.022 and 0.014, respectively), whereas no differences in laboratory values between groups were found at POD1. The hemoglobin levels, lymphocyte counts, and platelet counts did not differ between the groups at any of the sampled time points.

**DISCUSSION**

This prospective, randomized, controlled trial is the first to compare syndecan-1 levels during sevoflurane-remifentanil and propofol-remifentanil anesthesia in breast cancer patients who underwent mastectomy with DIEP flap reconstruction. With propofol-remifentanil anesthesia, the increase in syndecan-1 levels was less pronounced than that with sevoflurane-remifentanil anesthesia. Our results also demonstrate that the choice of anesthetic can have a significant effect on the shedding of syndecan-1 following DIEP flap breast reconstruction.

Similar to disease states, surgical procedures are known to cause EG shedding, and when different surgical procedures are compared, the extent of increase in syndecan-1 levels differs, presumably due to the invasiveness of the procedure [13,16,19,20]. While syndecan-1 levels increased only 20% after a minimally invasive gastric cancer surgery [16], major abdominal surgeries can result in a 40–70% increase [19]. Increases of 30–40% were observed in patients who underwent lung resection [13]. While syndecan-1 levels increased by an average of 68% at 1 h after major abdominal surgery [16], major abdominal surgeries can result in a 40–70% increase [19]. Increases of 30–40% were observed in patients who underwent lung resection [13], while levels as high as 65 times that of the baseline value have been reported in patients who had been on cardiopulmonary bypass [20]. In the current study, syndecan-1 levels increased by an average of 68% at 1 h after operation, compared with the baseline levels. Such an increase is similar to that of increases after a major abdominal surgery [19]. Although it is a relatively superficial procedure,
**Fig. 2.** Perioperative changes in the (A) mean arterial pressure (MAP), (B) heart rate (HR), (C) pulse pressure variation (PPV), and (D) remifentanil effect-site concentration (Ce). Values represent the estimated means with standard error from linear mixed models. Baseline: pre-induction, Intu <sub>10min</sub>: 10 min after intubation, GS <sub>end</sub>: mastectomy end, Micro <sub>start</sub>: microscopic reanastomosis start, Micro <sub>30min</sub>: 30 min into microscopic reanastomosis, Micro <sub>end</sub>: microscopic reanastomosis end, Situp <sub>10min</sub>: 10 min after sitting position, OP <sub>end</sub>: end of operation, PO <sub>1h</sub>: 1 h after operation, Ce: effect-site concentration. *Bonferroni-corrected P < 0.050 vs. sevoflurane group.

**Fig. 3.** Serum concentration of syndecan-1. Values represent the estimated means with standard error from linear mixed models. Intu <sub>10min</sub>: 10 min after intubation, Situp <sub>10min</sub>: 10 min after sitting position, PO <sub>1h</sub>: 1 h after operation. *Bonferroni-corrected P < 0.050 vs. sevoflurane group. †Bonferroni-corrected P < 0.050 vs. Intu <sub>10min</sub>. Diep can cause as much of an increase in syndecan-1 levels as major abdominal surgery, presumably, due to 1) the long duration of the surgical procedures, which often lasts several hours, and 2) the occurrence of ischemia–reperfusion injury during flap harvesting and subsequent revascularization.

When the two groups were compared, in the propofol group, the percentage of increase in syndecan-1 levels was 21% and 47% at 10 min after sit-up and 1 h after operation, respectively, whereas in the sevoflurane group, the percentage of increase was 57% at 10 min after sit-up and 93% at 1 h after operation. This difference in percentage increase between groups is significant enough to be comparable to the difference in syndecan-1 levels observed among four different surgical procedures [13,16,19,20]. To reiterate, our results indicate that the choice of anesthetics for mastectomy and


### Table 3. Postoperative Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sevoflurane group (n = 25)</th>
<th>Propofol group (n = 25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of recovery room stay (min)</td>
<td>46 ± 12</td>
<td>50 ± 14</td>
<td>0.235</td>
</tr>
<tr>
<td>Postoperative hospital stays (days)</td>
<td>8.4 ± 2.5</td>
<td>7.4 ± 1.0</td>
<td>0.077</td>
</tr>
<tr>
<td>Patients transfused within postoperative (48 h)</td>
<td>6 (26)</td>
<td>2 (8)</td>
<td>0.130</td>
</tr>
<tr>
<td>Postoperative adjuvant treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>4 (16)</td>
<td>3 (12)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Radiation</td>
<td>9 (36)</td>
<td>7 (28)</td>
<td>0.544</td>
</tr>
<tr>
<td>Immunotherapy</td>
<td>5 (20)</td>
<td>2 (8)</td>
<td>0.417</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td>14 (56)</td>
<td>19 (76)</td>
<td>0.136</td>
</tr>
<tr>
<td>Postoperative complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reoperation</td>
<td>4 (16)</td>
<td>1 (4)</td>
<td>0.349</td>
</tr>
<tr>
<td>Flap detachment</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Hematoma</td>
<td>3 (12)</td>
<td>1 (4)</td>
<td>0.609</td>
</tr>
<tr>
<td>Wound dehiscence</td>
<td>1 (4)</td>
<td>1 (4)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Venous congestion</td>
<td>2 (12)</td>
<td>1 (4)</td>
<td>0.609</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number (%).

### Table 4. Perioperative Laboratory Values

<table>
<thead>
<tr>
<th>Variable</th>
<th>Sevoflurane group (n = 25)</th>
<th>Propofol group (n = 25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>White blood cell count (10^9/μl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre&lt;sub&gt;op&lt;/sub&gt;</td>
<td>6.1 ± 2.7</td>
<td>5.9 ± 2.5</td>
<td>0.828</td>
</tr>
<tr>
<td>PO&lt;sub&gt;1&lt;/sub&gt;</td>
<td>13.2 ± 3.7</td>
<td>11.1 ± 2.9</td>
<td>0.022</td>
</tr>
<tr>
<td>POD&lt;sub&gt;1&lt;/sub&gt;</td>
<td>10.2 ± 2.5</td>
<td>9.5 ± 2.7</td>
<td>0.821</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre&lt;sub&gt;op&lt;/sub&gt;</td>
<td>12.6 ± 1.4</td>
<td>12.6 ± 1.8</td>
<td>0.916</td>
</tr>
<tr>
<td>PO&lt;sub&gt;1&lt;/sub&gt;</td>
<td>10.0 ± 1.2</td>
<td>10.3 ± 1.2</td>
<td>0.350</td>
</tr>
<tr>
<td>POD&lt;sub&gt;1&lt;/sub&gt;</td>
<td>9.0 ± 1.6</td>
<td>9.6 ± 1.4</td>
<td>0.220</td>
</tr>
<tr>
<td>Neutrophil count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre&lt;sub&gt;op&lt;/sub&gt;</td>
<td>3.8 ± 2.3</td>
<td>3.7 ± 2.2</td>
<td>0.940</td>
</tr>
<tr>
<td>PO&lt;sub&gt;1&lt;/sub&gt;</td>
<td>11.0 ± 3.3</td>
<td>8.9 ± 2.4</td>
<td>0.014*</td>
</tr>
<tr>
<td>POD&lt;sub&gt;1&lt;/sub&gt;</td>
<td>8.5 ± 2.2</td>
<td>7.8 ± 2.7</td>
<td>0.912</td>
</tr>
<tr>
<td>Lymphocyte count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre&lt;sub&gt;op&lt;/sub&gt;</td>
<td>1.8 ± 0.6</td>
<td>1.7 ± 0.6</td>
<td>0.559</td>
</tr>
<tr>
<td>PO&lt;sub&gt;1&lt;/sub&gt;</td>
<td>1.4 ± 0.6</td>
<td>1.3 ± 0.7</td>
<td>0.701</td>
</tr>
<tr>
<td>POD&lt;sub&gt;1&lt;/sub&gt;</td>
<td>0.9 ± 0.3</td>
<td>0.9 ± 0.4</td>
<td>0.612</td>
</tr>
<tr>
<td>Platelet count</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre&lt;sub&gt;op&lt;/sub&gt;</td>
<td>285 ± 80</td>
<td>262 ± 80</td>
<td>0.312</td>
</tr>
<tr>
<td>PO&lt;sub&gt;1&lt;/sub&gt;</td>
<td>205 ± 73</td>
<td>185 ± 47</td>
<td>0.250</td>
</tr>
<tr>
<td>POD&lt;sub&gt;1&lt;/sub&gt;</td>
<td>181 ± 54</td>
<td>182 ± 51</td>
<td>0.588</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. Pre<sub>op</sub>: pre-operation, PO<sub>1</sub>: 1 h after operation, POD<sub>1</sub>: 1st postoperative day. *Bonferroni corrected P < 0.05/3 = 0.017.

DIEP flap reconstruction can cause vastly different levels of increase in syndecan-1 levels. Inhalation anesthetics exerts some protective effects against EG degradation from ischemia–reperfusion injury [11,12]; however, clinical results have been inconclusive [13-15]. The results of the present study are more consistent with those of another study in which patients who underwent minimally invasive gastrectomy exhibited lower levels of syndecan-1 in the immediate postoperative period with propofol-remifentanil anesthesia than with sevoflurane-remifentanil anesthesia [16]. It should be noted that, since both propofol and sevoflurane anesthesia are balanced...
anesthesia techniques utilizing opioids, the effect of remifentanil combined with either propofol or sevoflurane needs to be considered when interpreting the results. In addition, in this study, the lower white blood cell and neutrophil counts in the propofol compared to the sevoflurane group at 1 h after surgery also indicate reduced inflammation. However, definitive conclusions regarding the mechanisms by which EG degradation occurs in DIEP flap reconstruction surgery and the effect of different anesthetic agents on these mechanisms cannot be made in the present study, and further experimental studies and clinical trials are needed.

DIEP flap surgery is a complex procedure that requires meticulous management of fluid input and output, maintenance of adequate perfusion, judicious use of vaspressors, and other manipulations to avoid or minimize thrombosis \[10\]. EG degradation can lead to interstitial edema due to increased vascular permeability, or thrombosis due to deranged hemostasis \[2,3\]. Therefore, focusing on the prevention of EG shedding could be an important strategy to improve the survival rates of flap in patients following DIEP flap reconstruction surgery. We propose to choose an anesthetic that minimizes syndecan-1 shedding, whenever possible.

A study reported an incidence of free flap failure of 0.9% \[21\], and another study, which examined 956 flap surgeries, reported that 48 out of those cases required revision, which is equal to 5% \[22\]. Considering the incidence of these complications, the present study was probably unable to detect differences in the incidence of revision or postoperative complications due to insufficient number of study subjects; future studies are hence warranted.

It should further be mentioned that the administered dose of norepinephrine was significantly lower in the propofol group than in the sevoflurane group. Although poor free flap perfusion as a consequence of vasopressor use is not robustly supported by reliable prospective clinical evidence, it remains a concern for many surgeons \[23,24\]. While MAP and PPV were similar in both groups, significantly lower doses of norepinephrine were administered in the propofol group to maintain statistically similar hemodynamics during the procedure. This could be another advantage of propofol-remifentanil anesthesia over sevoflurane-remifentanil anesthesia for DIEP flap breast reconstruction surgery.

This study has a few limitations that need to be mentioned. First, the last measurement of syndecan-1 was performed at 1 h after the operation, and we did not obtain samples for the analysis of syndecan-1 level thereafter. Peak syndecan-1 levels are thought to occur in the 24-h period after the main insult; however, we were unable to draw any conclusions regarding those syndecan-1 trends. This shortcoming should be addressed in future studies. Secondly, although our study was sufficiently powered to detect significant differences in syndecan-1 levels, it could not detect differences in the incidences of revision rates or postoperative complications. This will also need to be addressed in a further study, focused on the incidence of postoperative complications. Third, we did not measure ischemia time of the free flap, more specifically, the time from the end of flap harvesting to start of revascularization, which is known to influence the degree of ischemia-reperfusion injury. Finally, in the present study, the remifentanil dose administered was not controlled between the two groups, being consistently higher in the propofol group than in the sevoflurane group. This increased dosage of remifentanil may affect less increased level of syndecan-1 observed in propofol group \[25\]. Remifentanil which is a potent µ receptor agonist is known to exert immunosuppressive effects. Moreover, there are several proposed mechanisms and sites of action including a direct action on immunocytes, and modulation of the hypothalamic-pituitary-adrenal axis, sympathetic activity, and central immunity \[26,27\]. However, Zongze et al. \[28\] showed that remifentanil had a protective effect against sepsis via both suppression of inflammatory factor production and the inducible nitric oxide synthase expression. Thus, such confounding factors including ischemic time, dosage of remifentanil, total operation, and reconstruction time other than propofol, may have influenced our results. Therefore, further controlled studies are necessary.

In conclusion, propofol-remifentanil anesthesia led to a reduced increase in syndecan-1 levels compared to sevoflurane-remifentanil anesthesia in patients with breast cancer undergoing mastectomy and DIEP flap breast reconstruction. We demonstrated that DIEP flap breast reconstruction results in a significant increase in syndecan-1 levels, suggesting that it is associated with substantial EG degradation. Furthermore, the results suggest that propofol-remifentanil anesthesia may have a beneficial effect on free flap survival compared to sevoflurane-remifentanil anesthesia when used in patients undergoing mastectomy and DIEP flap breast reconstruction. Further large-scale controlled experimental studies and clinical trials are needed.

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the Korean Society of Anesthesiologists.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article but are available from the corresponding author on reasonable request.

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REFERENCES


Comparison of the effect of dexmedetomidine and midazolam under spinal anesthesia for cesarean delivery: a randomized controlled trial, single center study in South Korea

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Department of Anesthesiology and Pain Medicine, Nowon Eulji University Hospital, Seoul, Korea

Background: Cesarean section under spinal anesthesia may cause anxiety and hypotension. Administration of sedative drugs after delivery can diminish these side-effects, but may increase hemodynamic instability. We evaluated the effect of the administration of 0.7 μg/kg dexmedetomidine and compared it with that of 0.03 mg/kg midazolam for usefulness of sedation of the parturient after delivery during cesarean section.

Methods: After obtaining written consent and the ethics board approval, 60 parturients aged 20–43 years who underwent elective cesarean delivery under spinal anesthesia were recruited. A total of 0.5% hyperbaric bupivacaine (8–10 mg) and intrathecal fentanyl (10 μg) was given to induce anesthesia. Parturients were then randomly allocated to receive either midazolam (0.03 mg/kg; group M) or dexmedetomidine 0.7 (μg/kg; group D) after delivery. The primary outcome measure was patient satisfaction score. Secondary outcomes included vital signs; vasopressor dosage; incidence of shivering, nausea, and vomiting; incidence of bradycardia; time to sensory and motor recovery; postoperative nausea and vomiting score; and postoperative pain visual analog scale at 6, 24, and 48 h.

Results: Satisfaction scores for sedation were similar between the two groups. The systolic blood pressure, heart rate, oximetry saturation, and tympanic temperature were comparable between the two groups. The predicted mean systolic blood pressure of group D was 106.3 mmHg and that of group M was 107.5 mmHg. Both groups showed comparable adverse intraoperative and postoperative outcomes.

Conclusions: Dexmedetomidine and midazolam showed similar hemodynamic effects and patient satisfaction in parturients under spinal anesthesia.

Keywords: Cesarean section; Dexmedetomidine; Midazolam; Spinal anesthesia.

INTRODUCTION

Spinal anesthesia is one of the preferred routes of anesthesia administration for cesarean section [1]. It minimizes the side-effects of drugs on the fetus and provides rapid anesthesia for parturients. However, sympathetic vasomotor blockade effects, such as hypotension, nausea and vomiting, and shivering, can negatively affect the anesthesia experience of the parturient. Moreover, in a previous report of 5,080 cesarean sections in the United Kingdom, 6% of the
patients receiving spinal anesthesia did not experience completely pain free anesthesia and required conversion to general anesthesia or additional sedation or analgesia [2]. The role of the anesthesiologist is to provide a safe and comfortable anesthetic experience and help the parturient recover quickly without adverse effects.

Dexmedetomidine is a highly selective a2 agonist and widely used sedative drug during spinal anesthesia that causes sleep-like sedation, opioid sparing analgesia, analgesia, and organ protection [3,4]. Intravenous dexmedetomidine has been successfully used in parturients undergoing cesarean section with chronic spinal cord injury [5], as well as tethered cord syndrome [6]. However, dexmedetomidine is generally believed to have side-effects of hypotension and bradycardia [7,8]. Moreover, the simultaneous use of phenylephrine to prevent hypotension during cesarean section adds concerns of bradycardia. In contrast, midazolam is known for its hemodynamic stability and is widely used for sedation during cesarean section. Dexmedetomidine, 0.3 μg/kg, was effective in reducing shivering without hypotension in a parturient after spinal anesthesia during cesarean section. However, this low dose could not provide satisfactory sedation [9].

Here, we tried to evaluate the effect of 0.7 μg/kg dexmedetomidine and compare it with that of 0.03 mg/kg midazolam to maintain sedation equivalent to Ramsay sedation score of 3. This study aimed to compare the efficacy of intravenously administered dexmedetomidine and midazolam for postpartum sedation. We hypothesized that dexmedetomidine would provide better sedation satisfaction than midazolam with similar hemodynamic effects.

**MATERIALS AND METHODS**

1. **Study design**

This single-center, prospective, randomized controlled trial was conducted between November, 2021 and October, 2022 at the Nowon Eulji University Hospital. After obtaining approval from the Hospital Review Board (IRB no. 2021-09-018), the trial was registered in the UMIN clinical trial registry (trial identifier: UMIN000053324) prior to patient enrollment. This study was conducted in accordance with the Consolidated Standards for Reporting Trials guidelines.

Informed consent was obtained from all participants. Parturients aged 20–43 years with American Society of Anesthesiology physical status I or II who underwent elective cesarean delivery under spinal anesthesia were recruited. Exclusion criteria included patient refusal, preeclampsia, eclampsia, gestational hypertension, placenta previa, placenta accreta, placental abruption, American Society of Anesthesiology physical status III, multiple pregnancies, contraindications for spinal anesthesia, body mass index (BMI) > 39 kg/m², and gestational age less than 34 weeks. All the surgeries were performed by a single surgeon.

Demographic data, including age, weight, American Society of Anesthesiology class, comorbidities, gestational age, and history of pregnancy, were collected from all parturients. The investigators and patients were blinded to the group allocation. The patients were randomly assigned to the dexmedetomidine (group D, n = 30) or midazolam (group M, n = 30) group by an independent investigator who was not involved in anesthesia administration. Randomization was achieved using a web-based computer-generated list (www.randomization.com), and the patients numbers were placed in opaque sealed envelopes that were opened in the operating room by an independent anesthesiologist. The anesthesiologist was aware of the allocated group but only followed the anesthetic protocol of our study. Therefore, the data assessors were blinded but the caregivers were not.

2. **Anesthetic protocol**

All parturients were maintained on a nil per os diet for 8 h prior to anesthesia. Standard monitoring (electrocardiography, noninvasive blood pressure, and pulse oximetry saturation [SpO2]) was performed for each parturient after admission into the operating room. Systolic blood pressure (SBP) was checked at 1 min intervals until the babies were removed and then checked at 5 min intervals. All parturients were treated with prewarmed Hartmann’s solution (10 ml/kg) for 20 min to prevent hypotension. If the blood pressure decreased more than 20% from baseline pressure or the SBP decreased less than 90 mmHg, phenylephrine 50 μg was administered. Subsequently, 25–50 μg phenylephrine was administered according to the parturient’s response to phenylephrine at the anesthesiologist’s discretion. Ephedrine (4 mg) was administered if the heart rate was less than 50 min and the SBP was < 90 mmHg. Bradycardia was defined as a heart rate less than 50 bpm. When the heart rate was less than 45 bpm, glycopyrrolate 0.2 mg was administered. Single-shot spinal anesthesia was administered for cesarean delivery. The spinal anesthesia was administered at the L3-
L4 interspace. Intrathecal injection of 8–10 mg 0.5% bupivacaine and 10 mcg fentanyl was performed. A pinprick test was used to confirm adequate sensory nerve block at T4–T6. After delivery of the fetus and placenta, 0.1 mg carbetocin was injected, and Hartmann’s solution mixed with 10 units of oxytocin was continued at a rate of 30 ml/h. After carbetocin infusion, the patients in group D received 0.7 μg/kg intravenous dexmedetomidine. Group M received 0.03 mg/kg intravenous midazolam. The detailed drug preparation process was as follows. A single investigator responsible for the group assignments prepared the bolus and infused solution of the study drug. For preparation of a bolus of the study drug, either 0.9% isotonic saline (group D) or midazolam (0.03 mg/kg; group M) was diluted in 0.9% isotonic saline to a final volume of 5 ml in a 5 ml polyethylene syringe. For preparation of the loading dose of the study drug, 50 ml of either 0.9% isotonic saline (group M) or 0.7 μg/kg dexmedetomidine (diluted 4 μg per ml) was added in a 50 ml polyethylene syringe, which was labelled as “Loading X.” The loading dose was administered for 10 min.

Sedation was graded according to the Ramsay sedation scale at 10 min interval until the end of surgery. The target maintained sedation level was a Ramsay sedation scale score of 3. After surgery, the parturient was transported to the postanesthetic care unit (PACU). After sensory-level regression was achieved at T10, the parturient was transported to the ward. The parturient was administered intravenous patient-controlled analgesia with 900 μg fentanyl, 100 mg nefopam, and 0.075 mg palonosetron, diluted with normal saline to a total volume 100 ml (continuous, 2 ml/h; bolus, 0.5 ml; lockout 15 min), using a patient-controlled analgesia device for the postoperative 48 h.

3. Outcome measures

Hemodynamic parameters, such as heart rate, systolic blood pressure, SpO₂, and tympanic temperature, were recorded as follows: baseline; 5 min after spinal drug injection; baby out; 10 min after study drug administration; 30 min after study drug administration; end of surgery; and 10 min, 30 min, and 50 min after arrival in the PACU. All parameters were recorded by a coinvestigator who did not assign a group allocation and was not involved in the anesthesia practice. The recovery time at the motor level was checked until a modified Bromage Scale score of 2 was achieved. The recovery time of the sensory level was checked until a regression of the sensory level at T10 was obtained.

1) Primary outcomes

The primary outcome was the patient satisfaction score. Patient satisfaction scores were checked for intra- and postoperative experiences 6 h after the ward transfer. Table 1 provides questions regarding sedation during surgery and the experience in the PACU.

2) Secondary outcomes

Secondary outcomes were vital signs, including SBP, heart rate, oxygen saturation, and tympanic temperature, overall vasopressor dosage, incidence of shivering, nausea and vomiting (Table 2), incidence of bradycardia, time to sensory and motor recovery, and postoperative nausea and vomiting (PONV) score and postoperative pain visual analogue scale (VAS) score at 6, 24, 48 h after discharge from the PACU.

4. Statistical analysis

We calculated a sample size of 21 patients for each group based on data from a pilot study of ten cases in each group, as no previous studies were available. In the pilot study, the mean and standard deviation value of satisfaction score in the two predefined groups were 2.8 ± 0.4 and 2.2 ± 0.6, respectively. Thus, the effect size of the two groups was assumed to be 1.18. A sample size of 21 patients was derived for each group, calculated using the Wilcoxon–Mann–Whitney test, two-tailed, with significance level of 0.05, and a power of 0.95 (G power 3.1, Brunsbüttel). This was an exploratory study. For a better estimation of clinical relevance, 30 parturients were enrolled in each group. An independent two-sample t-test was used for normally distributed continuous variables, and data were presented as mean and standard deviation. The Mann–Whitney U test was used to as-

Table 1. Tools for Assessing the Intra- and Postoperative Satisfaction Quality Between the Two Groups

<table>
<thead>
<tr>
<th>Survey for Sedation during Surgery</th>
<th>Survey for Experience during PACU</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Inability to sleep at all</td>
<td>1. Felt uncomfortable and anxious in the PACU</td>
</tr>
<tr>
<td>2. Sleepy but unable to sleep well</td>
<td>2. Stayed awake and remembered everything but felt comfortable</td>
</tr>
<tr>
<td>3. Slept well</td>
<td>3. Had trouble remembering and felt drowsy in the PACU</td>
</tr>
<tr>
<td>4. Had trouble remembering even when in the infirmary</td>
<td>4. Had trouble remembering even when in the infirmary</td>
</tr>
</tbody>
</table>

PACU: postanesthetic care unit.
assess patient satisfaction scores. The Fisher’s exact test or chi-squared test was used for categorical variables (incidence of shivering, nausea and vomiting, bradycardia, and hypothermia). A two-way ANOVA with a mixed-effects model was used to analyze the change in SBP, heart rate, SpO₂, temperature, and sedation score between the two groups. The GraphPad Prism 9.0 software (GraphPad Inc.) was used for the analysis. Statistical significance was set at P < 0.050.

RESULTS

Sixty-four parturients were screened for inclusion in this study. Among them, three parturients did not meet the criteria, and one parturient declined to participate in the study (Fig. 1). Finally, 60 parturients completed the study, and randomization was performed using a computerized method. As a result, 30 parturients each were randomized to the dexmedetomidine (group D) and midazolam (group M) groups. Demographic characteristics (primipara, gestational age, weight, height, and BMI) and duration of surgery were similar between the two groups. The total fluid intake was higher in group D, and the highest block levels were similar. There were no differences in perioperative outcomes (Table 3). There was no significant difference in the median (1Q, 3Q) patient satisfaction scores during surgery or in the PACU (P > 0.050) (Table 4). Satisfaction score for rating the experience during surgery was asked at the time of postoperative 6 h: 15 parturients in group D (50.0%) answered that they slept well during surgery, the other 15 parturients (50.0%) answered they felt sleepful; 11 parturients in group M (36.7%) felt that they slept well, but 4 parturients (13.0%) answered that they could not sleep at all. Regarding the experience in the PACU, 24 (80.0%) and 22 (73.3%) parturients in each group, respectively, answered that they stayed awake and felt comfortable (Table 4). SBP was similar between the two groups. The predicted mean of SBP was 106.3 mmHg in group D and 107.5 mmHg in group M (Fig. 2A). Heart rate was similar between the two groups. Predicted mean of group D was 74 min and that of group M was 77 min; the difference between the predicted means was −3.2 min (Fig. 2B). In addition, vasopressor dosage and bradycardia incidence did not differ between the two groups. Oxygen saturation levels were similar between the two groups (Fig. 2C). Predicted mean oxygen saturation was 99% in both in groups. Temperatures were similar between the two groups (Fig. 2D). Predicted mean temperature of both groups was 36.0°C. Mean sedation score was 3.2 ± 1.0 in group D and 3.6 ± 1.2 in group M at 10 min after drug administration, whereas, at 30 min after the drug administration, the scores were 3.6 ± 1.0 in group D and 3.0 ± 1.2 in group M (Fig. 3). However, there was no difference in the sedation scores at each time point between the two groups.

For postoperative outcome measures, we evaluated the PONV score and VAS pain at rest, during movement, and at the worst VAS (uterine contraction pain) (Table 5). There were no differences in PONV and VAS scores at postoperative 6 h, 24 h, and 48 h.

DISCUSSION

This randomized controlled study demonstrated that 0.7 μg/kg dexmedetomidine and 0.03 mg midazolam provide

<table>
<thead>
<tr>
<th>Grade of shivering</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No shivering</td>
</tr>
<tr>
<td>1</td>
<td>One or more of the following: piloerection, peripheral vasoconstriction, peripheral cyanosis, but without visible muscle activity</td>
</tr>
<tr>
<td>2</td>
<td>Visible muscle activity confined to one muscle group</td>
</tr>
<tr>
<td>3</td>
<td>Visible muscle activity in more than one muscle group</td>
</tr>
<tr>
<td>4</td>
<td>Gross muscle activity involving the whole body</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade of nausea</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No nausea</td>
</tr>
<tr>
<td>1</td>
<td>Mild nausea</td>
</tr>
<tr>
<td>2</td>
<td>Moderate nausea</td>
</tr>
<tr>
<td>3</td>
<td>Severe or intense nausea</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ramsay sedation scale</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Patient awake, anxious, agitated, restless</td>
</tr>
<tr>
<td>2</td>
<td>Patient awake, cooperative, oriented, tranquil</td>
</tr>
<tr>
<td>3</td>
<td>Patient awake, responsive to commands only</td>
</tr>
<tr>
<td>4</td>
<td>Patient asleep, brisk response to light glabellar tap or loud auditory stimulus</td>
</tr>
<tr>
<td>5</td>
<td>Patient asleep, sluggish response to light glabellar tap or loud auditory stimulus</td>
</tr>
<tr>
<td>6</td>
<td>Patient asleep, no response to light glabellar tap or loud auditory stimuli</td>
</tr>
</tbody>
</table>
Fig. 1. Flow diagram based on CONSORT statement. CONSORT: Consolidated Standards for Reporting of Trials.

Table 3. Demographic Data and Perioperative Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group D (n = 30)</th>
<th>Group M (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>35.2 ± 3.0</td>
<td>35.2 ± 5.3</td>
<td>0.402</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.8 ± 9.9</td>
<td>71.9 ± 9.8</td>
<td>0.697</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>160.1 ± 5.2</td>
<td>159.1 ± 5.8</td>
<td>0.850</td>
</tr>
<tr>
<td>ASA (I/II)</td>
<td>7/23</td>
<td>8/22</td>
<td>0.635</td>
</tr>
<tr>
<td>Gestational age (wk)</td>
<td>38.1 ± 2.1</td>
<td>37.9 ± 1.8</td>
<td>0.545</td>
</tr>
<tr>
<td>Premi/multi</td>
<td>20/10</td>
<td>16/14</td>
<td>0.291</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>51.6 ± 11.4</td>
<td>53.9 ± 20.4</td>
<td>0.599</td>
</tr>
<tr>
<td>Block level (T)</td>
<td>4.3 ± 0.8</td>
<td>4.0 ± 0.7</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Total fluid intake (ml)</td>
<td>1,425 ± 479</td>
<td>1,558 ± 391*</td>
<td>0.040</td>
</tr>
<tr>
<td>Total phentolamine used (μg)</td>
<td>122.5 ± 89.4</td>
<td>96.2 ± 93.0</td>
<td>0.470</td>
</tr>
<tr>
<td>Total ephedrine used (mg)</td>
<td>2.5 ± 2.7</td>
<td>4.2 ± 5.3</td>
<td>0.296</td>
</tr>
<tr>
<td>Shivering score (0/1/2/3)</td>
<td>26/4/0/0/0</td>
<td>23/3/3/1/0</td>
<td>0.217</td>
</tr>
<tr>
<td>Nausea score (0/1/2/3)</td>
<td>27/0/1/2</td>
<td>29/0/1/0</td>
<td>0.697</td>
</tr>
<tr>
<td>Postdelivery bradycardia</td>
<td>3</td>
<td>1</td>
<td>0.300</td>
</tr>
<tr>
<td>Hypothermia (&lt; 35°C)</td>
<td>1</td>
<td>1</td>
<td>0.999</td>
</tr>
<tr>
<td>Time to sensory T10 (min)</td>
<td>133.2 ± 35.5</td>
<td>133.4 ± 16.0</td>
<td>0.986</td>
</tr>
<tr>
<td>Time to motor G2 (min)</td>
<td>93.5 ± 25.3</td>
<td>114.6 ± 15.4</td>
<td>0.090</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number only. ASA: American Society of Anesthesiologists. Group D: parturients who received 0.7 μg/kg dexmedetomidine, Group M: parturients who received 0.03 mg/kg midazolam. *Group D vs. group M, t-test, P < 0.050.
Table 4. Satisfaction Score

<table>
<thead>
<tr>
<th></th>
<th>Group D (n = 30)</th>
<th>Group M (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>During surgery</td>
<td>2.5 (2, 3)</td>
<td>2.5 (2, 3)</td>
<td>0.143</td>
</tr>
<tr>
<td>Number of patients</td>
<td>0/15/15</td>
<td>4/15/11</td>
<td></td>
</tr>
<tr>
<td>In the PACU</td>
<td>2 (2, 2)</td>
<td>2 (2, 2)</td>
<td>0.633</td>
</tr>
<tr>
<td>Number of patients</td>
<td>2/24/4/0</td>
<td>2/22/6/0</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as median (1Q, 3Q) or number only. None of the differences between the groups were statistically significant. PACU: postanesthetic care unit. Group D: parturients who received 0.7 μg/kg dexmedetomidine, Group M: parturients who received 0.03 mg/kg midazolam. Satisfaction score for sedation during surgery: 1, inability to sleep at all; 2, sleepy but unable to sleep well; and 3, slept well. Satisfaction score in the PACU: 1, felt uncomfortable and anxious in the PACU; 2, stayed awake and remembered everything but felt comfortable; 3, had trouble remembering and felt drowsy in the PACU; and 4, had trouble remembering even when in the infirmary.

Fig. 2. Changes in the systolic blood pressure (A), heart rate (B), SPO$_2$ (C), and body temperature (D). The graphs show the mean value and standard deviation of each variable for each time point during spinal anesthesia and at the PACU. All data were collected baseline, 5 min after induction of anesthesia, at the time of baby out, 10 min and 30 min after the drug administration at the end of surgery, and 10 min and 30 min at the PACU. SPO$_2$: oxygen saturation, PACU: postanesthetic care unit. Group D (●): parturients who received 0.7 μg/kg dexmedetomidine, Group M (□): parturients who received 0.03 mg/kg midazolam. All data are comparable at each time point between group D and group M.
similar hemodynamic effects and satisfactory sedation. In addition, there are few side-effects, such as nausea and vomiting, and the same requirement for vasopressor dosage. Parturients in each group had similar postoperative pain scores at rest, during movement, and during uterine contractions. In addition, a low incidence of shivering was observed in both groups.

In this study, we focused on the hemodynamic effects of dexmedetomidine during cesarean section under spinal anesthesia for several reasons.

Dexmedetomidine may induce biphasic hemodynamic alterations. Alpha-2–mediated vasoconstriction may result in transient tachycardia and elevated blood pressure. However, once the baroreceptor is upregulated and the vagal tone is activated, dexmedetomidine may induce hypotension with sympatholytic effects as a result of the reduced release of norepinephrine. In pregnant women, baseline heart rate, stroke volume, and cardiac output are already increased to meet the metabolic demand of the fetus; impairing the compensation of cardiovascular effects may affect parturient’s baseline cardiovascular function and cause organ damage [10]. However, in this study, our dexmedetomidine regimen resulted in hypotension similar to that of midazolam during uterine manipulation and placental separation after the baby was removed. The predicted mean SBP was 107 and 106 mmHg in the dexmedetomidine and midazolam groups, respectively. The difference in the mean predicted heart rate between the two groups was only 3 bpm.

It is assumed that a sudden decrease in heart rate is most prominent immediately after spinal anesthesia within 10 min, considering that induction delivery time usually take 5–10 min in the case of uncomplicated cesarean section in our study. In addition, the hemodynamic effect of carbexocin may increase the heart rate, which may affect this finding [11].

![Fig. 3. The change in Ramsay sedation score in the two groups. Group D (○): parturients who received 0.7 μg/kg dexmedetomidine, Group M (■): parturients who received 0.03 mg/kg midazolam. There is no difference between the sedation scores of group D and group M. T1: 10 min after drug administration, T2: 20 min after drug administration, T3: 30 min after drug administration, and T4: end of surgery.](image)

Table 5. Postoperative Outcomes

<table>
<thead>
<tr>
<th>Postoperative outcome</th>
<th>Group D (n = 30)</th>
<th>Group M (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PONV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 h</td>
<td>0.7 ± 1.1</td>
<td>0.5 ± 0.9</td>
<td>0.426</td>
</tr>
<tr>
<td>24 h</td>
<td>0.2 ± 0.6</td>
<td>0.4 ± 1.0</td>
<td>0.402</td>
</tr>
<tr>
<td>48 h</td>
<td>0.2 ± 0.5</td>
<td>0.1 ± 0.4</td>
<td>0.404</td>
</tr>
<tr>
<td>VAS for pain at rest</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 h</td>
<td>4.0 ± 2.0</td>
<td>3.6 ± 1.9</td>
<td>0.443</td>
</tr>
<tr>
<td>24 h</td>
<td>3.0 ± 1.6</td>
<td>2.8 ± 1.4</td>
<td>0.713</td>
</tr>
<tr>
<td>48 h</td>
<td>2.0 ± 1.4</td>
<td>1.9 ± 1.0</td>
<td>0.808</td>
</tr>
<tr>
<td>VAS for pain at movement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 h</td>
<td>5.2 ± 2.4</td>
<td>5.0 ± 1.8</td>
<td>0.631</td>
</tr>
<tr>
<td>24 h</td>
<td>4.3 ± 2.1</td>
<td>4.4 ± 1.8</td>
<td>0.802</td>
</tr>
<tr>
<td>48 h</td>
<td>3.5 ± 2.0</td>
<td>3.0 ± 1.3</td>
<td>0.338</td>
</tr>
<tr>
<td>VAS for worst pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 h</td>
<td>5.8 ± 2.1</td>
<td>5.5 ± 1.9</td>
<td>0.124</td>
</tr>
<tr>
<td>24 h</td>
<td>4.5 ± 2.1</td>
<td>4.9 ± 1.7</td>
<td>0.480</td>
</tr>
<tr>
<td>48 h</td>
<td>3.9 ± 2.1</td>
<td>3.5 ± 1.5</td>
<td>0.381</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. PONV: postoperative nausea and vomiting. VAS: visual analog scale. Group D: parturients who received 0.7 μg/kg dexmedetomidine, Group M: parturients who received 0.03 mg/kg midazolam.
Furthermore, our dexmedetomidine dosage was an appropriate option even under a high vagal tone. Only 3 patients among 30 reported bradycardia under 45 bpm and were treated well with ephedrine or atropine after the baby was delivered. However, Kim and Ahn [7] reported a higher incidence of bradycardia when dexmedetomidine was administered during spinal anesthesia. They suggested that initial heart rate was a significant individual predictive factor for the occurrence of bradycardia during dexmedetomidine use [7]. In this study, mean heart rate after baby out in group D was 81.3 ± 12.4. The most profound decrease in the heart rate of dexmedetomidine was observed at 10 min after the loading infusion.

Commonly used sedation agents include midazolam, ketamine, fentanyl, and propofol but the risks from these agents include, but are not limited to, apnea, hallucination, and impaired memory function [12]. Intravenous dexmedetomidine is commonly used for sedation in the nonpregnant patient population through a site in the locus coeruleus and dorsal raphe nucleus; it mimics natural sleep and produces analgesia [13]. Dexmedetomidine is a suitable adjuvant to spinal anesthesia due to its more selective α-2A receptor agonist activity and by acting at the spinal level, laminae VII and VIII of ventral horns. These actions are likely to prolong spinal anesthesia after intravenous dexmedetomidine administration [14]. However, in this study, we did not observe prolongation of the block compared to midazolam. Sivachalam et al. [15] compared the effects of dexmedetomidine and midazolam on the duration of spinal anesthesia and found a prolonged mean time for two dermatomal regressions with dexmedetomidine. We used only the loading dose and measured the sensory recovery time to the T10 sensory level and not the two-level regression time.

Dexmedetomidine increases the frequency of smooth muscle contractions in the uterus [16]. There is a predomiance over alpha-2 receptors over alpha-1 in the human myometrium. These effects may have hindered the prolongation of sensory block by dexmedetomidine in our results. Intraoperative dose of 0.7 μg/kg dexmedetomidine for a short duration did not affect the postoperative contraction pain characteristics. Pain scores in both groups were similar. Therefore, parturients experienced similar satisfaction during surgery and during the PACU experience. Therefore, the contraction effect on the uterus, if any, may be temporary and not very large at our utilized dose. Additionally, our dexmedetomidine regimen did not increase the incidence of bradycardia or hypotension. The overall phenylephrine dose was slightly higher in the dexmedetomidine group; however, the difference was not statistically significant. We did not use prophylactic phenylephrine infusion in our study because we tried to measure the effect of blood pressure on each study drug effect. Instead, we used hydration with a crystalloid solution before and during spinal anesthesia.

Xiong et al. [17] reported that ED₉₀ of dexmedetomidine for adequate sedation in postpartum parturients was 1.58 μg/kg, but they made the calculation with the adjusted body weight formula and not exact body weight, and the infusion duration was 15 min; finally, their sedation level was deep, which refers to a observer’s alertness sedation score of less than 3. Hu et al. [18] studied 1 μg/kg of dexmedetomidine and compared its effect with saline or midazolam (0.02 mg/kg). They found equal efficacy in preventing nausea and vomiting after spinal anesthesia.

Our study had several limitations. First, the sample size calculation was based on our pilot study because there were no similar previous studies. Therefore, future studies with a larger number of patients may be required to confirm our findings. Second, during the loading dose infusion, carbetocin bolus injection was simultaneously administered; therefore, vital signs during the early periods of drug injection may be affected by other factors.

Third, we measured satisfaction scores based on the subjective feelings of sleep during surgery. The objective clinical score of the Ramsay sedation scale indicated satisfactory sedation for almost all patients receiving midazolam and dexmedetomidine, except for two patients in the midazolam group. Patients with pregnancy-induced complications or hypertension were excluded. Therefore, the safety and hemodynamic effects of dexmedetomidine should be tested in high-risk populations.

In summary, intraoperative administration of a loading dose of dexmedetomidine during cesarean delivery produced a similar decrease in SBP and heart rate and a similar satisfaction with sedation. Therefore, an intravenous 0.7 μg/kg dexmedetomidine loading dose is a suitable option for an adjunct drug to provide successful single shot spinal anesthesia.

**FUNDING**

This study was supported by the Korean Society of Obstetric Anesthesiologists Research Fund.
CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS


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REFERENCES

Transient decrease in B-type natriuretic peptide level after liver transplantation does not ensure favorable post-transplant 30-day outcomes

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Background: High B-type natriuretic peptide (BNP) levels within the first 3 postoperative days (postBNP\_POD3) after liver transplantation (LT) are greatly predictive of the 30-day mortality. We evaluated clinical impact of transient decrease in postBNP\_POD3 compared to pretransplant BNP (preBNP) level on mortality and major adverse cardiac event (MACE) within 30 days after LT.

Methods: We retrospectively evaluated 3,811 LT patients who measured delta BNP (deltaB-NP), defined by serial postBNP\_POD3 minus preBNP. Thirty-day all-cause mortality and MACE were estimated in patients with deltaBNP < 0 (n = 594, 15.6%) and > 0 (n = 3,217, 84.4%), respectively. Kaplan-Meier survival and multivariable Cox regression analysis were used.

Results: Within 30 days, 100 (2.6%) of all patients died. Unexpectedly, 30-day mortality rate (6.1% [95% CI: 4.2–8.4%] vs. 2.0% [95% CI: 1.5–2.5%], P < 0.001) and MACE (24.2% [95% CI: 20.4–28.5%] vs. 15.3% [95% CI: 14.0–16.7%], P < 0.001) were higher in patients with deltaBNP < 0 compared to those with deltaBNP > 0, respectively. Patients with deltaBNP < 0 had higher preBNP level (median [interquartile range], 251 [118, 586] vs. 43 [21, 92] pg/ml, P < 0.001) and model for end-stage liver disease score (26 [14, 37] vs. 14 [9, 23], P < 0.001) and more transfused intraoperatively. DeltaBNP < 0 remained significant after adjustments for potential confounders in multivariable analysis of 30-day mortality and MACE.

Conclusions: DeltaBNP < 0 within the first 3 postoperative days is mainly attributed to pre-LT severe liver and cardiac disease status, therefore, transient decrease in BNP level after LT does not ensure favorable post-LT 30-day outcomes.

Keywords: Liver transplantation; Major adverse cardiovascular event; Mortality; Natriuretic peptide, brain.

INTRODUCTION

Because of high early and late cardiovascular death after liver transplantation (LT) in the modern era, identification of vulnerable heart and severity of cardiac disease are crucial in patients with end-stage liver disease (ESLD) undergoing LT [1-3]. Recent studies demonstrated the routine monitoring of peri-LT B-type natriuretic peptide (BNP) provides risk stratification for early mortality as a practical and useful biomarker in LT [4]. Specifically, high peak BNP levels > 400 pg/ml within the first 3 postoperative days (postBNP\_POD3) after LT are highly prevalent in advanced liver disease and are
considered as highly vulnerable to become acute heart failure (HF) or “HF likely” status shortly after LT [4,5]. In this regard, physicians may suppose improved cardiac status with expecting favorable post-LT outcomes if there are decreases in postBNPPOD3 compared to pre-LT BNP (preBNP) level immediately after LT. However, it is unclear whether preBNP is initially higher from the beginning before LT than postBNPPOD3 in this clinical situation.

In this study, we evaluated clinical impact of transient decrease in postBNPPOD3 compared to preBNP level on 30-day mortality and major adverse cardiac event (MACE) within 30 days after LT, after adjusting with revised cardiac risk index (RCRI), the most frequently validated model for perioperative cardiac risk stratification [6].

MATERIALS AND METHODS

Patients and data collection

A total of 3,811 consecutive, prospectively registered patients who underwent living-donor LT or deceased-donor LT from 2010 to 2020 were enrolled after excluding patients with less than 18 years old, re-transplantation, history of open-heart surgery, and incomplete data without measuring serial preBNP and postBNPPOD3.

Patient demographics, medical history, model for end-stage liver disease score (MELDs), and laboratory and intraoperative variables were obtained automatically using a fully computerized data extraction software (ABLE). Mortality data were extracted from patients’ electronic medical records and the updated record of the institution’s LT registry. This study was approved from the Institutional Review Boards of Asan Medical Center (protocol number: 2022-0436).

BNP measurement

Serial BNP levels were measured pre- and post-operative (the ADVIA Centaur CP Immunoassay System) as a part of our institution’s routine cardiac workup since 2008 regardless of the symptoms or signs of acute or chronic HF. BNP levels measured more than once within 3 postoperative days after LT and their peak value (postBNPPOD3) was chosen for the analysis, and those who did not measure either preBNP or postBNPPOD3 were excluded.

PreBNP was selected with the most proximate to the date of LT within 7 pre-LT days, when multiple measurements were done preoperatively.

Delta BNP (deltaBNP) was defined as the difference with serial preBNP and postBNPPOD3 (deltaBNP = postBNPPOD3 - preBNP).

RCRI and post-reperfusion syndrome (PRS)

The traditional RCRI was evaluated for the multivariable analysis. The RCRI is the most frequently validated model for perioperative cardiac risk stratification and is recommended by many guideline committees [6]. Scoring system and variables included in the RCRI are as follows (worth 1 point each): history of ischemic heart disease, congestive heart failure, cerebrovascular disease, high-risk surgery (i.e., liver transplant), preoperative insulin use, and preoperative creatinine level > 2 mg/dl.

PRS was defined as a severe hemodynamic perturbation more than 1 min within the first 5 min after graft reperfusion during LT [2].

Outcomes

The primary endpoint was 30-day all-cause mortality rate after LT and MACE. MACE was defined as the composite of postoperative cardiovascular mortality, atrial fibrillation, ventricular arrhythmias, ST-T wave changes with chest tightness, myocardial infarction, pulmonary embolism, and stroke within 30 days after LT.

Statistics

Data were expressed as mean ± standard deviation or median (interquartile range) for continuous variables, and number (percentage) for categorical variables. In univariate statistical comparisons for the patients with deltaBNP > 0 and < 0, the chi-square test or Fisher’s exact test was used for categorical variables, Student’s t-test and Mann-Whitney test for continuous variables, as appropriate. The Kaplan-Meier survival curve was used to depict the risk of within 30 days all-cause mortality.

To evaluate the relationship between clinical, biochemical parameters, liver disease severity, cardiac risk index and mortality events, multivariate or a Cox proportional multiple regression model was built. With MACE as outcome, multivariable logistic regression model was performed. To obtain adjusted hazard ratios (HR) for mortality or odds ratio for MACE from a multivariable or a Cox regression model, co-
variates included were age, sex, RCRI, MELD score, intraoperative red blood cell (RBC) transfusion amount, PRS and patients with deltaBNP < 0, respectively. The proportional hazards assumption of deltaBNP can was checked using scaled Schoenfeld residuals (P = 0.430). Statistical analyses were conducted in R (Version 4.1.2, R Foundation for Statistical Computing), with packages of ‘moonBook [7]; autoReg [8]; “survminer [9] “survival [10]” and a two-sided significance level of 0.05.

RESULTS

Of 3,811 LT recipients included, their age was median 54 (48, 59) years and men were 2,769 (72.7%). The MELDs were median 15 (10, 26) and total bilirubin was median 2.2 (1.0, 10.5) mg/dl. The primary causes of liver disease were hepatitis B or C virus-related liver cirrhosis (60.9%), alcoholic liver disease (24.7%) and others (14.4%) (Table 1). Prevalence of RCRI category 1, 2, and 3 were 66.2%, 26.5%, and 7.3%, respectively (Table 1).

Characteristics in patients with deltaBNP < 0

Patients with deltaBNP < 0 had higher MELD score compared to those with deltaBNP > 0 (26 [14, 37] vs. 14 [9, 23], P < 0.001). They also showed higher risk of RCRI preoperatively and suffered from more transfusion intraoperatively. However, the rate of intraoperative postreperfusion syndrome were similar (Table 1). Fig. 1 shows individual changes in BNP, demonstrating that patients with deltaBNP < 0 (n = 594, 15.6%) had higher preBNP level compared to those with deltaBNP > 0 (251 [118, 586] vs. 43 [21, 92] pg/ml, P < 0.001).

<table>
<thead>
<tr>
<th>Variable</th>
<th>DeltaBNP &gt; 0 (n = 3,217)</th>
<th>DeltaBNP &lt; 0 (n = 594)</th>
<th>Total (n = 3,811)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>54.0 (49.0, 59.0)</td>
<td>54.0 (47.0, 60.0)</td>
<td>54.0 (48.0, 59.0)</td>
<td>0.139</td>
</tr>
<tr>
<td>Male</td>
<td>2,368 (73.6)</td>
<td>401 (67.5)</td>
<td>2,769 (72.7)</td>
<td>0.003*</td>
</tr>
<tr>
<td>MELD score</td>
<td>14 (9, 23)</td>
<td>26 (14, 37)</td>
<td>15 (10, 26)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Viral liver disease</td>
<td>2,050 (63.7)</td>
<td>269 (45.3)</td>
<td>2,319 (60.9)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Alcoholic liver disease</td>
<td>655 (20.4)</td>
<td>178 (30.0)</td>
<td>833 (21.9)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Diabetes</td>
<td>810 (25.2)</td>
<td>133 (22.4)</td>
<td>943 (24.7)</td>
<td>0.163</td>
</tr>
<tr>
<td>Hypertension</td>
<td>592 (18.4)</td>
<td>120 (20.2)</td>
<td>712 (18.7)</td>
<td>0.329</td>
</tr>
<tr>
<td>RCRI</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>1</td>
<td>2,225 (69.2)</td>
<td>299 (50.3)</td>
<td>2,524 (66.2)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>780 (24.5)</td>
<td>220 (37.0)</td>
<td>1,009 (26.5)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>203 (6.3)</td>
<td>75 (12.6)</td>
<td>278 (7.3)</td>
<td></td>
</tr>
<tr>
<td>Intractable ascites</td>
<td>991 (30.8)</td>
<td>257 (43.3)</td>
<td>1,248 (32.7)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Orthotopic LT</td>
<td>446 (13.9)</td>
<td>231 (38.9)</td>
<td>677 (17.8)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Hydrothorax</td>
<td>438 (13.6)</td>
<td>99 (16.7)</td>
<td>537 (14.1)</td>
<td>0.057*</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.8 (0.6, 1.0)</td>
<td>1.0 (0.7, 1.8)</td>
<td>0.8 (0.6, 1.1)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>INR</td>
<td>1.4 (1.2, 1.8)</td>
<td>1.7 (1.4, 2.3)</td>
<td>1.4 (1.2, 1.9)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>2.0 (1.0, 6.9)</td>
<td>9.2 (1.9, 25.1)</td>
<td>2.2 (1.0, 10.5)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>pRBC (units)</td>
<td>8.0 (3.0, 16.0)</td>
<td>12.0 (6.0, 20.5)</td>
<td>8.0 (3.0, 16.0)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>PRS</td>
<td>1,940 (60.3)</td>
<td>377 (63.5)</td>
<td>2,317 (60.8)</td>
<td>0.160</td>
</tr>
<tr>
<td>BNP (pg/ml)</td>
<td>43 (21, 92)</td>
<td>251 (118, 586)</td>
<td>54 (24,130)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>postBNP&lt;sub&gt;preop&lt;/sub&gt; (pg/ml)</td>
<td>197 (95, 423)</td>
<td>132 (73, 287)</td>
<td>183 (90, 405)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>DeltaBNP (pg/ml)</td>
<td>130 (52, 330)</td>
<td>–76 (–241, –24)</td>
<td>95 (24, 273)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>MACE</td>
<td>493 (15.3)</td>
<td>144 (24.2)</td>
<td>637 (16.7)</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>30-day mortality</td>
<td>64 (2.0)</td>
<td>36 (6.1)</td>
<td>100 (2.6)</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

Values are presented as median (IQR, 3Q) or number (%). BNP: B-type natriuretic peptide, MELD: model for end-stage liver disease, RCRI: revised cardiac risk index, LT: liver transplantation, INR: international normalized ratio, pRBC: packed red blood cells transfused, PRS: post-reperfusion syndrome, postBNP<sub>preop</sub>: peak BNP levels within the first 3 postoperative days, MACE: major adverse cardiovascular events. *P < 0.05 was considered statistically significant.

www.anesth-pain-med.org
Thirty-day mortality and MACE

Within 30 days, 100 (2.6%) of all patients died. However, unexpectedly, 30-day mortality rate (6.1% [95% confidence interval, 95% CI: 4.2–8.4%] vs. 2.0% [95% CI: 1.5–2.5%], P < 0.001) and MACE (24.2% [20.4–28.5%] vs. 15.3% [14.0–16.7%], P < 0.001) were higher in patients with deltaBNP < 0 compared to those with deltaBNP > 0, respectively (Table 1). Fig. 2 shows the Kaplan-Meier survival curve of the risk of within 30 days all-cause mortality.

In Cox proportional HR analysis for 30-day mortality, sex, MELD score, transfusion amount, and deltaBNP < 0 remained as significant variables, whereas, age, RCRI, transfusion amount, MELD score, deltaBNP < 0 was remained in the multivariable analysis of MACE (Figs. 3, 4).

DISCUSSION

In the current study, we hypothesized that transient decreases in postBNP_{POD3} compared to pre-LT BNP (preBNP) level immediately after LT, i.e. deltaBNP < 0, favorable post-LT outcomes might be expected if the decrease in postBNP_{POD3} could imply the improvement of cardiac status after LT. However, patients with deltaBNP < 0 after LT showed higher rates of 30-day mortality and MACE. We considered that these are attributed mainly to high preBNP level and high MELD score in patients with deltaBNP < 0. These results
suggest that pre-LT high BNP level and severe liver disease status might be main determinant of poor 30-day outcomes irrespective of transient decrease of post-LT BNP level.

There are several potential explanations for these findings. One possibility is that there was more blood loss during LT in association with more severe liver disease, which implies greater loss of intravascular volume loss during LT. In fact, transfusion amount and MELD score were higher in those with deltaBNP < 0 in the current study.

Several studies demonstrated that the BNP increase after LT was markedly prevalent in advanced liver disease and was associated with increased risk of 30-day mortality and worse outcomes [4,11-13].

Kwon et al. [4] showed that strong correlates of preBNP > 400 pg/ml were MELD score, kidney failure, respiratory failure, and congestive HF. In contrast, the strongest correlate of postBNP\textsubscript{POD3} > 400 pg/mL increase was preBNP level, hyponatremia, MELD score, massive intraoperative transfusion, and intractable ascites. They specifically emphasized that patients with preBNP of 1,000-2,000 pg/ml and BNP > 2,000 pg/ml showed 14.8% and 25% 30-day post-LT mortalities.

In the current study showed that patients with deltaBNP < 0 had also higher preBNP level, therefore, patients with unusually high preBNP should examine their cardiac status again and modifiable risk factors thoroughly reevaluated before LT and should receive the optimal medical treatment.

One important point that deserves emphasis is that serial measurement of BNP is recommended for the risk stratification of mortality after LT regardless of our study results [12,14]. Rodseth et al. [12] also demonstrated that additional postoperative BNP measurement enhanced risk stratification for the composite outcomes of death or nonfatal myocardial infarction at 30 days and more than 180 days after noncardiac surgery compared with a preoperative BNP measurement alone.

The RCRI, which is recommended by many guideline committees, one of the most frequently validated models for perioperative cardiac risk stratification [5,15]. We adjusted

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>1.00 (0.98–1.02, P = 0.704)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.01 (0.99–1.03, P = 0.419)</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>0.58 (0.39–0.87, P = 0.009*)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.56 (0.37–0.85, P = 0.007*)</td>
<td></td>
</tr>
<tr>
<td><strong>RCRI 1 vs. 2</strong></td>
<td>1.78 (1.16–2.73, P = 0.008* )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.88 (0.56–1.38, P = 0.570)</td>
<td></td>
</tr>
<tr>
<td><strong>RCRI 1 vs. 3</strong></td>
<td>2.37 (1.29–4.35, P = 0.006* )</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.88 (0.46–1.68, P = 0.688)</td>
<td></td>
</tr>
<tr>
<td><strong>MELD score</strong></td>
<td>1.08 (1.07–1.10, P &lt; 0.001*)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.07 (1.05–1.09, P &lt; 0.001*)</td>
<td></td>
</tr>
<tr>
<td><strong>pRBC transfusion</strong></td>
<td>1.03 (1.02–1.03, P &lt; 0.001*)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.02 (1.02–1.03, P &lt; 0.001*)</td>
<td></td>
</tr>
<tr>
<td><strong>PRS</strong></td>
<td>1.15 (0.76–1.73, P = 0.504)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.92 (0.60–1.39, P = 0.683)</td>
<td></td>
</tr>
<tr>
<td><strong>DeltaBNP</strong></td>
<td>3.12 (2.07–4.69, P &lt; 0.001*)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.64 (1.07–2.51, P = 0.023*)</td>
<td></td>
</tr>
</tbody>
</table>

In Fig. 3, Hazard ratios of univariable and multivariable analysis for 30-day mortality. RCRI: revised cardiac risk index, MELD: model for end-stage liver disease, pRBC: packed red blood cells transfused, PRS: post-reperfusion syndrome, BNP: B-type natriuretic peptide, CI: confidence interval. *P < 0.05 was considered statistically significant.
this risk index to evaluate the 30-day mortality risk and MACE and then the deltaBNP < 0 remained significant. However, previous study showed that the 30-day mortality rates with RCRI of 1, 2, and ≥ 3 were 2.0%, 3.6%, and 4.7% after LT and revealed poor discriminative performance the RCRI in LT (C-statistic = 0.58) [4]. Nonetheless, adding preBNP, postBNPPOD3, and both BNP values to the RCRI improved reclassification analysis to 22.5%, 29.5%, and 33.1% of 30-day mortality prediction, respectively [4]. Therefore, the routine monitoring of peri-LT BNP provides risk stratification for early mortality as a useful biomarker in LT [16-19].

Our study has several limitations, first, prospective multicenter study is recommended because our study is retrospective. Secondly, we did not follow the BNP level further in patients with mortality and MACE, therefore further study is needed including serial BNP level monitoring. Thirdly, the patients with high preBNP (i.e., high DeltaBNP) may indicate higher possibility of cardiac diseases. Those with higher decrease of BNP levels may show higher mortality compared to those with normal or slightly increased preoperative BNP. Therefore, the result our study should be interpreted with caution. Further studies investigating the classification of cardiac status or patients with similar levels of preoperative BNP are needed in the near future.

In conclusion, DeltaBNP < 0 within the first 3 postoperative days is mainly attributed to pre-LT severe liver and cardiac disease status, therefore, transient decrease in BNP level after LT does not ensure favorable post-LT 30-day outcomes.

These findings suggest that determinants of mortality and MACE are multiple and cannot reliably be predicted simply from changes in initial improvement of BNP, thereby special attention should also be paid to patients with deltaBNP < 0.

**FUNDING**

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**Fig. 4.** Odds ratios of univariable and multivariable analysis for major adverse cardiovascular events (MACE). BMI: body mass index, RCRI: revised cardiac risk index, MELD: model for end-stage liver disease, pRBC: packed red blood cells transfused, PRS: post-reperfusion syndrome, BNP: B-type natriuretic peptide, CI: confidence interval. *P < 0.05 was considered statistically significant.
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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Post-dural puncture headache prevention and treatment with aminophylline or theophylline: a systematic review and meta-analysis

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1Gastroenterohepatology Research Center, Shiraz University of Medical Sciences, 2Colorectal Research Center, Shiraz University of Medical Sciences, 3Department of e-Learning Planning in Medical Sciences, (Centre of Excellence for e-Learning), Shiraz University of Medical Sciences, 4Department of Anesthesiology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

Background: Post-dural puncture headache (PDPH) is one of the most common complications in patients undergoing spinal anesthesia. The present systematic review and meta-analysis aimed to assess the therapeutic and prophylactic effects of aminophylline and theophylline on PDPH.

Methods: Relevant studies were identified by searching the following electronic databases, without language restriction, until June 2020: Scopus, EMBASE, MEDLINE, Google Scholar, Web of Science, Cochrane Library-CENTRAL, and CINAHL Complete. Random effects models were used to calculate the standardized mean difference (SMD) and risk ratios (RRs) with 95% confidence intervals (95% CI) to assess the therapeutic and prophylactic effects of aminophylline and theophylline on PDPH, respectively. The Cochrane tool was used for the quality assessment of the included studies. The certainty of the evidence was rated using the Grading of Recommendations Assessment, Development, and Evaluation method.

Results: Of the 1,349 initial records, 15 met our eligibility criteria (6 studies on therapeutic and 9 on prophylactic effects). A significant reduction in the pain score was observed following aminophylline/theophylline treatment (SMD = –1.67; 95% CI, –2.28 to –1.05; P < 0.001, I² = 84.7%; P < 0.001). Subgroup analysis revealed that the therapeutic effect was significantly higher when these agents were compared to placebo than when conventional therapies were used. The risk of PDPH after aminophylline administration was not significantly reduced (RR = 0.74; 95% CI, 0.42 to 1.31; P = 0.290).

Conclusions: Theophylline and aminophylline have therapeutic, but not prophylactic, effects on PDPH.

Keywords: Aminophylline; Post-dural puncture headache; Systematic review; Theophylline.

INTRODUCTION

Lumbar puncture is a surgical procedure used primarily to sample cerebrospinal fluid (CSF) or to inject medications, including anesthetics [1-3]. Post-dural puncture headache (PDPH) is one of the most common complications observed

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in patients undergoing lumbar puncture and is usually accompanied by photophobia, nausea, neck stiffness, and subjective hearing symptoms [4]. During lumbar puncture, the size, shape, and orientation of the spinal needles and the patient’s position can affect the likelihood of developing PDPH. There are also factors associated with PDPH risk, including age (higher risk for patients between 18 and 40 years), female sex, low body mass index, chronic headaches, and previous PDPH history [5]. The incidence of PDPH after spinal anesthesia and lumbar puncture (with a standard traumatic needle) is < 3% and 11%, respectively [4].

The epidural blood patch is considered an effective strategy for PDPH prevention in high-risk patients and for PDPH treatment in severe or debilitating forms. Nonetheless, there are several concerns regarding its application owing to its invasiveness, need for anesthesia practitioners, and questionable efficacy [5]. Furthermore, lying down, drinking plenty of fluids, and non-steroidal anti-inflammatory drugs are routinely recommended for PDPH prevention after dural puncture [6]. However, there is poor evidence regarding the efficacy of these recommendations compared with immediate mobilization [7]. Therefore, additional clinical studies are needed to identify effective pharmacological options for PDPH prevention or treatment [8].

Methylxanthines are purine alkaloids mainly known for their bronchodilator and stimulatory effects. Some previous studies have reported conflicting evidence on the effects of methylxanthine derivatives, including aminophylline and theophylline, on PDPH [9-11]. A recent meta-analysis investigated the impact of methylxanthines on the incidence and severity of PDPH. In this study, 10 randomized controlled trials (RCTs) were analyzed, and a significant therapeutic effect of aminophylline against PDPH was reported [12]. Therefore, our study sought to better understand the effect of aminophylline and theophylline on PDPH prevention and treatment through a more comprehensive search of multiple electronic databases, without language restriction, and to evaluate the certainty of evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE).

**MATERIALS AND METHODS**

**Search strategy**

The protocol for this systematic review and meta-analysis was written using the guidelines of the Cochrane Handbook, registered in the International Prospective Register of Systematic Reviews (registration number: CRD42020211990), and published in a peer-reviewed journal [13]. Databases of EMBASE, Scopus, Google Scholar, PubMed/MEDLINE, Web of Science, the CINAHL Complete, and Cochrane Library-CENTRAL were searched between January 1, 1980, and June 30, 2020, using the following key search terms: “post-dural puncture headache,” “headache,” “post lumbar puncture headache,” “aminophylline,” and “theophylline.” No restrictions on publication language or study type were applied. A complete search strategy is available in a previously published protocol [13]. Moreover, the reference lists of all relevant studies, theses, proceedings, and conference papers were sought to ensure that all eligible studies were included.

**Study selection**

In the first screening stage, two authors (RBB and SSZ) reviewed the titles and abstracts of the papers using a checklist. The final selection of studies was carried out independently by two contributors (RBB and MM), following a review of the full texts of the studies obtained during the screening phase. Disputes between these reviewers were resolved by consensus or by a third expert’s opinion (ARS). The following studies were included in the current research: 1) trials on the preventive or therapeutic effects of intravenous or oral administration of aminophylline/theophylline on PDPH compared to placebo or conventional therapy (complete bed rest, hydration, acetaminophen codeine, and pethidine), 2) studies on participants (male, female, or both sexes) who underwent lumbar puncture before surgery (all surgeries); and 3) interventions evaluating the incidence or severity of PDPH pre- and post-intervention, as our primary outcome. Furthermore, our secondary outcomes were the assessment of aminophylline/theophylline effects based on the participants’ characteristics, type of control and intervention, route of intervention administration, and methodological quality of the studies and finding the source of heterogeneity accordingly.

Studies were excluded if they were in the pediatric population or did not provide information regarding outcomes.

**Quality assessment**

Cochrane’s tool was used to evaluate the methodological quality of the studies [14]. Accordingly, we considered ran-
dom sequence generation, allocation concealment, blinding of personnel, participants, outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias in each study. The overall risk of bias was rated as “high,” “low,” or “moderate.”

Data extraction

Three authors (RBB, SSZ, and MM) assessed eligible studies. In cases of disagreement, discussion between reviewers or the fourth expert’s opinion (ARS) was used to reach a consensus. We extracted the following information from each study: name of the first author, publication year, country, study design and location, participants’ characteristics, sample size, quality of paper, type of operation, headache scale, dosage of intervention, type of comparison arm, mean and standard deviation (SD) of pain scores in both groups, and the number of patients with and without headache in both intervention and control groups. The authors independently calculated the required data for the included studies or contacted the study authors to collect data if the included studies had incomplete data. Papers were excluded if the authors did not respond to the queries three times. Data extraction was performed using Web Plot Digitizer software when the outcome variables were reported only by graphs.

Quantitative data synthesis and statistical analysis

Statistical analyses were performed using STATA version 13.1 (StataCorp, USA). Cohen’s Kappa statistics were used to assess inter-agreement scores between reviewers during the selection process (0.895). We calculated the risk ratios (RRs) for dichotomous data using the random effects model and Mantel-Haenszel method with 95% confidence intervals (CIs). The standardized mean difference (SMD) and 95% CI were also applied to evaluate the effect of aminophylline/theophylline on PDPH severity. We extracted the mean and SD of the visual analog scale (VAS) or numerical rating scale (NRS) before and after the trial. To compute the mean change, we used the following formula: the amount at the end of the study minus the baseline amount in the treatment and control groups. The SD of the mean difference was computed as follows (if not reported): SD = square root [(SD pre-treatment)² + (SD post-treatment)² - (2 × SD pre-treatment × SD post-treatment)], assuming 0.5 as a conservative estimate for R [14]. The procedure of Hozo et al. [15] was also used to estimate the mean and SD values when the median and range or 95% CIs were reported.

We used the Q-statistic and I² statistic tests to investigate the statistical heterogeneity. Heterogeneity levels of 0–40%, 30–60%, 50–90%, and 75–100% were categorized as “probably not significant,” “moderate heterogeneity,” “substantial heterogeneity,” and “considerable heterogeneity,” respectively [16].

For the therapeutic effects of aminophylline/theophylline on PDPH, subgroup analysis was performed based on age (< 32 and ≥ 32 years), type of control group (placebo and conventional therapy), time of pain assessment after aminophylline/theophylline consumption (≤ 12 and > 12 h), route of treatment administration (intravenous and oral), type of intervention (theophylline and aminophylline), and quality of studies (low and moderate vs. high). In terms of prophylactic effect, subgroup analysis was considered based on age (< 32 and ≥ 32 years), study population (patients undergoing cesarean section and lower extremity surgery), and quality of studies (high and moderate).

A sensitivity analysis was conducted using the leave-one-out method to evaluate the effect of each study on the overall effect size. Meta-regression was performed to assess the association between effect size, age, and time of pain assessment following aminophylline treatment. Funnel plot, Begg’s test, and Egger’s test were used to identify potential publication bias when an outcome was assessed in 10 or more studies. Statistical significance was set at P < 0.05.

Certainty of the evidence

The certainty of the evidence was assessed based on the GRADE approach. Each outcome was scored as high, moderate, low, or very low. There were five domains for downgrading (risk of bias, inconsistency, indirectness, imprecision, and publication bias) and three criteria for upgrading outcomes (large magnitude of association, dose–response gradient, and residual plausible bias and confounding) [17].

RESULTS

The selection process for the meta-analysis is illustrated in Fig. 1. First, 2019 reports were identified. After eliminating duplicates, 1,049 articles remained. Based on titles and abstracts, 1,028 articles were excluded. Thus, 21 potentially relevant articles were selected and examined in detail. Finally, six studies were excluded for one or more of the following reasons: non-RCT trial (n = 2) [18,19]; conference abstract,
with no available data (n = 1) [20]; inappropriate data (n = 2) [21]; and use of aminophylline in combination with other components without a suitable control group (n = 1) [22]. After ultimate evaluation, 15 eligible studies (6 on therapeutic and 9 on prophylactic effects) met the inclusion criteria and were appropriate for inclusion in the final meta-analysis.

### Characteristics of the included studies

Table 1 presents the characteristics of the included studies. Data on the therapeutic effects of aminophylline or theophylline on PDPH were obtained from six eligible studies, including 195 and 194 participants in the control and intervention groups, respectively (four studies on theophylline and two on aminophylline effects). These trials included 17 [31] to 62 [1] participants. These studies were published between 2007 and 2021 and were conducted in Iran (one study) [32], Egypt (two studies) [24,29], China (one study) [1], Turkey (one study) [31], and India (one study) [30]. The participants’ mean age ranged from 26.23 [29] to 40.06 [32] years. All trials were conducted for both sexes. The duration of the intervention ranged from 4 [31] to 24 h [30].

Regarding the prophylactic impact of aminophylline on PDPH (Table 2), nine studies with sample sizes varying from 60 to 200 were evaluated. Six of these studies focused on participants who underwent cesarean sections [10,23,26-
**Table 1.** Characteristic of Studies That Evaluated the Therapeutic Effect of Aminophylline/theophylline on PDPH

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Study population</th>
<th>Number of participants (control group, intervention group)</th>
<th>Time of pain assessment following aminophylline/theophylline (h)</th>
<th>Dosage of aminophylline/theophylline</th>
<th>Control group</th>
<th>Outcome</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ergün et al., 2008 [31]</td>
<td>Turkey</td>
<td>M/F</td>
<td>31.88</td>
<td>Patients who had undergone lumbar puncture for diagnosis or epidural anesthesia and subsequently developed PDPH</td>
<td>16, 17</td>
<td>4</td>
<td>Theophylline, 200 mg, iv</td>
<td>5% dextrose</td>
<td>VAS</td>
<td>High</td>
</tr>
<tr>
<td>Wu et al., 2018 [1]</td>
<td>China</td>
<td>M/F</td>
<td>36.5</td>
<td>Patients with PDPH</td>
<td>64, 62</td>
<td>0.5</td>
<td>Aminophylline, 50 mg, iv</td>
<td>Normal saline</td>
<td>VAS</td>
<td>Low</td>
</tr>
<tr>
<td>Sakr et al., 2018 [29]</td>
<td>Egypt</td>
<td>M/F</td>
<td>26.23</td>
<td>Patient with lower extremity and lower abdominal surgery under spinal anesthesia</td>
<td>30, 30</td>
<td>1, 7, 13, 19</td>
<td>Theophylline, 250 mg orally + Paracetamol</td>
<td>Paracetamol</td>
<td>NRS</td>
<td>Unclear</td>
</tr>
<tr>
<td>Sen et al., 2014 [30]</td>
<td>India</td>
<td>M/F</td>
<td>30</td>
<td>Patients under spinal anesthesia</td>
<td>20, 20</td>
<td>1, 8, 16, 24</td>
<td>Theophylline, 400 mg orally</td>
<td>Conservative treatment*</td>
<td>VAS</td>
<td>High</td>
</tr>
<tr>
<td>Fawaz et al., 2021 [24]</td>
<td>Egypt</td>
<td>M/F</td>
<td>32.77</td>
<td>Patients with PDPH</td>
<td>35, 35</td>
<td>2, 6, 12</td>
<td>Aminophylline, 250 mg, iv</td>
<td>1 g paracetamol, iv</td>
<td>VAS</td>
<td>Low</td>
</tr>
<tr>
<td>Mahoori et al., 2013 [32]</td>
<td>Iran</td>
<td>M/F</td>
<td>40.06</td>
<td>Patients with PDPH</td>
<td>30, 30</td>
<td>2</td>
<td>Theophylline, tablet 250 mg three times per day</td>
<td>Acetaminophen 500 mg three times per day</td>
<td>VAS</td>
<td>High</td>
</tr>
</tbody>
</table>


28,33], and three assessed subjects undergoing extremity surgeries [11,25,34]. The included studies were published between 2014 and 2021 and conducted in Iran (seven studies) [11,23,25,26,28,33,34], Egypt (one study) [27], and China (one study) [10]. The mean age of the participants ranged from 25 [27] to 45.7 [25] years.

**Meta-analysis and subgroup results of the therapeutic effect of aminophylline/theophylline on PDPH**

Fig. 2 shows a significant reduction in VAS or NRS pain scores in the aminophylline/theophylline group compared to the placebo or conventional therapy control group (SMD = -1.67; 95% CI, -2.28 to -1.05; P < 0.001), with significant heterogeneity ($I^2 = 84.7\%$; P < 0.001).

Table 3 shows the results of the subgroup analysis. When the data were sub-grouped by the type of control group, the pooled effect size was significantly different between studies using placebo (SMD = -2.51; 95% CI, -2.93 to -2.09; P < 0.001) and conventional therapy (SMD = -1.25; 95% CI, -1.68 to -0.81; P < 0.001). There were no significant differences between the subgroups in age (P = 0.48), time of VAS score assessment (P = 0.230), type of intervention (P = 0.820), route of drug administration (P = 0.290), and quality of studies (P = 0.480). Moreover, the heterogeneity was significantly reduced following subgroup analyses by age ($I^2 = 30.3\%$; P = 0.230) and type of control group ($I^2 = 0.0\%$; P = 0.940).
Table 2. Characteristic of Studies That Evaluated the Prophylactic Effect of Aminophylline on PDPH

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Study population</th>
<th>Number of participants (control group, intervention group)</th>
<th>Time of pain assessment following aminophylline (h)</th>
<th>Dosage of aminophylline</th>
<th>Control group</th>
<th>Outcome</th>
<th>Risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dehghan-pisheh et al., 2019</td>
<td>Iran</td>
<td>F</td>
<td>30</td>
<td>Women undergoing cesarean surgery under spinal anesthesia</td>
<td>100, 100</td>
<td>Total 24, 48, 72</td>
<td>1 mg/kg iv</td>
<td>Normal saline</td>
<td>NRS</td>
<td>Low</td>
</tr>
<tr>
<td>Ghanei et al., 2015</td>
<td>Iran</td>
<td>F</td>
<td>30</td>
<td>Women undergoing cesarean surgery under spinal anesthesia</td>
<td>100, 100</td>
<td>6 to 12, 12 to 24, → 24</td>
<td>2 mg/kg iv combined with conventional therapy</td>
<td>Conventional therapy*</td>
<td>VAS</td>
<td>Low</td>
</tr>
<tr>
<td>Naghibi et al., 2014</td>
<td>Iran</td>
<td>M/F</td>
<td>45,7</td>
<td>Patients undergoing lower extremity surgery</td>
<td>35, 34</td>
<td>6 to 48</td>
<td>1.5 mg/kg iv</td>
<td>Normal saline</td>
<td>VAS</td>
<td>Low</td>
</tr>
<tr>
<td>Yang et al., 2019</td>
<td>China</td>
<td>F</td>
<td>27,2</td>
<td>Women undergoing cesarean surgery under combined spinal epidural anesthesia</td>
<td>58, 59</td>
<td>24, 48, 72</td>
<td>250 mg of aminophylline oral</td>
<td>Normal saline</td>
<td>NR</td>
<td>Low</td>
</tr>
<tr>
<td>Mohamed et al., 2021</td>
<td>Egypt</td>
<td>F</td>
<td>25</td>
<td>Women undergoing cesarean surgery under spinal anesthesia</td>
<td>52, 52</td>
<td>24, 48, 72</td>
<td>100 μg/kg/min diluted in 50 ml normal saline (0.9%) infusion for 30 minutes</td>
<td>Normal saline</td>
<td>VAS</td>
<td>Unclear</td>
</tr>
<tr>
<td>Sadeghi et al., 2012</td>
<td>Iran</td>
<td>F</td>
<td>26,11</td>
<td>Women undergoing cesarean surgery under spinal anesthesia</td>
<td>60, 60</td>
<td>24, 48</td>
<td>1 mg/kg iv</td>
<td>NR</td>
<td>VAS</td>
<td>Unclear</td>
</tr>
<tr>
<td>Hasannasab et al., 2018</td>
<td>Iran</td>
<td>F</td>
<td>28,3</td>
<td>Women undergoing cesarean surgery under spinal anesthesia</td>
<td>70, 70</td>
<td>8, 24, 48, 72</td>
<td>1 mg/kg iv</td>
<td>Normal saline</td>
<td>VAS</td>
<td>Low</td>
</tr>
<tr>
<td>Jabalameli et al., 2019</td>
<td>Iran</td>
<td>M/F</td>
<td>35</td>
<td>Patients undergoing lower extremity surgery</td>
<td>30, 30</td>
<td>6, 12, 18, 24, 48, 72</td>
<td>1.5 mg/kg iv</td>
<td>Normal saline</td>
<td>VAS</td>
<td>Low</td>
</tr>
<tr>
<td>Jabalameli et al., 2016</td>
<td>Iran</td>
<td>M/F</td>
<td>30,5</td>
<td>Patients undergoing lower extremity surgery</td>
<td>34, 34</td>
<td>6, 12, 18, 24, 48, 72</td>
<td>1.5 mg/kg iv</td>
<td>Normal saline</td>
<td>VAS</td>
<td>Unclear</td>
</tr>
</tbody>
</table>

PDPH: post-dural puncture headache, NR: not reported, NRS: numerical rating scale, VAS: visual analog scale. *Complete bed rest, hydration, and acetaminophen codeine and pethidine.

Meta-analysis and subgroup results of the prophylactic effect of aminophylline on PDPH

Fig. 3A shows the prophylactic effect of aminophylline on PDPH at all time points after its administration (nine studies, 1,078 participants) [10,11,23,25-28,33,34]. Moreover, Fig. 3 panels B, C, and D demonstrate the prophylactic effect of aminophylline against PDPH at 24 h (eight studies, 1,009 participants) [10,11,23,26-28,33,34], 48 h (eight studies, 787 participants) [10,11,23,25-27,33,34], and 72 h after aminophylline administration.
Fig. 2. Forest plot displaying standard mean difference (SMD) and 95% confidence intervals (CIs) for the therapeutic impact of aminophylline on severity of post-dural puncture headache compared with placebo or conventional therapy as a control group.

Table 3. Results of Subgroup Analysis of Therapeutic Effect of Aminophylline on Post-dural Puncture Headache

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number of studies</th>
<th>SMD</th>
<th>95% CI</th>
<th>P value within subgroup</th>
<th>I² (%)</th>
<th>P value for heterogeneity</th>
<th>P value for subgroup difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 32</td>
<td>3</td>
<td>-1.87</td>
<td>-2.37 to -1.36</td>
<td>&lt; 0.001</td>
<td>30.3</td>
<td>0.230</td>
<td>0.480</td>
</tr>
<tr>
<td>≥ 32</td>
<td>3</td>
<td>-1.44</td>
<td>-2.52 to -0.36</td>
<td>0.009</td>
<td>92.9</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Type of control group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>2</td>
<td>-2.51</td>
<td>-2.93 to -2.09</td>
<td>&lt; 0.001</td>
<td>0.0</td>
<td>0.940</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Conventional therapy*</td>
<td>4</td>
<td>-1.25</td>
<td>-1.68 to -0.81</td>
<td>&lt; 0.001</td>
<td>56.2</td>
<td>0.070</td>
<td></td>
</tr>
<tr>
<td>Time of VAS score measurement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 12 h</td>
<td>3</td>
<td>-1.36</td>
<td>-2.19 to -0.53</td>
<td>0.001</td>
<td>81.4</td>
<td>0.005</td>
<td>0.230</td>
</tr>
<tr>
<td>&gt; 12 wk</td>
<td>3</td>
<td>-1.98</td>
<td>-2.59 to -1.37</td>
<td>0.001</td>
<td>69.1</td>
<td>0.030</td>
<td></td>
</tr>
<tr>
<td>Route of aminophylline</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intravenous</td>
<td>3</td>
<td>-2</td>
<td>-3.07 to -0.92</td>
<td>&lt; 0.001</td>
<td>89.8</td>
<td>&lt; 0.001</td>
<td>0.290</td>
</tr>
<tr>
<td>Oral</td>
<td>3</td>
<td>-1.34</td>
<td>-1.96 to -0.72</td>
<td>&lt; 0.001</td>
<td>68.0</td>
<td>0.040</td>
<td></td>
</tr>
<tr>
<td>Type of intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td>4</td>
<td>-1.59</td>
<td>-2.28 to -0.91</td>
<td>&lt; 0.001</td>
<td>76.0</td>
<td>0.006</td>
<td>0.820</td>
</tr>
<tr>
<td>Aminophylline</td>
<td>2</td>
<td>-1.77</td>
<td>-3.22 to -0.33</td>
<td>0.010</td>
<td>94.0</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Quality of studies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>3</td>
<td>-1.63</td>
<td>-2.64 to -0.62</td>
<td>0.002</td>
<td>83.3</td>
<td>0.002</td>
<td>0.480</td>
</tr>
<tr>
<td>Moderate/high</td>
<td>3</td>
<td>-1.72</td>
<td>-2.61 to -0.83</td>
<td>&lt; 0.001</td>
<td>88.9</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
</tbody>
</table>

SMD: standardized mean difference, CI: confidence interval, VAS: visual analog scale. *Complete bed rest, hydration, and acetaminophen codeine and pethidine.

Our results revealed a non-significant reduction in the risk of PDPH at all time points (RR = 0.74; 95% CI, 0.42 to 1.31; P = 0.290, I² = 45.5%; P = 0.07), 24 h (RR = 0.68, 95% CI, 0.37 to 1.25; P = 0.210, I² = 60.8%), and 48 h after aminophylline administration (RR = 0.65, 95% CI, 0.38 to 1.09; P = 0.100, I² = 33.1%). Nonetheless, a non-significant increase was ob-
served in the risk of PDPH at 72 h following aminophylline administration (RR = 1.11, 95% CI, 0.69 to 1.79; P = 0.650, I² = 0%).

As shown in Table 4, there were no significant differences in the subgroup analyses stratified by age (P = 0.290) and study population (P = 0.290). Nonetheless, a significant difference was observed in the risk of PDPH between moderate-quality (RR = 0.25; 95% CI, 0.10 to 0.63; P = 0.003) and high-quality studies (RR = 1.08; 95% CI, 0.66 to 1.75; P = 0.750). Furthermore, heterogeneity also decreased in this subgroup (I² = 0%; P = 0.730).

**Sensitivity analysis and publication bias**

Neither trial had a significant influence on the summary effect in either of the analyses. As our outcomes were reported in less than ten studies, publication bias tests were not performed.

**Meta-regression**

Meta-regression was performed for the participants’ age and time of pain assessment following aminophylline administration. None of the two factors had a significant effect on pain score (t = 0.44; 95% CI, -0.17 to 0.23 and t = -1.11; 95% CI, -0.07 to 0.02; respectively) (Supplementary Fig. 3).

**Certainty of the evidence**

The overall certainty of the evidence was moderate and very low for the therapeutic and prophylactic effects of theophylline/aminophylline on PDPH, respectively (Supplementary Table 1).

**DISCUSSION**

In the present study, we investigated the therapeutic effects of theophylline and aminophylline on PDPH. This impact was significantly higher when these methylxanthines were compared with placebo than with conventional therapies. Furthermore, we observed no prophylactic effects of aminophylline on PDPH. The quality of the studies, type of control group, and age were detected as sources of heterogeneity in the present study.

PDPH is one of the most common complications of lumbar puncture, which is usually accompanied by nausea, vomiting, stiff neck, hearing loss, tinnitus, and photophobia and may influence the quality of life and hospital discharge of patients [19]. There remains a great deal to learn regarding the pathophysiology of PDPH [35]. This headache is primarily due to a CSF leak following a dural puncture with resultant intracranial hypotension and, subsequently, downward traction on pain-sensitive intracranial structures caused by gravity in the standing position. In contrast, intracranial volume restoration by dilating cerebral blood vessels as a compensatory adaptation may further exacerbate PDPH symptoms [5].

Different interventions are available to reduce numerous types of pain, such as PDPH, with varying degrees of success and risks [36-38]. Bed rest, intravenous hydration, and analgesic medications are conservative therapies for PDPH. Theophylline and its salt formulation (aminophylline) are methylxanthines with proposed therapeutic effects in PDPH. According to the present systematic review and meta-analysis, theophylline/aminophylline was effective in reducing pain severity after PDPH onset. These methylxanthines are superior to acetaminophen [24], conservative treatment (comprising caffeine) [30], and placebo for pain relief in PDPH. Furthermore, no adverse effects were reported following aminophylline/theophylline administration in these patients [10,29,30]. These results are in line with those of a previous meta-analysis of five studies reporting a lower pain score in patients receiving aminophylline (MD = -1.34; 95% CI, -1.76 to -0.91). Nonetheless, a comparison between aminophylline and conservative treatments was not conducted in this study [12].

Multiple prophylactic strategies for PDPH have been studied, but their clinical effectiveness has not yet been established. Bed rest and hydration are routinely recommended by clinicians for the prevention of PDPH following dural puncture. Nonetheless, according to a Cochrane review, there is no evidence to support the benefits of routine bed rest and fluid supplementation in preventing PDPH onset [7]. In the present meta-analysis, we observed no beneficial effect of theophylline/aminophylline on the risk of PDPH. However, subgroup analysis revealed prophylactic effects in moderate-quality studies. In another meta-analysis, Hung et al. [12] demonstrated no significant preventive effect of aminophylline against PDPH at 24, 48, or 72 h. However, subgroup analysis was not performed to assess the impact of several factors, including study quality, on the findings.

Aminophylline is suggested to have pain-relief effects in PDPH through cerebral vasoconstriction by interfering with calcium uptake by the sarcoplasmic reticulum of endothelial
Fig. 3. Forest plot displaying risk ratio (RR) and 95% confidence intervals (CIs) for the prophylactic impact of aminophylline on post-dural puncture headache compared with a control group (A) and after 24 (B), 48 (C), and 72 h (D). (Continued to the next page)
cells, blocking phosphodiesterase, increasing the intracellular cyclic adenosine monophosphate concentration, contraction of intracranial blood vessels by antagonizing adenosine function, increasing CSF secretion by stimulating sodium and potassium pumps, and blocking the transmission of pain perception [19].

The strengths of the present systematic review and meta-analysis are the search for several electronic databases without language restriction, performing meta-regression, and conducting subgroup analysis to detect sources of het-
erogeneity and the effects of subgroups on the pooled estimates. However, considerable between-study statistical and methodological heterogeneity and the low number of included studies, most of which were performed in Asia or were of low quality, are the major limitations of the present study. Therefore, the findings should be interpreted with caution. Further studies are needed to confirm these results because of the moderate and very low certainty of the present evidence.

According to the present systematic review and meta-analysis, theophylline and aminophylline had analgesic effects on PDPH. Nonetheless, we observed no prophylactic effect of aminophylline on PDPH.

### SUPPLEMENTARY MATERIALS

Supplementary data including a questionnaire results of risk of bias assessment, meta-regression, and certainty of evidence can be found online at https://doi.org/10.17085/apm.22247.

### FUNDING

This study was supported by the Vice Chancellor for Research and Technology of Shiraz University of Medical Sciences (code: 21331). The funder had no role in the study design, analysis, decision to publish, or manuscript preparation.

### ACKNOWLEDGMENTS

Our sincere gratitude goes to the Vice-Chancellor for Research at Shiraz University of Medical Sciences for approving this systematic review and meta-analysis (ID: 21331).

### CONFLICTS OF INTEREST

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

### DATA AVAILABILITY STATEMENT

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

### AUTHOR CONTRIBUTIONS


### Table 4. Results of Subgroup Analysis of Prophylactic Effect of Aminophylline on Post-dural Puncture Headache

<table>
<thead>
<tr>
<th>Variables</th>
<th>Number of studies</th>
<th>RR</th>
<th>95% CI</th>
<th>P value within subgroup</th>
<th>I² (%)</th>
<th>P value for heterogeneity</th>
<th>P value for subgroup difference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (yr)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>4</td>
<td>0.46</td>
<td>0.11 to 1.94</td>
<td>0.290</td>
<td>54.5</td>
<td>0.08</td>
<td>0.290</td>
</tr>
<tr>
<td>≥ 30</td>
<td>5</td>
<td>0.97</td>
<td>0.48 to 1.60</td>
<td>0.650</td>
<td>42.9</td>
<td>0.13</td>
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</tr>
<tr>
<td><strong>Study population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Patients undergoing cesarean</td>
<td>6</td>
<td>0.85</td>
<td>0.39 to 1.82</td>
<td>0.670</td>
<td>46.6</td>
<td>0.09</td>
<td>0.290</td>
</tr>
<tr>
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<tr>
<td>Patients undergoing lower</td>
<td>3</td>
<td>0.58</td>
<td>0.23 to 1.42</td>
<td>0.230</td>
<td>46.2</td>
<td>0.15</td>
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<td>extremity surgery</td>
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<td><strong>Quality of studies</strong></td>
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<td></td>
</tr>
<tr>
<td>High</td>
<td>6</td>
<td>1.08</td>
<td>0.66 to 1.75</td>
<td>0.750</td>
<td>16.4</td>
<td>0.30</td>
<td>0.006</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
<td>0.25</td>
<td>0.10 to 0.63</td>
<td>0.003</td>
<td>0.0</td>
<td>0.73</td>
<td></td>
</tr>
</tbody>
</table>

RR: relative risk, CI: confidence interval.
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Wound infiltration or transversus abdominis plane block after laparoscopic radical prostatectomy: a randomized clinical trial

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Background: Regional anesthesia techniques are commonly used for postoperative pain management during laparoscopic surgery. Our aim was to compare the analgesic efficacy of pre-incisional subcutaneous wound infiltration (WI) with that of the transversus abdominis plane (TAP) block as part of a multimodal analgesic approach in laparoscopic radical prostatectomy.

Methods: In this prospective, double-blinded, randomized controlled clinical trial, 60 patients were assigned to either TAP or WI group. The main outcome was acute postoperative pain control assessed using the mean numeric rating scale (NRS) at the 24 hours postoperatively. The secondary outcomes were opioid requirements, procedure-related complications, overall complications, and length of stay.

Results: In this study, 60 patients were randomized: 30 to TAP group and 28 to WI (two were excluded due to conversion to open surgery). We found no significant difference in the median (1Q, 3Q) NRS scores during the 24 h postoperatively neither at rest (TAP, 0 (0, 1) vs. WI, 0 (0, 1), P = 0.812), nor during movement (TAP, 1 (0, 2) vs. WI, 1 (0, 2), P = 0.708). There were no statistical differences in the postoperative intravenous morphine requirements in the TAP vs. WI groups during the same period (1.7 ± 3.1 vs. 1.8 ± 4.1 mg; P = 0.910). Only one patient in the TAP group presented with postoperative nausea and vomiting.

Conclusions: Both pre-incisional subcutaneous WI and TAP blockade were associated with very low pain scores as part of a non-opioid multimodal analgesic regimen in laparoscopic radical prostatectomy. This study did not demonstrate the benefits of WI over TAP.

Keywords: Enhanced recovery after surgery; Laparoscopic prostatectomy; Multimodal analgesia; Transversus abdominis plane block; Wound infiltration.

INTRODUCTION

Laparoscopic radical prostatectomy (LRP) is an established minimally invasive procedure for the treatment of prostate cancer. It is associated with a shorter hospital stay and less postoperative pain than the open approach [1,2]. Although laparoscopy is minimally invasive, it is associated with postoperative pain primarily at the trocar and extraction wound sites, with the highest degree of pain occurring on the first postoperative day [3].

Currently, postoperative analgesic treatment principles are directed towards facilitating early postoperative mobili-
zation and enhanced recovery. These are achieved through multimodal analgesic strategies based on the concurrent use of primarily non-opioid analgesics, which can have additive, if not synergistic, effects that produce superior analgesia, thereby decreasing opioid use and opioid-related side effects. These strategies frequently involve the use of different regional anesthesia techniques, with a preference for minimally invasive approaches over more aggressive anesthetic approaches to avoid possible complications [4,5].

Transversus abdominis plane (TAP) blockade and surgical wound infiltration (WI) are two common regional techniques used in multimodal analgesia that provide pain relief and reduce opioid consumption in a variety of surgical procedures [6-8]. TAP blocks neural afferents from the anterolateral abdominal wall (T6 to L1) by injecting a local anesthetic into the transversus abdominis fascial plane under ultrasound guidance or anatomical landmarks [6]. Although safe and effective, complications related to TAP such as nerve or vascular injuries have been reported [9-11], and the technique requires training and experience, is operator-dependent, and preferably performed under ultrasound guidance, leading to increased cost and resources. Furthermore, previous studies reported an average procedure time of 10 min [12], which might be problematic in the absence of parallel-processing space for regional anesthetic procedures [13]. In comparison, surgical WI with local anesthetics is a simple, safe, and low-cost technique for postoperative analgesia, which may provide an equally effective analgesia in the correct setting [14].

Several studies have compared the effectiveness of WI and TAP in different urologic [15], colonic [7,16], and gastrointestinal laparoscopic procedures [17], but no prospective comparative data are available for LRP.

Our hypothesis was that pre-incisional subcutaneous WI could be an alternative to TAP blockade for acute pain management in LRP as part of a multimodal analgesic approach, providing adequate analgesia and promoting enhanced recovery.

The aim of this prospective, double-blind, randomized controlled clinical trial was to compare the analgesic efficacy of WI and TAP in the first 48 h after LRP by analyzing numeric rate scale (NRS) values and opioid consumption.

MATERIALS AND METHODS

This was a single-center, prospective, controlled, double-blinded randomized trial with two parallel arms performed between September 7, 2020 and June 19, 2022. The study protocol was registered at EudraCT.gov (Identifier number: 2019-004089-16) on October 14, 2019 and approved by the Institutional Review Board committee (approval number 15/19) on April 30, 2020. This study was conducted in accordance with the principles of the Declaration of Helsinki. The results are reported according to the current consolidated standards of reporting trials guidelines.

Recruitment, randomization, and blinding

All the patients scheduled to undergo LRP between September 2020 and June 2022 were screened for participation in the trial.

Exclusion criteria were: 1) age < 18 years, 2) American Society of Anesthesiologists score ≥ IV, 3) body mass index ≥ 35 kg/m², 4) history of allergy to local anesthetics, opioids, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), or metamizole, 4) chronic opioid use, 5) conversion to open surgery, or 6) patient’s refusal. Patients who did not meet the exclusion criteria and agreed to participate signed an informed consent form during their visit for preoperative anesthesia.

On the day of surgery, consenting patients were randomly assigned to either a TAP block or WI (1:1) using a random allocation sequence concealed in 60 consecutively numbered sealed opaque envelopes. The patients were blinded to study allocation.

At the end of the surgery, surgical dressings were applied in the same fashion (at the incision and TAP infiltration sites), regardless of group allocation.

The anesthesiologists and nurses who performed the NRS pain assessments in the post-anesthesia care unit (PACU) and hospitalization ward were blinded to the allocation group.

Anesthesia and perioperative management

All surgical procedures were performed by the same group of specialized surgeons and anesthesiologists. The same standardized procedures for orotracheal general anesthesia were used in both groups: midazolam (1–2 mg) intravenous (IV) prior to induction, followed by fentanyl (1.5 µg/kg), propofol (1.5–2 mg/kg), and rocuronium (0.6 mg/kg). Subsequently, regional anesthesia was administered according to the assigned group.

WI group: Prior to skin incision, two syringes containing
40 ml of 0.375% ropivacaine were prepared and handed-over to the surgeon, who infiltrated the subcutaneous tissues of the incision sites (15 ml at the mini-laparotomy site and 25 ml distributed at the trocar sites).

TAP group: Prior to skin incision, an ultrasound-guided mid-axillary TAP block was performed. A high-frequency linear probe (Sonosite MicroMAXXTM, Sonosite Inc.) was placed midway between the costal margin and iliac crest, and the transversus abdominis muscle was located behind the rectus abdominis and below the internal oblique muscle. Twenty milliliters of 0.375% ropivacaine was administered via a 22 G Quincke spinal needle inserted in-plane on each side of the abdomen. An ultrasound-evident interfacial local anesthetic spread was considered a successful block.

Extraperitoneal LRP was performed using five trocars (a 12 mm infraumbilical trocar, two 5 mm trocars, and two 10 mm trocars in the lower right and left quadrants).

Anesthesia was maintained using target-controlled propofol infusion to achieve a patient state index between 25 and 50, and remifentanil infusion at 0.1 µg/kg/min for hemodynamic management. Rocuronium (0.6 mg/kg/h) was administered to ensure muscle relaxation. No additional analgesics were administered during surgery. All patients received postoperative nausea and vomiting (PONV) prevention drugs i.e., IV dexamethasone (4 mg) after induction of anesthesia and IV ondansetron (4 mg) 30 min before the end of surgery. At the end of surgery, patients were awoken from general anesthesia and transferred to the PACU for observation for 4 h.

All patients were prescribed a standardized multimodal non-opioid analgesic regimen in the postoperative period, which included IV paracetamol (1 g/8 h), IV NSAIDs (dextrotoprofen 50 mg/8 h; not administered in case of renal failure), and IV metamizole (2 g/8 h). IV Morphone (2 mg/20 min as needed for an NRS value > 3) was prescribed as rescue medication in cases of inadequate pain control. After 4 h of observation in the PACU, if the clinical parameters permitted, oral intake was initiated, and patients were transferred to the hospital ward, where our hospital’s acute-pain team conducted the protocol-driven follow-up.

Postoperative complications were considered if they occurred during the hospital stay after the surgery. PONV was treated with on-demand IV ondansetron (4 mg/8 h, as needed) during the entire postoperative period. On the second postoperative day, if oral intake was tolerated, multimodal analgesia was changed to oral medications—paracetamol (1 g/8 h) and metamizole (575 mg/8 h) or dextrotoprofen (25 mg/8 h) in all patients (depending on renal function). Despite this, if the patient reported a NRS value > 3 at rest, oral tramadol (50 mg) was administered as needed in both groups. Tramadol consumption was calculated and reported as milligrams of morphine equivalents (MMEs).

Oral paracetamol (1 g/8 h) was prescribed to all patients at discharge.

Outcomes

The study was conducted during the first 48 h after surgery. The primary endpoint was the NRS values at rest (NRSr) and during movement (NRSm, coughing in the PACU) at the 24 h post-operatively. As a secondary endpoint, pain assessment were also done at 1, 2, 3, 4, 6, 12, 18, 36, and 48 h post-operatively. Patients rated their pain from 0 (no pain) to 10 (worse pain imaginable) according to a previously validated NRS [18]. The exploratory secondary endpoint to determine analgesic efficacy was MMEs administered during the first 48 h.

Secondary outcomes were procedure-related complications and adverse effects, intraoperative hemodynamic events (hypotensive or hypertensive), length of surgery, PONV, time to first flatus, time to sitting and ambulation, in-hospital postoperative complications, and length of stay.

All recorded parameters were registered prospectively and stored in an IRB-approved database.

Statistics

According to a previous study, a two-point difference in NRS values can be considered as a clinically significant difference [8,19] with a standard deviation of 2.5 [19]; 25 patients will be required in each group at a significance level of 5% and a power level of 80% to detect a difference between groups. Smaller differences may still be considered significant by some authors; however, our study was not designed to detect such differences. We increased the sample size by 20% (30 patients) to account for possible exclusions or losses to follow-up.

Results are reported as means and standard deviations for quantitative data and percentages or ranks for qualitative data. The Kolmogorov–Smirnov test was used to evaluate data distribution. The independent samples t-test or U-Mann Whitney test were used to compare differences in the means and the Pearson chi-square test for categorical data. Fisher’s exact test was applied in place of the chi-
A multivariate analysis using linear regression for continuous data was performed to identify factors associated with NRS values at the first 48 hours postoperatively. The effect size measures were reported as 95% confidence interval (CI). All P values were two-sided. Statistical significance was set at $P < 0.05$. Statistical analyses were performed using the Statistical Package of Social Sciences (version 22.0, SPSS Inc.)

**RESULTS**

From September 2020 to June 2022, 67 patients were assessed for eligibility, of which seven were not enrolled on the basis of exclusion criteria or refusal. Sixty patients were enrolled in the trial and were randomized. Two patients were excluded after being allocated to the WI group because of conversion to open surgery. The remaining 58 patients were analyzed (Fig. 1).

Baseline characteristics were similar in both groups except for diabetes, which was more common in the WI group ($P = 0.038$), and age, which was lower in TAP patients ($P = 0.031$). The patient characteristics are summarized in Table 1.

The details of intraoperative hemodynamic management,
surgical features, and lengths of surgery are presented in Table 2. No hypotensive events were observed during the surgery. No patient experienced complications related to regional analgesia, and there were no intraoperative events attributable to the systemic effects of local anesthetics in either group.

Median NRS values registered at rest and during cough/movement during the immediate postoperative period in PACU (0–4 h period); at rest: at 1 h P = 0.844; at 2 h P = 0.736, at 3 h P = 0.700; at 4 h P = 0.971; during cough: 1 h P = 0.698; at 2 h P = 0.834, at 3 h P = 0.922; at 4 h P = 0.618) and on the hospitalization ward (6–48 h period; at rest: 6 h P = 0.816; at 12 h P = 0.395, at 18 h P = 0.472; at 24 h P = 0.812, at 36 h P = 0.358, at 48 h P = 0.397; during cough: 6 h P = 0.974; at 12 h P = 0.712, at 18 h P = 0.691; at 24 h P = 0.708, at 36 h P = 0.572, at 48 h P = 0.929) did not show statistically significant differences and are shown in Figs. 2 and 3 respectively.

We performed an exploratory analysis of the opioid requirements. There were no statistical differences in the postoperative MME requirements in the TAP and WI groups during the entire 48-h period (1.7 ± 3.1 vs. 1.8 ± 4.1 mg; P = 0.914) or when analyzing the early (0–4 h) and late (4–48 h) periods separately (TAP, 1.6 ± 2.9 mg vs. WI, 1.1 ± 1.8 mg for the early period and TAP, 0.1 ± 0.5 mg vs. WI, 0.6 ± 3.0 mg for the late period).

There were no postoperative complications related to the TAP or WI technique or complications associated with the systemic effects of the local anesthetic in any of the patients. The difference in the incidence of overall complications between the two groups was not statistically significant (P = 1.000). In the TAP group, a case of ureteral fistula required surgical reintervention, a case of bladder perforation was managed conservatively, and a case of obturator nerve injury required rehabilitation. In the WI group, cases of bladder perforation and hemorrhage did not require surgical intervention. PONV was very rare in both groups, and only one patient in the TAP group experienced PONV.

Results of the linear regression analysis showed that mean NRS values at the 48 hours postoperatively were independently associated with total opioid requirements (95% CI, 0.49 [0.03-0.09]; P < 0.001), while surgery duration (P = 0.698), age (P = 0.383), lymphadenectomy (P = 0.895), surgical postoperative complications (P = 0.432) and diabetes mellitus (P = 0.844) were not independently associated.

Neither of the secondary outcomes presented significant differences between the 2 groups (Table 3).

<table>
<thead>
<tr>
<th>Variable</th>
<th>TAP (n = 30)</th>
<th>WI (n = 28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of surgery (min)</td>
<td>241 ± 44</td>
<td>222 ± 37</td>
<td>0.083</td>
</tr>
<tr>
<td>Time of anesthesia (min)</td>
<td>300 ± 50</td>
<td>288 ± 45</td>
<td>0.321</td>
</tr>
<tr>
<td>Hypertensive episode</td>
<td>7 (24.1)</td>
<td>6 (21.4)</td>
<td>0.807</td>
</tr>
<tr>
<td>Lymphadenectomy</td>
<td>5 (16.7)</td>
<td>7 (25.0)</td>
<td>0.434</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number (%). TAP: transversus abdominis plane, WI: wound infiltration. Hypotensive events were defined by a systolic blood pressure decrease of 20% below baseline. Hypertensive events were defined by a systolic blood pressure increase of 20% above baseline. The length of surgery was recorded as the elapsed time in hours between the documented times of incision and closure.

**DISCUSSION**

Effective pain management is key for optimal postoperative recovery and an essential component of enhanced recovery protocols [20]. However, direct high-level evidence is often lacking to support an optimal approach, even in commonly performed procedures, such as laparoscopic prostatectomy. The current study is the first prospective randomized trial comparing two regional analgesic approaches coupled with non-opioid-based multimodal analgesia for LRP. The results of this study did not show benefits of either lo-coregional technique modality for acute pain management in LRP, while showing excellent pain scores when these techniques were applied as part of a standardized non-opioid-based multimodal regimen.

The choice of an ideal pain management strategy should be based not only on its safety and efficacy, but also on the ease of administration and cost. From this perspective, although WI showed no differences in terms of pain control compared with TAP, WI could be considered more advantageous because it is less time-consuming and not dependent on the availability of ultrasound equipment or specially trained personnel, and complications after WI are rare [21].

In our study, both analgesic strategies provided excellent pain control, with mean NRS values < 2 in the first 48 h, both at rest and during movement. Our results were in accordance with those of studies on other types of surgeries, such as laparoscopic colectomy [7,16], where similar levels of pain control were observed for WI and TAP. In those studies, although no differences were observed between the two techniques, similar to the results of our study, the recorded pain intensity was generally higher than our data. This could
Fig. 2. Numeric rate scale (NRS) scores at rest during the first 48 postoperative hours in the TAP and WI groups. Median (line within box), interquartile range (box) and range (error bars) are shown. No statistically significant differences are observed between the analgesic efficacies of the two procedures. TAP: transversus abdominis plane, WI: wound infiltration.

Fig. 3. Numeric rate scale (NRS) scores during movement during the first 48 postoperative hours in the TAP and WI groups. Median (line within box), interquartile range (box) and range (error bars) are shown. No statistically significant differences are observed between the analgesic efficacies of the two procedures. TAP: transversus abdominis plane, WI: wound infiltration.

Table 3. Secondary Outcomes of 58 Patients Undergoing Laparoscopic Radical Prostatectomy Managed according to TAP Group or WI Group

<table>
<thead>
<tr>
<th>Variable</th>
<th>TAP (n = 30)</th>
<th>WI (n = 28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>First flatus (h)</td>
<td>18.2 ± 12.5</td>
<td>20.1 ± 11.2</td>
<td>0.510</td>
</tr>
<tr>
<td>Time to sitting (h)</td>
<td>23.0 ± 14.1</td>
<td>23.0 ± 19.3</td>
<td>0.955</td>
</tr>
<tr>
<td>Time to ambulation (h)</td>
<td>33.1 ± 24.9</td>
<td>34.6 ± 29.7</td>
<td>0.838</td>
</tr>
<tr>
<td>Length of stay (d)</td>
<td>3.3 ± 2.0</td>
<td>3.8 ± 3.8</td>
<td>0.512</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. TAP: transversus abdominis plane, WI: wound infiltration.

be due to the timing of the regional anesthesia administration, which was pre-incisional in our study, which could influence the effectiveness of postoperative analgesia by blocking sensory flow in the periphery before the creation of the painful stimulus [22,23], or the intrinsic differences in the type of procedure (extraperitoneal vs. intraperitoneal LRP); however, a study that compared both approaches of LRP showed that narcotic analgesic requirements were similar [24].

Another important aspect of our study was the multimod-
al analgesic regimen that accompanied both types of regional anesthesia. We used a standardized hospital protocol based on scheduled administration of paracetamol, NSAIDS, and metamizole, because several studies have demonstrated decreased opioid use with this approach [5,25]. In fact, we observed that opioid requirements were not only similar between the groups but were also extremely low. The results of other studies which compared WI and TAP in laparoscopic surgery also showed similar opioid requirements between the two groups; however, the average consumption was significantly higher in both groups [16-18]. This may be due to the fact that the multimodal analgesic regimen we used relied on non-opioid agents that may have synergistic effects and allow the administration of regularly scheduled rather than as-needed doses. Minimizing the use of postoperative opioids is a major advantage for controlling the effect of medical practices on the opioid epidemic and minimizing opioid-related side effects, such as PONV.

Our study had some limitations. Abdominal wall sensitivity tests were not performed to assess TAP blocks because they were performed after the start of general anesthesia. However, it is well known that the extent of sensory blockade may not necessarily reflect the analgesic effect of the TAP block [26], and we did not observe intraoperative hypertensive episodes, which might occur due to inadequate analgesia [27]. Another potential limitation was that an unblinded surgeon could have affected postoperative patient care. Furthermore, we did not include a control group (without a block) because both techniques had been shown to provide better analgesic effects than a placebo [28].

In conclusion, the results of our prospective trial indicate that WI is not superior to TAP in achieving pain control during the first 48 h after LRP when combined with a non-opioid-based multimodal pain management strategy. Arguably, given that the pain scores and opioid requirements were very low in both groups, it is likely that the modalities were equally efficient, although this clinical trial was not designed to assess this hypothesis directly.

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**CONFLICTS OF INTEREST**

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

**DATA AVAILABILITY STATEMENT**

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

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Video-assisted thoracoscopic surgery (VATS) is a minimally invasive procedure with reduced surgical stress and postoperative pain compared with open thoracotomy. However, it is associated with significant acute pain regardless of wound size [1]. Paravertebral block (PVB), erector spinae plane block (ESPB), serratus anterior plane block, and intercostal block have been proposed as analgesic techniques for VATS [2,3]. PVB is strongly recommended, but is often contraindicated in some patients, such as those receiving antithrombotic therapy. ESPB has recently garnered attention owing to its proven non-inferior analgesic efficacy compared to PVB and its safety profile in reducing the occurrence of pneumothorax [4]. However, the mechanism underlying the action of ESPB remains unclear. In particular, the diffusion of local anesthetics into the paravertebral space is uncertain when the ESPB approach is used [5].

Moreover, the mid-point transverse process-to-pleura block (MTPB) and costotransverse foramen block (CTFB)
have been proposed [6,7]. They are conceptually classified as intertransverse process blocks (ITPB) by the American Society of Regional Anesthesia and Pain Medicine (ASRA) and European Society of Regional Anaesthesia and Pain Therapy (ESRA) consensus on standardizing nomenclature [8]. ITPB is expected to be more effective than ESPB in ensuring a more reliable local anesthetic diffusion into the paravertebral space. Reports of its efficacy have been rising; however, data on catheter placement and continuous administration of local anesthetics are limited, with only a few reports on MTPB [9]. The space behind the superior costotransverse ligament, which is the target site of MTPB, is surrounded by the intertransverse ligament and muscles, fatty tissue, and the superior costotransverse ligament [5]. During the continuous administration of local anesthetics via MTPB, fixation of the inserted catheter into this space and the stability of its effect are uncertain. Continuous administration of local anesthetics through ESPB has been well studied, and catheter placement along the fascial surface is expected to provide stability. ESPB is classified as a superficial nerve block with few contraindications [10].

In cases of VATS, in which a deep nerve block is contraindicated, ESPB may be considered as an alternative; however, ITPB may be more effective than ESPB through bolus administration. Therefore, we combined the bolus ITPB and continuous ESPB in our report. Here, we report a case series of anesthetic management during VATS using a combination of bolus ITPB and continuous ESPB. We have submitted the consent forms for these three patients to the Editorial office, so there are no discrepancies.

CASE REPORT

1. Case 1

A 72-year-old man (164 cm, 58.1 kg) with a history of diabetic neuropathy was diagnosed with lung cancer during a medical checkup. He was scheduled to undergo thorascoscopic pulmonary lobectomy with four ports (two each in the fifth and eighth intercostal spaces). Neuraxial anesthesia and PVB were avoided to negate the effects of the nerve block if neurosensory abnormalities were exacerbated postoperatively; therefore, we considered general anesthesia combined with bolus CTFB and continuous ESPB.

Rapid induction was achieved using 0.2 μg/kg/min of remifentanil, 40 mg of propofol, and 50 mg of rocuronium, which were added after establishing peripheral intravenous access. After induction of general anesthesia and placement of the patient in the right lateral position, a puncture at the Th5–6 level, which was the location of the main port, was created under ultrasound guidance. In addition, saline solution was injected to check the needle tip. After confirming the needle tip position, 20 ml of 0.25% levobupivacaine was injected as CTFB (Fig. 1). Color Doppler was used to continuously check the position of the needle tip while the local anesthetic was injected. Subsequently, a catheter was inserted into the erector spinae plane at the same vertebral level (Fig. 2), an infuser pump (COOPDECH Balloonjector Medical Co., LTD; 0.17% levobupivacaine, 4 ml/h; bolus, 4 ml; lockout time, 60 min) was connected, and postoperative continuous analgesia was initiated. The patient’s hemodynamics remained stable during the surgery with the administration of 4% desflurane and remifentanil (0.03 μg/kg/min). Operating and anesthetic times were 186 min and 269.

![Fig. 1. Ultrasonographic visualization of a costotransverse foramen block (case 1). Color Doppler was used to confirm local anesthetic administration. ESM: erector spinae muscle, NR: neck of the rib, TP: transverse process. Yellow arrow: needle pathway.](image1)

![Fig. 2. Ultrasound image after catheterization into the erector spinae plane (case 1). Normal saline solution was used to confirm the correct catheter insertion position. ESM: erector spinae muscle, NS: normal saline solution, TP: transverse process. White arrowhead: catheter.](image2)
min, respectively. The patient received 300 µg of intravenous fentanyl (100 µg immediately before the surgery, 100 µg at the time of wound closure, and 100 µg added during the surgery at the discretion of the anesthesiologist in charge) and 1,000 mg of acetaminophen intraoperatively.

Postoperative pain was measured using an 11-point numerical rating scale (NRS; 0, no pain; 10, worst pain imaginable). The patient’s postsurgical NRS scores at 2 h, 24 h, and 48 h were 4, 2, and 0 at rest, respectively. The NRS scores at 24 h and 48 h postoperatively were 3 and 5, respectively, upon movement. A postoperative pinprick test revealed an effective area from the parasternal to the anterior axillary line up to Th3–6.

The postoperative pain did not worsen after block termination. The ESPB catheter was removed 42 h postoperatively, and the patient was discharged from the hospital on postoperative day (POD) 6.

2. Case 2

A 35-year-old man (164 cm, 79.6 kg) with right pulmonary apex pneumothorax from lung fistula formation due to nontuberculous mycobacteriosis was scheduled for fistula closure with three-port VATS (one and two in the sixth and eighth intercostal spaces, respectively). He refused epidural anesthesia because of the fear induced by his first surgery; therefore, he was managed perioperatively with general anesthesia and intravenous patient-controlled analgesia (IV-PCA) for the first time. Nausea occurred frequently with IV-PCA. During the second fistula closure, general anesthesia was induced and a single dose of ESPB (0.25% levobupivacaine, 30 ml, at the Th5–6 level) was administered to reduce opioid consumption; however, postoperative nausea still occurred due to the IV-PCA connection. For the third instance, we decided to add a continuous nerve block. Rapid induction was achieved using 0.2 µg/kg/min of remifentanil, 140 mg of propofol, and 50 mg of rocuronium, which were added after establishing peripheral intravenous access. Anesthesia was maintained with 6% desflurane and remifentanil (0.08–0.20 µg/kg/min). After induction of general anesthesia and placement of the patient in the left lateral position, MTPB was administered with 15-ml bolus of 0.25% levobupivacaine at the Th5–6 and Th7–8 levels. The needle tip was checked using the method described in case 1, and the catheter was placed in the space widened with normal saline beneath the erector spinae plane of Th7–8, where the thoracic drain would be placed postoperatively. The anesthesiologist in charge decided to increase the remifentanil dosage to 0.2 µg/kg/min because of the additional intraoperative dissection of the seventh rib and a 10-cm skin incision; however, the patient’s vital signs indicated that opioid might have been sufficient. Continuous ESPB (0.17% levobupivacaine, 4 ml/h) was administered postoperatively. The operating and anesthetic times were 132 min and 252 min, respectively. The patient received 300 µg of intravenous fentanyl (100 µg immediately before the surgery, 100 µg at the time of wound closure, and 100 µg added during the surgery at the discretion of the anesthesiologist in charge) and 1,000 mg of acetaminophen intraoperatively. The postoperative NRS scores at 2 h, 24 h, and 48 h were 0, 1, and 0, respectively, at rest and without a bolus requirement. The NRS score after movement at 24 h and 48 h postoperatively was 5 for both. The NRS was audible; however, the pinprick test was not performed because of the wound dressing on the 10-cm skin incision. Postoperative nausea was not observed, and the catheter was removed on POD 2.

3. Case 3

A 70-year-old man (168 cm, 72.4 kg) with right upper lobe lung cancer was scheduled to undergo right upper lobectomy with four-port VATS (two each in the fourth and seventh intercostal spaces). He had undergone percutaneous coronary intervention on the left anterior descending and circumflex branches 8 years prior because of angina pectoris with other complications such as diabetes, stroke, chronic atrial fibrillation, chronic renal failure, and spinal canal stenosis. Antithrombotic therapy with apixaban and clopidogrel was withdrawn 2 days and 14 days, respectively, preoperatively. Although neuraxial block or PVB was not absolutely contraindicated, they were not performed because of the risk of hematoma and the patient’s early postoperative anticoagulation schedule. Rapid induction was achieved using 0.25 µg/kg/min of remifentanil, 100 µg of fentanyl, 40 mg of propofol, and 70 mg of rocuronium, which were added after establishing peripheral intravenous access. Anesthesia was maintained with 1.3% sevoflurane and remifentanil (0.11–0.18 µg/kg/min). After induction of general anesthesia and placement of the patient in the left lateral position, MTPB was administered with a 20-ml bolus of 0.25% levobupivacaine at the Th5–6 and Th7–8 levels. The placement of the needle tip and catheter was checked using the method mentioned in case 2. Continuous ESPB (0.17% levobupivacaine, 4 ml/h) was administered postoperatively. Operating and
anesthetic times were 150 min and 237 min, respectively. The patient received 150 μg of intravenous fentanyl (100 μg at the time of anesthesia induction and 50 μg at the time of wound closure) and 1,000 mg of acetaminophen intraoperatively. His postoperative NRS scores at 2 h, 24 h, and 48 h were 0, 3, and 0, respectively, at rest and without a bolus requirement. A postoperative pinprick test revealed an effective area at Th4–8 of the anterior axillary line. The NRS scores after movement at 24 h and 48 h postoperatively were 8 and 5, respectively. The ESPB catheter was removed on the afternoon of POD 1 to resume the antithrombotic therapy.

**DISCUSSION**

VATS is a minimally invasive surgical option for patients with lung malignancy or pneumothorax. However, it often requires multiple intercostal port holes, which cause unbearable postoperative pain. Guidelines for enhanced recovery recommend epidural anesthesia and PVB as postoperative analgesia techniques for lung surgeries, such as VATS and open thoracotomy [2]. However, epidural anesthesia is ineffective in preventing chronic pain and adverse events, including urinary retention, hypotension, and muscle weakness, whereas PVB is used in VATS for procedure-specific postoperative management, as recommended by the ESRA [3].

PVB must be avoided as epidural anesthesia in patients undergoing antithrombotic therapy [10]. Although PVB is highly recommended, performing it in high-risk patients may not be advisable because of its high failure rate (10%) [11] and possible complications, such as pneumothorax. The analgesic management strategy in VATS for procedure-specific postoperative pain management proposed by ESRA recommends ESPB as grade A for a single shot and grade B for continuous administration [3]. Thus, ESPB is considered a good alternative to PVB; however, its mechanism of action remains unclear. Some proposed mechanisms of action include analgesic effects mediated by elevated local anesthetic plasma concentrations due to systemic absorption, nerve innervation of the thoracolumbar fascia, and immunomodulatory analgesic effects through the lymphatic system [5]. Whether ESPB induces blockade through the direct spread of local anesthetics to the paravertebral space remains controversial.

ITPB is considered more effective than ESPB because it involves the administration of a local anesthetic into a space deeper than the erector spinae plane and shallower than the superior costotransverse ligament, which forms the posterior part of the paravertebral space. MTPB and CTFB techniques were first reported in 2017 and 2020, respectively [6,7]. Although these blocks differ in terms of local anesthetic administration, they are conceptually classified as ITPB by the ASRA/ESRA nomenclature [8]. In the single-injection technique, the superiority of ESPB and ITPB has not yet been studied; however, when the diffusion pathway is considered, ITPB may be more effective because local anesthet-

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**Fig. 3.** Schema representing the point of local anesthetic administration by the nerve blocks. ESPB targets the erector spinae plane, PVB targets deeper than the SCTL, and CTFB and MTPB target sites deeper than the erector spinae plane but shallower than the SCTL. These blocks allow the local anesthetic to reach the PVS more easily compared to ESPB (orange arrows). It should be noted that the puncture point and CTFB image can only be obtained by moving the probe slightly more medially. CTFB: costotransverse foramen block, ESPB: erector spinae plane block, MTPB: mid-point transverse process-to-pleura block, PVB: paravertebral block, PVS: paravertebral space, SCTL: superior costotransverse ligament, TP: transverse process.
ics diffuse more reliably into the paravertebral space (Fig. 3) [5]. Therefore, we chose ITPB for single-injection blocks.

The single-injection block approach was tailored for each case. In case 1, CTFB was selected because the patient was relatively thin and CTFB images could be obtained easily. Shibata et al. [7] also reported the use of CTFB in two female patients weighing 48–50 kg. Conversely, MTPB was selected for overweight patients with body mass indices > 25. Although image rendition may largely depend on the operator’s skill and performance of ultrasound equipment, the influence of body size on the effect of CTFB and MTPB remains unclear. For single-shot MTPB, the time to first opioid demand was 12 h for VATS [12], and for single-shot CTFB, the duration of the blockade was 6–8 h [7]. Therefore, additional analgesia methods were considered necessary to obtain analgesia overnight. Considering the side effects of opioids, a continuous peripheral nerve block is preferred over IV-PCA.

Catheter insertion for the continuous administration of anesthetics with MTPB is difficult [9], and the actual fixation of the catheter in the retro-superior costotransverse ligament space and the stability of its effect are uncertain. In contrast, in a cadaveric study on ESPB, the diffusion of local anesthetics into the paravertebral space was controversial [13]. However, the following factors suggest the possibility of diffusion into the paravertebral space in a living human: (a) the posterior wall of the paravertebral space is slit-like and not completely closed by the superior costotransverse ligament [14], (b) pleural negative pressure due to breathing, and (c) erector spinae muscle contraction.

Although there are concerns regarding hematoma formation with continuous ESPB with catheter placement, the latest guidelines classify ESPB as a superficial nerve block [10]. Therefore, we inserted a catheter into the erector spinae plane and administered continuous ESPB. In fact, in the present cases, including case 3, apparent hematoma or findings suggestive of a hematoma were not observed.

The best way to continuously administer ESPB is debatable. Intermittent mechanical dosing methods are typically effective; however, continuous ESPB dosing using disposable balloon injectors has also been reported [15]. As a superior method of administration has not yet been established, continuous ESPB with a balloon injector, to which we were accustomed, was selected. Opioids were not required post-operatively, and a combination of peripheral nerve blocks, acetaminophen, and nonsteroidal anti-inflammatory drugs were used to manage postoperative analgesia.

In summary, when a deep nerve block such as PVB cannot be administered, ESPB may be considered as an alternative. There have been negative reports on ESPB regarding its originally proposed mechanism of action: the diffusion of local anesthetics into the paravertebral space. MTPB and CTFB, which were classified under ITPB, seem to be more reliable than ESPB in this aspect. However, evidence of ITPB in terms of analgesia with catheter placement and continuous administration has been lacking. Thus, we considered the clinical evidence for continuous ESPB and the safety of ESPB as a superficial nerve block. This report is significant as it shows that bolus ITPB and continuous ESPB may be superior to a combination of single-dose ESPB and continuous ESPB, as an alternative to PVB. To our knowledge, this is the first report on the combined use of bolus ITPB and continuous ESPB in VATS. These cases support the combined use as an effective postoperative analgesia strategy in cases where deep nerve blocks, such as PVB, cannot be used in VATS.

FUNDING

None.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

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Difficult airway is a challenging situation in which a trained anesthesiologist experiences difficulty or failure with one or more of the following: facemask ventilation, laryngoscopy, supraglottic airway ventilation, tracheal intubation, extubation, or invasive airway [1]. After easy facemask ventilation and full laryngoscopy visualization, it can be perplexing to experience difficulty with tracheal intubation when a challenge was not anticipated. Difficult intubation occurs due to anatomical airway abnormalities. Prediction of difficult intubation can be possible using physical characteristics such as obesity, restricted mandibular protrusion, higher Mallampati classification, short thyromental distance, and immobility of the neck [1,2]. However, anatomical abnormalities involving the larynx and trachea are frequently asymptomatic [3] and can remain unsuspected until difficult tracheal intubation during anesthesia. The narrowing anatomy of the upper airway that includes any part of the larynx and trachea is termed laryngotracheal stenosis (LTS). Major risk factors for LTS include previous tracheal intubation and prolonged duration; however, they are frequently overlooked during a pre-anaesthetic evaluation because the patient may not exhibit symptoms suggestive of an airway abnormality [4].

Background: Difficult airway occurs due to anatomical abnormalities of the airway that can be predicted through airway assessments; however, abnormalities beyond the vocal cord can be clinically asymptomatic and undetected until intubation failure to advance the endotracheal tube.

Case: We present a case of an unanticipated difficult airway in a stuporous 80-year-old female with a recent history of intracerebral hemorrhage and prolonged intubation. She required emergency ventriculo-peritoneal shunt surgery due to the progression of her hydrocephalus. Under anesthesia, facemask ventilation was easy and video laryngoscopy provided a full view of the glottis; however, endotracheal tube (ETT) entry failed. We suspected stenosis beyond the vocal cord, and a smaller diameter ETT was inserted and maintained for airway management during emergency surgery. Postoperative neck computed tomography findings revealed laryngotracheal stenosis (LTS).

Conclusions: Anesthesiologists should be aware that LTS may be asymptomatic and consider difficult airway guidelines in patients with history of prolonged endotracheal intubation.

Keywords: Airway management; Endotracheal intubation; Laryngostenosis; Stupor; Ventriculo-peritoneal shunt.
We present a case of an unanticipated difficult airway in a stuporous 80-year-old patient with hydrocephalus who required emergency ventriculo-peritoneal (V-P) shunt surgery. After failing to advance an endotracheal tube (ETT) beyond the vocal cord despite a full view of the glottis using a video laryngoscope, we suspected anatomical narrowing of the larynx, and a smaller diameter ETT was inserted and maintained for airway management during surgery. Postoperatively, the patient remained intubated because difficult extubation was expected, and a neck computed tomography (CT) scan revealed LTS.

**CASE REPORT**

The publication of this case report was authorized by the Institutional Review Board (no. 2022-12-019), and the requirement for informed consent was waived.

An 80-year-old female (156 cm, 60 kg) with American Society of Anesthesiologists physical status classification IV required emergency V-P shunt surgery for her progressing hydrocephalus. She had been on medication for 12 years after being diagnosed with hypertension and cerebral infarction. Her most recent medical history includes admission to the emergency room four weeks ago for a stuporous level of consciousness. She was sedated due to agitated behavior and intubated in the emergency room with 7.5-mm inner diameter (ID) and 10.0-mm outer diameter (OD) plain cuffed ETT (Rüsch® Super Safety Clear™, Teleflex Medical) for ventilatory support. Brain CT indicated intracerebral hemorrhage in the left thalamus; subsequently, the patient underwent emergency surgery for stereotactic hematoma removal and external ventricular drainage. She remained stuporous and was mechanically ventilated in the neurosurgery intensive care unit (NSICU). On the third postoperative day, ETT cuff leakage was discovered, and the patient was re-intubated in the NSICU with another 7.5-mm ID and 10.0-mm OD plain cuffed ETT. Tracheostomy was scheduled for the tenth postoperative day, but it was not performed because the patient’s family members refused consent. The total duration of ETT placement was three weeks in the NSICU. After extubation, she was transferred to the general ward, and oxygen (2 L/min) was administered through a nasal cannula. Pulse oximetry readings were maintained from 97% to 99% without ventilatory support.

On the eighth day in the general ward, the neurosurgeon observed a dull response to external stimuli during routine rounding, and an external ventricular drainage obstruction was discovered. Brain CT indicated acute development of hydrocephalus, and the neurosurgeon requested emergency surgery for V-P shunt placement. A preoperative evaluation of emergency surgery was carried out. The patient did not exhibit any clinical signs of respiratory distress. Arterial blood gas analysis with oxygen (2 L/min) supply via the nasal cannula remained within the normal range (PaO$_2$ 114.9 mmHg, PaCO$_2$ 40.6 mmHg), and her chest x-ray was unremarkable (Fig. 1).

In the operating room, the patient was uncooperative, but had regular spontaneous breathing with no signs of excessive effort, wheezing, or stridor. The patient was monitored with electrocardiograph electrodes, noninvasive blood pressure, pulse oximeter, and electromyograph TwitchView® (Blink Device Co.). The oximetry reading was 98% in room air. After 3 minutes of preoxygenation, we administered propofol at 1.5 mg/kg, rocuronium at 0.6 mg/kg, and remifentanil at 0.05 μg/kg/min through continuous infusion. Facemask ventilation was performed for 3 minutes without excessive resistance.

Intubation was initiated after the train-of-four count confirmed deep neuromuscular block. Video laryngoscope Insigheters® (iS3, Shenzen Insigheters Medical Technology Co.) was used for intubation as part of the department’s routine for safe intubation in the operating room. The video laryngoscopy provided us with a full view of the glottis (Fig. 2). The posterior one-half of the true vocal cord was not fully visible. After 3 minutes of facemask ventilation, we administered propofol at 1.5 mg/kg, rocuronium at 0.6 mg/kg, and remifentanil at 0.05 μg/kg/min through continuous infusion. Facemask ventilation was performed for 3 minutes without excessive resistance.

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visible due to posterior glottic edema. There was no visible narrowing or stenosis of the subglottic space. Initial intubation was attempted with 7.0-mm ID and 9.7-mm OD Shiely™ Lo-Contour flexible reinforced cuffed ETT (Covidien Ireland Limited). However, the tip of the tube failed to advance 2 cm beyond the vocal cord. A second attempt was made immediately using 6.5-mm ID and 8.8-mm OD Shiely™ Lo-Contour flexible reinforced cuffed ETT, which also failed entry in the same way. Video laryngoscope was removed, and facemask ventilation was resumed.

Facemask ventilation was without excessive pressure and the oximetry reading remained at 100%.

We informed the neurosurgeon of the suspected narrowing beyond the glottis and recommended comprehensive airway evaluation, including consultation with an otolaryngologist. However, the neurosurgeon stated that emergency surgery could not be delayed due to the severity of hydrocephalus and requested for an additional intubation attempt using a smaller diameter ETT. An emergency airway cannulation was prepared in the event of airway obstruction, and a third intubation attempt was made using a 5.5-mm ID and 7.5-mm OD Shiely™ Lo-Contour flexible reinforced cuffed ETT. The tube advanced with resistance beyond the vocal cord, and ventilation was confirmed using capnography. The tracheal tube cuff was gently inflated using a pressure cuff gauge (Mallinckrodt™ Hand Pressure Gauge, Covidien Deutschland GmbH) until the pressure reached 20 cmH₂O. Ventilation was performed without excessive airway pressure, with a peak inspiratory pressure between 25 and 30 cmH₂O. We administered 5 mg of dexamethasone to reduce airway edema that may have been caused by multiple intubation attempts. The surgery was completed as planned, and the patient remained intubated and transported to the NSICU under manual ventilation with an oxygen supply of 8 L/min. Postoperative neck CT findings confirmed LTS involving the bottom part of the larynx (subglottis) and the cervical portion of the trachea (Fig. 3). Enlargement of both thyroid glands with multiple nodules was incidentally found. Otolaryngologist was consulted, and family members gave consent to surgical tracheostomy which was performed on

![Image](image.png)

**Fig. 2.** Video laryngoscopy image was captured immediately after the second intubation failure. Posterior half of the true vocal cord is not fully visible due to edema. Erosion and inflammation are apparent in the posterior glottis.

![Image](image.png)

**Fig. 3.** Axial (A), coronal (B), and midline sagittal section (C) of computerized tomography of the neck with 5.5 mm internal diameter cuffed reinforced endotracheal tube in place. Focal stenosis (white triangle) of the upper airway involves the subglottis and cervical part of the trachea. Enlargements of both thyroid glands with multiple nodules do not affect the cartilage structure of trachea.
the fifth postoperative day after V-P shunt surgery. The patient remained bedridden in a stuporous mental state with ventilation support for an additional 6 days before being transferred to another hospital. There were no other respiratory complications.

**DISCUSSION**

LTS comprises a broad set of diagnoses characterized by narrowing anatomy of the upper airway, including the glottis, supraglottis, subglottis, and trachea, and is associated with severe and potentially fatal respiratory compromise [3]. LTS is most commonly acquired from prolonged intubations in which the endotracheal cuff pressure exceeds the tracheal mucosa’s mean capillary pressure (> 30 mmHg) [3, 5]. Excessive pressure leads to ischemia, granulation tissue formation, and scarring within the lumen strictures [4, 5]. The most common symptoms of LTS from any etiology are hoarseness, wheezing, stridor, and nonproductive cough [3-5]. However, because the majority of patients are asymptomatic until the trachea is reduced to at least more than half of its original diameter, medical history and physical examination may not predict difficult airways [5].

We did not suspect anatomical narrowing below the glottis until after the intubation entry failure. During our emergency pre-anesthetic evaluation, the patient displayed no signs of respiratory distress, such as stridor or wheezing, and we were unable to assess for throat pain, hoarseness, or dysphonia due to the patient’s stupor. Preoperative arterial blood gas analysis was normal, and a chest x-ray prior to surgery revealed no evidence of tracheal abnormality (Fig. 1). The patient did not exhibit abnormal anatomical characteristics of difficult intubation predictors such as obesity, mandibular protrusion, high Mallampati classification, short thyromental distance, and immobility of the neck. Furthermore, we were given an initial impression of easy airway management because of the patient’s recent history of two successful intubations by non-anesthesiologists.

Tracheal intubation is a major factor in the development of LTS. Larger and less flexible ETT, excessive cuff pressure (> 30 mmHg), and poor intubating conditions such as insufficient sedation or muscle relaxation are major factors of tracheal injury. A larger ETT can impinge on laryngeal structures, causing vocal cord damage, and contact the subglottic mucosa, causing lacerations, erosions, or tracheal rupture [5, 6]. Larger tubes have a longer cuff, which will lie more proximally in the trachea closer to the vocal cords and be associated with a longer segment of mucosal tracheal compression [6]. Furthermore, prolonged endotracheal intubation is strongly associated to the development of LTS, which can also result in tracheomalacia, tracheoesophageal fistula, granuloma, or other tracheal structural changes [7]. Therefore, patients who require prolonged intubation, defined as more than 7 to 14 days of intubation, should consider tracheostomy [7, 8]. The proper ETT size for our patient, a female with a height of 156 cm, should have been 7.0-mm ID or smaller. Prior intubations using 7.5-mm ID plain cuff ETT by other departments may have been attributed to tracheal injury in addition to three weeks of prolonged intubation in NSICU.

The 2022 American Society of Anesthesiologists Practice Guideline for Management of the Difficult Airway defines difficult intubation as tracheal intubation that necessitates multiple attempts. Failed intubation attempts after general anesthesia induction necessitates a non-emergency pathway when mask ventilation is adequate, which includes considering awakening the patient or using alternative intubation approaches [1]. After our intubation entry failure, awakening the patient under mask ventilation would have been the safest approach because anatomical narrowing was suspected. Comprehensive airway evaluation with an otolaryngologist consultation can identify the cause of failed entry and enable us to plan for airway management, such as tracheostomy before surgery. However, in our case, the emergency surgery could not be postponed, and successful airway management was critical.

Alternative intubation techniques such as the use of a supraglottic airway device or laryngeal mask airway (LMA) can be used for difficult intubation when mask ventilation is possible [1]. According to Parmet et al. [9], LMA has a 94% success rate in providing rescue ventilation in difficult airway management. Agarwal and Shobhana [10] advocate the use of LMA in patients undergoing short neurosurgeries. However, in the case of our patient who required V-P shunt surgery, LMA was not ideal because manipulation in the neck occurs while tunneling the ventricular catheter to the peritoneum, and because the head is not fixed, the LMA can be displaced during surgery [11]. Therefore, we decided to retry tracheal intubation with a small tube after preparing the tracheostomy so that it could be performed immediately in an emergency. However, repeated intubation attempts should be approached with caution because they can cause further structural injury and obstruction, eventually leading to respiratory compromise and arrest [12, 13]. The Difficult
Airway Society (DAS) guidelines recommend limiting intubation attempts to $3 + 1$ [12]. Because we had used video laryngoscopy since the first intubation attempt, we considered the third to be the final intubation attempt. Fortunately, the third intubation attempt was successful.

During our third intubation attempt, a 5.5-mm ID reinforced cuffed ETT advanced beyond the vocal cord with resistance, indicating anatomical narrowing of the subglottis and possibly trachea injury. Intubation with a small tracheal tube raises concerns about the safety and conduct of anesthesia. Small-diameter ETT has a smaller luminal cross-sectional area and higher resistance to airflow, resulting in higher peak inspiratory pressure during positive ventilation and increased resistance to expiratory airflow [6,8]. Small ETT may easily become obstructed from the patient’s viscous secretions that require suction with an elevated risk of lung collapse and hemodynamic instability when the ratio between other diameters of the suction catheter and the ID of the tracheal tube surpasses 50%, as well as the risk of aspiration and air-leak under positive pressure ventilation due to inability to seal the trachea [6]. Our patient experienced none of the aforementioned issues during surgery.

We followed the DAS guidelines for the management of tracheal extubation, which define “at-risk” extubation as when risk stratification indicates that the patient may be unable to maintain his/her own airway after extubation or reintubation may be difficult [14]. We decided to postpone extubation because our patient met both factors of “at-risk” extubation; thus, the patient required a comprehensive airway assessment, such as a neck CT and otolaryngologist consultation, in a non-emergency setting. Fortunately, no additional damage, such as bleeding, was found in the postoperative neck CT results. However, if fiberoptic bronchoscopy-assisted intubation had been conducted as described by Hasegawa et al. [15], it would have been possible to confirm tracheal stenosis as well as perform atraumatic intubation in situations where surgery could not be postponed.

This case describes our experience of a stuporous patient with undiagnosed LTS whose vocal cords were visible using video laryngoscopy but whose airway management was difficult due to ETT entry failure. In similar situations, we recommend following guidelines for difficult airway management, as well as following extubation guidelines to reassess the risk of extubation. Anesthesiologists should be aware that LTS may be asymptomatic and perform comprehensive airway evaluations with fiberoptic bronchoscopy and imaging studies in addition to multidisciplinary approach in patients with risk factors for LTS, such as a history of prolonged endotracheal intubation. Lastly, prevention of LTS should be conducted in the routine practice of airway management by understanding the characteristics of ETT and avoiding traumatic intubations.

**Funding**

None.

**Conflicts of Interest**

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

**Data Availability Statement**

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

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**References**


1. Online manuscript review process and guidelines for submission

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

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

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

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

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

2. Mandatory English editing for Korean authors

APM has made English editing mandatory for manuscripts submitted on or after September 1, 2013. Authors are responsible for the cost of editing. For English manuscripts, please submit them to a professional editing service after acceptance and upload the edited file and certificate of editing in the manuscript submission system. Manuscripts edited by an individual and not through a professional editing service will not be accepted. Manuscripts submitted in Korean will be translated into English by the Society after acceptance, and Korean version will be published only on the website (www.anesth-pain-med.org).
Anesthesia and Pain Medicine (APM) is the official scientific journal of the Korean Society of Neuroscience in Anesthesiology and Critical Care (KSNACC), the Korean Society for Anesthetic Pharmacology (KSAP), the Korean Society of Obstetric Anesthesiologists (KSOA), the Korean Society of Pediatric Anesthesiologists (KSPA), the Korean Neuromuscular Research Society (KNRS), the Korean Society of Cardiothoracic and Vascular Anesthesiologists (KSCVA), the Korean Society of Transplantation Anesthesiologists (KSTA), the Korean Spinal Pain Society (KSPS), and the Korean Society for Airway Management (KSAM). The abbreviated title is “Anesth Pain Med”. It is published in English four times a year on the last day of January, April, July, and October.

I. Editorial Policy

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

II. General Information

1. Publication types

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

2. Language

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

3. Submission of manuscripts

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

4. Data Availability Statement

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

- The datasets generated during and/or analyzed during the current study are available in the [NAME] repository, [PERSISTENT WEB LINK TO DATASETS]
- The datasets generated during and/or analyzed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.
- The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.
- Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.
- All data generated or analyzed during this study are included in this published article [and its supplementary infor-
5. Preprint policy (Posted on January 9, 2023)

A preprint can be defined as a version of a scholarly paper that precedes formal peer review and publication in a peer-reviewed scholarly journal. APM allows authors to submit a manuscript that have been posted on preprint platform to the journal. It is not treated as duplicate submission or duplicate publication. APM recommend authors to disclose it with only single DOI during the submission process. Otherwise, it may be screened from the plagiarism check program — Similarity Check (iThenticate).

Preprint submission will be processed through the usual peer-review process. In addition, the preprint's history will be tracked by additional independent editor, with an emphasis on the posting procedure and format.

If the manuscript with preprint is accepted for publication, authors are recommended to update the information at the preprint platform with a link to the published article in APM, including DOI at APM. It is strongly recommended that authors cite the article in APM instead of the preprint.

Moreover, APM does not permit referencing a preprint as a reference unless there is an exceptional circumstance that the authors can justify.

If the authors of a submitted article differ from those of the preprint, the authors must explain the change in authorship and demonstrate that it complies with ICMJE recommendations.

6. Disclosure of Artificial Intelligence (AI) Programs

Artificial Intelligence (AI) programs (e.g. ChatGPT or other similar software) cannot be considered as authors of submitted manuscripts because they do not meet the requirements for authorship. For instance, they cannot understand the role of authors or take responsibility for the content of the paper. Additionally, AI cannot meet the authorship criteria set by organizations such as the International Committee of Medical Journal Editors (ICMJE). This includes having the ability to give final approval for publication and being accountable for the accuracy and integrity of the work.

Furthermore, AI lacks the capacity to comprehend a conflict of interest statement, and cannot legally sign such a statement. Additionally, AI does not have independent affiliation from its creators, nor can it hold copyright.

Therefore, when submitting a paper, authors should not include AI as authors but rather acknowledge the use of AI and provide transparent information about how it was used in writing the manuscript. As the field of AI is rapidly evolving, authors using AI should declare this fact and provide specific technical details about the AI model used, including its name, version, source, and the method of application in the paper. This is in line with the ICMJE recommendation of acknowledging writing assistance.

7. Peer review process

The APM has an online submission and peer review system at http://submit.anesth-pain-med.org/.

APM reviews all manuscripts received. A manuscript is first reviewed for its layout and adherence to the aims and scope of the journal. If the manuscript does not fit the aims and scope of the Journal or does not adhere to the Instructions for authors, it may be returned to the author immediately after receipt and without a review. Before reviewing, all submitted manuscripts are inspected by Similarity Check powered by iThenticate (https://www.crossref.org/services/similarity-check/), a plagiarism-screening tool.

APM uses double-blind review, which means that both the reviewer and author identities are concealed from the reviewers, and vice versa, throughout the review process. To facilitate this, authors need to ensure that their manuscripts are prepared in a way that does not give away their identity. If one or more of editors are involved as authors, the editor(s) should not be involved in the peer reviewer selection, evaluation, or decision process. Submitted manuscripts will be reviewed by 2 or more experts in the corresponding field. The editor selects peer referees by recommendation of the Editorial Board members or from the specialist database owned by the Editorial Board. The Editorial Board may request authors to revise the manuscripts according to the reviewer’s opinion. After revising the manuscript, the author should upload the revised files with a reply to each item of the reviewer’s opinion. Additions and amendments to the revised manuscript should be highlighted in red. The author’s revisions should be completed within 60 days after the request. If it is not received by the due date, the Editorial Board will not consider it for publication.

To extend the revision period to more than 60 days, the author should negotiate with the Editorial Board. The manu-
The script review process should be finished the second review. If the reviewers wish further review, the Editorial Board may consider it. The Editorial Board will make a final decision on the approval for publication of the submitted manuscripts and can request any further corrections, revisions, and deletions of the article text if necessary. Statistical editing is also performed if the data need professional statistical review by a statistician. The review and publication processes that are not described in the Instructions for Authors will be incorporated into the Editorial Policy Statements approved by the Council of Science Editor Board of Directors, available at: www.councilscienceeditors.org/. The peer review process takes usually four to eight weeks after the manuscript submission.

We neither guarantee the acceptance without review nor very short peer review times for unsolicited manuscripts. Commissioned manuscripts are also reviewed before publication.

8. Article processing charge and publication fee

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

Our policy of article processing charge, even waived or issued, does not affect the entire review process.

9. Copyrights and secondary publication

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

10. Open access

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

III. Research and Publication Ethics Guidelines

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

1. Conflict-of-interest statement

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

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

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

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

2. Statement of informed consent

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

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

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

4. Protection of human and animal rights

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

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

5. Registration of the clinical research

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

6. Reporting guidelines

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

7. Author and authorship

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

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

Correction of authorship after publication: APM does not correct authorship after publication unless a mistake has been made by the editorial staff. Authorship may be changed before publication but after submission when an authorship correction is requested by all of the authors involved with the manuscript.

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

8. Plagiarism and duplicate publication

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

1) Intellectual theft
   Deliberate copying of large blocks of text without attribution
2) Intellectual sloth
   Copying of “generic” text, e.g., a description of a standard technique, without clear attribution
3) Plagiarism for scientific English
   Copying of verbatim text, often from multiple sources
4) Technical plagiarism
   Use of verbatim text without identifying it as a direct quotation but citing the source
5) Self-“plagiarism”
   Manuscripts are only accepted for publication if they have not been published elsewhere. Manuscripts published in this journal should not be submitted for publication elsewhere. Duplicate submissions identified during peer review will be immediately rejected, and duplicate submissions that are discovered after publication will be retracted. It is mandatory for all authors to resolve any copyright issues when citing a figure or table from a different journal that is not open access.

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

IV. Manuscript Preparation

APM recommends compliance with some or all of the following guidelines (https://www.equator-network.org).

- CONSORT for reporting of randomized controlled trials (http://www.consort-statement.org)
- STARD for reporting of diagnostic accuracy studies (http://www.stard-statement.org)
- STROBE for reporting of observational studies in epidemiology (http://www.strobe-statement.org)
- PRISMA for reporting of systematic reviews (http://www.prisma-statement.org)
- MOOSE for reporting of Meta-analyses of observational studies (https://jamanetwork.com/journals/jamasurgery/article-abstract/2778476)
- CARE for reporting of clinical cases (https://www.care-statement.org)
- AGREE for reporting clinical practice guidelines (http://www.agreetrust.org/resource-centre/agree-reporting-checklist/)
- ARRIVE for reporting of animal pre-clinical studies (https://arriveguidelines.org/arrive-guidelines)

1. Word processors and format of manuscripts

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

2. Abbreviation of terminology

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

Ex) target controlled infusion (TCI)

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

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

3. Word spacing

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

2) Leave no space when using a hyphen between words.
   Ex) intra-operative

2) When using parentheses, leave 1 space on each side in English, and leave no space in the Korean manuscript.

3) When using brackets in parentheses, apply square brackets.
   Ex) ([ ])}
4) Manuscripts in Korean should obey the rules of Korean spelling (www.korean.go.kr).

4. Citations

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

Ex) Kim et al. [1]

2) Citations should be applied after the last word.

Ex) It is said that hypertension can be induced [1] and the way to injure the brain [2] is...

Ex) Choi and Kim [1] reported...

3) Apply citations before a comma or period.

Ex) ....is reported [1],

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

5. Arrangement of manuscript

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

6. Organization of manuscript

1) Clinical or experimental research

(1) Cover page (upload separately)

① Title

Title should be concise and precise. The first word should be capitalized. Drug names in the title should be written with generic names, not brand names. For the title, only the first letter of the first word should be capitalized.

Ex) Effect of smoking on bronchial mucus transport velocity under total intravenous anesthesia ......... [○]

Ex) Effect of Smoking on Bronchial Mucus Transport Velocity under Total Intravenous Anesthesia ......... [×]

Provide drug names as generic names, not product names.

Ex) In CPR, Isosorbide Dinitrate is, ......... [○]

Ex) In CPR, Isosorbide Dinitrate (Isoket®) is, ......... [×]

Ex) In CPR, Isoket® is, ......... [×]

② Running title

A running title should be provided with no more than 40 characters, including letters and spaces in Korean, or 10 words in English. If this title is inappropriate, the Editorial Board may revise it.

③ Author information

First name, middle initial, and last name of each author, with their highest academic degree(s) (M.D., Ph.D., etc.), and institutional affiliations; make sure the names of and the order of authors as they appear on the Title Page and entered in the system match exactly.

④ Previous presentation at conferences

Title of the conference, date of presentation, and the location of the conference may be described.

⑤ Funding statement

Disclosure of all financial support for the work, including departmental or institutional funding/support, is mandatory.

⑥ Conflicts of interest

Any conflicts of interest for any or all authors within the 36 months of submission. If there are no competing interests, please add the following statement: “The authors declare no competing interests.” If any of these elements are not applicable to your submission, write “not applicable” after the number and topic; for example, “Prior Presentations: Not applicable.”

(2) Manuscript

① Title and Running title (without author information)

It should be the same as the Cover page.

② Abstract

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

③ Introduction
The introduction should address the article’s purpose concisely and include background information relevant to the paper’s purpose.

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

Institute and author names should be avoided.

When reporting experiments with human or animal subjects, the authors should indicate whether they received approval from the Institutional Review Board for the study. When reporting experiments with animal subjects, the authors should indicate whether the Institutional Board supervised the handling of the animals for the Care and Use of Laboratory Animals. Demographic data should be included in the materials and methods section if applicable.

As a rule, subsection titles are not recommended. If several study designs were used, then subtitles can be used without assigning numbers.

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

• Units Laboratory information should be reported using the International System of Units [SI], available at: https://www.nist.gov/pml/special-publication-811
  <Exceptions>
  A. The unit for volume is "L," while others should be written as "dl, ml, μl."
  Ex) 1 L, 5 ml
  B. The units for pressure are mmHg or cmH₂O, instead of Pascal.

C. Use Celsius for temperature. °C
D. Units for concentration are M, mM, μM.
  Ex) μmol/L; [ ]
E. When more than 2 items are presented, diagonal slashes are acceptable for simple units.
  Negative exponents should not be used.
  Ex) mg/kg/min [O], mg · kg⁻¹ · min⁻¹ [×]
F. Leave 1 space between number and units, except %, °C.
  Ex) 5 mmHg
  Ex) 5%, 36°C
G. Units of time
  Ex) hour: 1 h = 60 min = 3,600 s, day: 1 d = 24 h = 86,400 s

• Machines and equipment
  According to the 11th edition of the American Medical Association, provide model name and manufacturer’s name. Do not present the country.
  For drug names, use generic names. If a brand name should be used, insert it in parentheses after the generic name. Provide® or ™ as a superscript and the manufacturer’s name.

• Ions
  Ex) Na⁺[O], Mg²⁺[O], Mg⁺²[×], Mg⁺²[×]
  Ex) Premedicated magnesium [O]
  Ex) Premedicated Mg⁺² [O]

⑤ Results
Results should be presented in a logical sequence in the text, tables, and figures, giving the main or most important findings first. Do not repeat all the data provided in the tables or figures in the text; emphasize or summarize only the most important observations. Results can be sectioned by subsection titles but should not be numbered. The citation of tables and figures should be provided as Table 1 and Fig. 1.

Type or print each table on a separate page. Figures should be uploaded as separate tif, jpg, pdf, gif, ppt files.

⑥ Statistics
Precisely describe the methods of statistical analysis and computer programs used. Mean and standard deviation should be described as mean ± SD, and mean and standard error should be written as mean ± SEM. Median and interquartile should be described as median (1Q, 3Q). When displaying P values, use a capital P and do not put a “." between "P" and “value”.

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

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

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

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

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

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

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

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

I. Results must be written in significant figures. The measured and derived numbers should be rounded 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/m$^2$ should be expressed as 2.42 (0.31) L/min/m$^2$.

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

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

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

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

References
- References should be obviously related to documents and should not exceed 50 in number. The number of references should not exceed 100 in reviews. However, the number of references has no limitation in systematic review and meta-analysis. References should be numbered consecutively in the order in which they are first mentioned in the
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


The reference style for APM is conveniently available as an out-of-the-box style within both EndNote and RefWorks.

Table

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

Legends for figures and photographs

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

(3) Figures and Photographs

1. APM encourages authors to use color to increase the clarity of figures. Please note that color figures are used without charge for online reading. However, since it will be charged upon the publication, authors may choose to use colors only for online reading.

2. Standard colors should be used (black, red, green, blue, cyan, magenta, orange, and gray). Avoid colors that are difficult to see on the printed page (e.g., yellow) or are visually distracting (e.g., pink). Figure backgrounds and plot areas should be white, not gray. Axis lines and ticks should be black and thick enough to frame the image clearly. Axis labels should be large enough to be easily readable, and printed in black.

3. Figures should be uploaded as separate tif, jpg, pdf, gif, or ppt files. The width of figure should be 84 mm (one column). The contrast of photos or graphs should be at least 600 dpi. The contrast of line drawings should be at least 1,200 dpi. Number figures as “Fig. (Arabic numeral)” in the order of their citation (ex. Fig. 1).

4. Photographs should be submitted individually. If Fig. 1 is divided into A, B, C, and D, do not combine it into 1, but submit each of them separately. Authors should submit line drawings in black and white.

5. In horizontal and vertical legends, the letter of the first English word should be capitalized.

6. Connections between numbers should be denoted by “*”, not “~”. Do not space the numbers (ex. 2–4).

7. An individual should not be recognizable in photographs or X-ray films unless written consent has been obtained from the subject and is provided at the time of submission.

8. Pathological samples should be pictured with a measuring stick.

(4) Video (movie) clip(s)

The APM publishes supplemental video (movie) clip(s) that will be available online. Authors should submit videos according to our video submission guidelines.

1. Each video clip should clearly illustrate the primary findings within an adequate amount of viewing time and should be discussed in the text. Authors should provide appropriate labeling (e.g., arrows, abbreviations of anatomic structures, etc.) in the video clips. However, all identifying information, including patient names and/or ID numbers, hospital names, and dates of the procedures, should be removed.

2. Video clips should contain succinct teaching points that must be supported by the current literature or standard reference texts, preferably those most accessible to the general reader. The adequacy of the teaching points will be evaluated during the review process and finally confirmed by the Editorial Board at the end of the review process.

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

4. The video clip(s) should have simple file names (e.g., Video 1, Video 2) and should include the appropriate extension (e.g., .mov, .mpg, .avi).

5. The maximum number of video clips is 20.

6. The video clip(s) should be playable on Microsoft Windows OS. The video clip(s) should be tested for playback before submission, preferably on computer not used for their creation, to check for compatibility.
issues.
⑦ Individual video files should be a minimum of 480 × 320 pixels (smaller clips will not be accepted) and a maximum of 2 GB. Files of < 15 MB will be rejected outright unless special arrangements have been made with the editorial board prior to submission. Approval of > 2 GB files will be made at the end of the review process.
⑧ Supplemental still images that correspond to the respective video clip(s) should be, but are not always required to be, accompanied by legends. The video clip file name(s) should refer to the corresponding figure number(s).
⑨ The author will be able to find additional information in the Figures and photographs section.

2) Case Reports
A case report is almost never a suitable means to describe the efficacy of a treatment or a drug; instead, an adequately powered and well-controlled clinical trial should be performed to demonstrate such efficacy. The only context in which a case report can be used to describe efficacy is in a clinical scenario, or population, that is so unusual that a clinical trial is not feasible. Case reports of humans must state in the text that informed consent to publication was obtained from the patient or guardian. Copies of written informed consents should be kept. If necessary, the editor or reviewers may request copies of these documents. If these steps are impossible, Institutional Review Board approval should be obtained prior to submission. The rarity of a disease condition is itself not an acceptable justification for a case report.
(1) Cover page: Same as that for clinical and experimental studies.
(2) Abstract: All case reports should contain a structured abstract that is written only in English. Provide an abstract of no more than 150 words. It should contain 3 subsections: Background, Case, and Conclusions. A list of keywords, with a minimum of 3 and maximum of 10 items, should be included at the end of the abstract.
(3) Introduction: Should not be separately divided. Briefly describe the case and background without a title.
(4) Case report: Describe only the clinical information that is directly related to the diagnosis and anesthetic management.
(5) Discussion: Briefly discuss the case, and state conclusions at the end of the case. Do not structure the conclusion section separately.
(6) References: The number of references should be less than 20. 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 are invited only by editorial board. If authors want to submit an unsolicited review article, please contact editorial office (apm@anesthesia.or.kr). Review articles should include unstructured abstracts written in English equal to or less than 250 words. The organization should be in order of abstract, introduction, text following each title, conclusion and references. Figures and tables should be provided in English. Body text should not exceed 30 A4-sized pages, and the number of figures and tables should each be less than 6. However, if necessary, the number of pages, the number of figures, and tables can be added in accordance with the decision of the editorial committee.

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 the same as those of Letters to the Editor.

6) Images and Videos in APM
   (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.