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REVIEW ARTICLES

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Aims and Scope

Anesthesia and Pain Medicine (APM) is the official scientific journal of Korean Society of Neuroscience in Anesthesiology and Critical Care (KSNACC), The Korean Society for Anesthetic Pharmacology (KSAP), The Korean Society of Obstetric Anesthesiologists (KSOA), The Korean Society of Pediatric Anesthesiologists (KSPA), Korean Neuromuscular Research Society (KNRS), Korean Society of Cardiothoracic and Vascular Anesthesiologists (KSCVA), Korean Society of Transplantation Anesthesiologists (KSTA), and The Korean Spinal Pain Society (KSPS) and Korean Society of Regional Anesthesia (KSR). The abbreviated title is “Anesth Pain Med”. It is published four times a year on the last day of January, April, July, and October in English. The mission of APM is to improve safety and quality of care of related patients and clinical practice of anesthesiologists by publishing definitive articles in the field of anesthesiology including practice of perioperative management, critical care, and pain medicine. The scopes of APM are as follows: anesthesiology-related issues from affiliated neuroanesthesiology (KSNACC), experimental, laboratory works or clinical relevance of anesthetic pharmacology (KSAP), anesthesiology for operative delivery, pain relief in labor, care of the critically ill parturient, perinatal physiology and pharmacology (KSOA), anesthetic care, perioperative management, and alleviation of pain in children (KSPA), physiology of neuromuscular transmission and block, pharmacology of neuromuscular blocking agents and their reversal agents, principles and applications of neuromuscular monitoring, and drug interaction between neuromuscular blocking agents and other substances (KNRS), anesthesiology for cardiothoracic and vascular surgery and management of patients undergoing various surgeries for patients with cardiac, pulmonary, and vascular diseases (KSCVA), perioperative anesthesia care of transplantation surgery, physiology or pharmacology related with transplantation anesthesiology (KSTA), pathophysiology, pharmacology, and all respects of spine related pain (KSPS), clinical techniques of regional blocks, anatomy, patient safety issues, basic sciences such as pharmacology of local anesthetics or sedative drugs (KSR).

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EXPERIENCE THE BRIDION EFFECT

Bridion (sugammadex) offers significantly fast and predictable recovery in most patients with moderate to profound rocuronium-induced neuromuscular blockade (NMB).¹⁻²

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Reappearance of 1–2 PTCs: 98% of Bridion (sugammadex) patients had recovered to a TOF ratio of 0.9 compared with only 11% of neostigmine patients within 5 minutes. The median range (interquartile range) time to recovery of the TOF ratio to 0.9 was 2.7 (1.1–2.6) to 1.4 min in the Bridion (sugammadex) group versus 49.0 min in the neostigmine group.²

Indication of Bridion is reversal of neuromuscular blockade induced by rocuronium or vecuronium.¹

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INTRODUCTION

Recently, the use of ultrasonography has become popular in operating rooms. The lumbar neuraxial block was traditionally performed using a surface landmark-guided technique. However, ultrasound (US)-guided technique has been more frequently used for neuraxial block. This article reviews the sonoanatomy of the lumbar spine, US-guided techniques for neuraxial block, and current evidence for the clinical usefulness of US-guided lumbar neuraxial block.

GROSS ANATOMY OF THE LUMBAR VERTEBRAE

The lumbar vertebra is composed of the vertebral body, pedicle, transverse process, superior articular process, inferior articular process, lamina, and spinous process. The gaps between two adjacent vertebrae can be divided into the interspinous and interlaminar spaces. The interlaminar space is bounded by the bases of the spinous processes, laminae, inferior articular processes, and superior articular processes (Fig. 1). For successful dural puncture, the spinal needle should be entered through the interlaminar space.

SONOANATOMY OF THE LUMBAR VERTEBRAE

To obtain ultrasonographic view of the lumbar spine, a curved-array probe is placed on the patient’s back in sitting or lateral decubitus position with lumbar spine flexion. An US probe can be applied in three basic ways: sagittal, transverse, and diagonal views. The angle of the probe can be adjusted medially in the parasagittal plane or tilted cephalad or caudad in the transverse plane to obtain the best image of the target structures. Although the diagonal view is not commonly used for preprocedural US imaging, it can be used for real-time US-guided neuraxial block.
SAGITTAL VIEWS OF THE LUMBAR SPINE

There are five basic sagittal plane views of the lumbar spine according to the probe location and direction. By moving the probe from a lateral position to the midline of the neuraxis, sagittal transverse process, sagittal articular process, sagittal lamina, and sagittal spinous process views can be obtained (Fig. 2A–D). From the probe position having the sagittal articular process view or sagittal lamina view, the parasagittal oblique view can be obtained by tilting the probe medially towards the midline (Fig. 2E). The parasagittal oblique view can be obtained by tilting the probe medially towards the midline (Fig. 2E). The parasagittal oblique view can be used for the determination of optimal intervertebral level for puncture by identifying the intervertebral level at which the posterior complex (ligamentum flavum–dura complex) and the anterior complex (the posterior longitudinal ligament, posterior surface of the vertebral body, and intervertebral disc) are visualized most clearly. It is also useful to select the intervertebral level at which the interlaminar height is the largest.

TRANSVERSE VIEWS OF THE LUMBAR SPINE

There are two basic transverse views for lumbar neuraxial block: transverse spinous process view and transverse interlaminar view. The transverse spinous process view is used to determine the midline composed of connecting spinous process tips (Fig. 3A). The transverse interlaminar view can be obtained by sliding the probe in a cephalad or caudad direction from the transverse spinous process view (Fig. 3B). Slight cephalad or caudad tilt in the transverse interlaminar view may be needed to obtain the image showing the dural sac located between the anterior and posterior complexes (Fig. 3C).

DIAGONAL VIEW OF THE LUMBAR SPINE

The diagonal view can be obtained by rotating the probe approximately 45 degrees from the sagittal articular process view, resulting in a combination of transverse and sagittal views. In this view, the spinous process of the upper vertebral body, interlaminar space, and lamina of the lower vertebral body can be visualized. It can be used for real-time US-guided neuraxial block (Fig. 4).

US-GUIDED TECHNIQUES FOR LUMBAR NEURAXIAL BLOCK

A systematic approach to US-guided lumbar neuraxial block in adults has been well-described in a previous re-
Fig. 2. Sagittal views of the lumbar spine. (A) Sagittal transverse process view, (B) sagittal articular process view, (C) sagittal lamina view, (D) sagittal spinous process view, (E) parasagittal oblique view. TP: transverse process, AP: articular process, L: lamina, SP: spinous process, PC: posterior complex, AC: anterior complex, SC: spinal canal (intrathecal space).

Fig. 3. Transverse views of the lumbar spine. (A) Transverse spinous process view, (B) transverse interspinous process view, (C) tilted transverse interspinous process view. SP: spinous process, AP: articular process, L: lamina, PC: posterior complex, AC: anterior complex, SC: spinal canal (intrathecal space).
Ultrasonography can be used in two basic ways for lumbar neuraxial block: preprocedural US scanning or real-time US-guidance. A low-frequency (e.g., 2–5 MHz), curved-array US probe is usually used. To optimize sonographic images, adjustment of depth (usually 7–10 cm), focus positioning, and gain settings on the US machine are essential. During US-guided neuraxial block, it is crucial to remove gel or chlorhexidine from the skin before needle insertion to avoid potential neurologic complications, including adhesive arachnoiditis [2,3].

**Preprocedural US-assisted midline approach**

1. Confirm the midline based on the spinous processes by placing the US probe over the midline in a horizontal orientation (the transverse spinous process view).
2. Locate the interlaminar space using the parasagittal oblique view or transverse interlaminar view and choose the most appropriate intervertebral level for neuraxial puncture.
3. Determine the needle insertion point and angle of needle trajectory using the transverse interlaminar view. The US probe can be tilted cephalad or caudad to visualize the intrathecal space. Remember the three-dimensional angle of the probe where the posterior and anterior complexes are visualized most clearly.
4. Estimate the depth of needle insertion by measuring the distance from the skin to the posterior complex.
5. Perform neuraxial block by inserting a needle at the predetermined insertion point with the insertion angle.

**Preprocedural US-assisted paramedian approach based on bony structures**

1. Confirm the neuraxial midline based on the spinous processes as per the transverse spinous process view.
2. Locate the interspinous space using the transverse view. If possible, identify the interlaminar space using the parasagittal oblique view and select the intervertebral level for neuraxial puncture.
3. Having identified the midline, spinous process, and interlaminar space, insert a spinal needle at the point approximately 1 cm superior to the lower spinous process and 1 cm lateral to the midline, or at the point approximately 1 cm inferior to the caudad tip of the upper spinous process and 1 cm lateral to the midline.
4. Slight medial (5–10 degree) and cephalad (5–10 degree) angulation of needle insertion may be needed similar to a conventional paramedian approach.

The abovementioned approach is similar to the conventional paramedian approach in dependence on the location of key bony structures. However, with the help of a US scan, more precise identification of underlying bony structures is possible. This approach can be useful in extremely obese patients or when the quality of US images is inadequate.

**Preprocedural US-assisted paramedian approach based on the parasagittal oblique view**

1. Confirm the midline in the transverse spinous process view and apply the probe in a longitudinal direction 1–2 cm lateral to the midline with a slight medial tilt.
2. Identify the interlaminar space in the parasagittal oblique view and select the intervertebral level that provides the largest interlaminar space.
3. Determine the medial angle of the sagittal plane providing the clearest image of the interlaminar space. Slight cephalad or caudad angulation of the probe may be necessary in some cases.
4. Estimate the depth of needle insertion by measuring the distance from the skin to the posterior complex.
5. Insert a needle at the designated insertion point with the designated angle.

Paramedian approach based on the parasagittal oblique view has potential advantages over the midline approach using the transverse interlaminar view because the parasagittal oblique view provides better visibility of the interlaminar space than the transverse interlaminar view, especially in the elderly. When the US beam reaches the spinal canal in the parasagittal oblique view, the needle can also reach the canal through the same pathway. When using US-assisted paramedian approach, cephalad or caudad needle angulation may not be required. This approach can be the most direct way to the intrathecal or epidural space through the interlaminar space considering only medial angulation.

**Real-time US-guided neuraxial block**

Real-time US-guided neuraxial block is a feasible and promising technique that can result in successful neuraxial anesthesia in difficult cases [4,5]. However, it is tricky to perform because of the large size of the probe, small gauge of the needle, and relatively deep target structure. There are several methods to perform real-time US-guided neuraxial block, including sagittal, transverse, and diagonal in-plane approaches.

Real-time US-guided spinal anesthesia using in-plane approach based on the parasagittal oblique view can increase first-attempt success rate compared to the landmark-guided paramedian approach technique [6]. Needle approach from the non-dependent side may lead to dry tap due to gravity, even if the needle tip is placed in the intrathecal space. A prospective observational study showed that real-time US-guided spinal anesthesia using in-plane approach based on the diagonal view was successfully performed in 97 out of 100 consecutive patients within three median needle passes [7]. Probe application site can be slightly moved to secure the room for puncture site and needle manipulation during the transverse in-plane paramedian approach [8]. Electromagnetic needle tracking system can also be used for real-time US-guided spinal anesthesia [9].

**US-guided neuraxial block in patients with scoliosis**

Preprocedural US assistance may have potential benefits in neuraxial block for patients with scoliosis. Systematic algorithms to guide neuraxial techniques in patients with scoliosis have been described previously [10,11]. Several earlier publications have demonstrated that the use of ultrasonography is useful for spinal anesthesia in patients with scoliosis [5,12,13]. The lateral curvature of the sciotic spine can be confirmed by marking out all spinous process tips using ultrasonography. Simple spinal radiographs or computed tomography are also helpful. In addition to the lateral curvature, rotational change of the vertebral body should be considered when performing neuraxial block in these patients. During the paramedian approach, it is easier to insert a needle on the convex side of the vertebral column after confirming the spinous process considering the needle insertion angle. For example, in the paramedian approach, if the rotation of the vertebral body is approximately 15 degrees in a patient with scoliosis, the needle insertion site is on the convex side of the spinous processes, therefore, the angle of needle trajectory would be perpendicular to the skin towards the interlaminar space (Fig. 5A). On the other hand, when using the midline approach through the interspinous space in a patient with scoliosis, the angle of needle insertion would be 15 degrees off the sagittal plane towards the convex side (Fig. 5B).

**USEFULNESS OF US-GUIDED NEURAXIAL BLOCK**

US imaging can provide important clinical information for a successful neuraxial block. Ultrasonography aids in identification of the accurate puncture level by providing information, such as the widest inter-laminar space, depth to the dura from the skin, and accurate spinal level.

To achieve successful neuraxial blockade, accurate identification of the intervertebral spaces is crucial. US imaging is also useful in localizing the intervertebral spaces and identifying lumbar vertebral level. Although many anesthesiologists used to identify the vertebral level by palpation when performing neuraxial blockade, previous studies
consistently showed that identification of the intervertebral level using palpation is unreliable [14–17]. Preprocedural neuraxial US imaging not only provides the anatomical details of the intervertebral space and bony structures but also the optimal skin puncture point and needle insertion angle, and these are valuable for improving the ease of performing neuraxial blockade [18,19].

Preprocedural neuraxial US imaging can facilitate dural puncture or epidural catheterization by predicting the distance from the skin to the epidural or intrathecal space. Many studies demonstrated that US-determined depth to the epidural or intrathecal space was well-correlated with the actual needle depth [20–23]. Moreover, the information on the distance from the skin to the epidural space can decrease the rate of failed labor epidural analgesia and reduce the number of epidural attempts, even by trainees [24]. It should be noted, however, that the depth predicted by ultrasonography can underestimate the true distance from the skin to the epidural or intrathecal space because of tissue compression by the probe for image optimization.

The accurate identification of the intervertebral level is also related to safety issues in neuraxial blockade. Ultrasonography more accurately determines the intervertebral level than palpation [17]. The level of the conus medullaris varies from T12 to L3 [25]. Although most studies on US-assisted neuraxial blockade evaluated safety outcomes as secondary outcome measures [26], preprocedural US imaging may help in avoiding conus medullaris injury, which can be caused by unintended dural puncture in the level above the L1-L2 interspace.

**UP-TO-DATE LITERATURE REVIEW**

The utility of US imaging in improving technical performance of neuraxial blockade has been evaluated in various patient populations. Table 1 shows the results of randomized controlled trials regarding the efficacy of US-guided neuraxial blockade compared with landmark-guided technique.

**Obstetric population**

Early studies on US-assisted neuraxial block were conducted in obstetric patients. In a series of randomized controlled trials from 2001 to 2002, Grau et al. [27,28] reported that preprocedural US imaging was associated with fewer needle passes and better analgesic efficacy in labor epidural analgesia. Additionally, for parturients with anticipated technical difficulty, including history of difficult epidural puncture, anatomical alteration of the lumbar spine, and body mass index > 33 kg/m², US assistance resulted in fewer needle passes, fewer puncture sites, lower pain score, and improved patient satisfaction [29].

However, more recent studies have shown inconsistent results. Nassar and Abdelazim [30] reported that US imaging increased the rate of successful procedure at the first attempt and reduced the number of needle passes compared to the palpation technique for combined epidural-spinal anesthesia (CSE). Perna et al. [31] also reported that US assistance enhanced technical performance of labor epidural analgesia, by providing anatomical information on the location of the intervertebral space, optimal needle insertion point, and tilting angle of the epidural needle. In contrast, other studies failed to highlight the benefits of preprocedural US imaging in obstetric patients [32–35]. Possible explanations for the conflicting results are
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<td>- 63.8% in US group vs. 38.2% in control group (P = 0.001) - Difficulty: 18.1% in US group vs. 30.0% in control group (P = 0.09)</td>
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Table 1. Continued

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<td>Park et al., 2020 [13]</td>
<td>Patients who had lumbar scoliosis or history of lumbar spine surgery</td>
<td>Spinal</td>
<td>Three experienced anesthesiologists</td>
<td>The number of needle passes</td>
<td>1.5 (1, 3) in US group vs. 6 (2, 9.3) in control group (P &lt; 0.001)</td>
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<td>involving L2-L5 vertebrae</td>
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<td>Elsharkawy et al., 2017 [46]</td>
<td>Patients undergoing total knee or total hip arthroplasty with difficult</td>
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BMI: body mass index, CSE: combined spinal-epidural anesthesia, US: ultrasound, CSF: cerebrospinal fluid. *Values are presented as mean ± SD or median (1Q, 3Q).
the characteristics of the study subjects and proceduralists. All these studies evaluated the utility of ultrasonography in parturients with palpable anatomical landmarks. In this population, the benefit of US imaging may be underestimated because neuraxial blockade is usually not complicated in lean patients or those who had normal vertebral anatomy. Regarding the proceduralists, experienced anesthesiologists performed the US scan and neuraxial blockade in two studies [32,34], while skin puncture was performed by trainees after ultrasonographic examination by experts in another study [35]. The guidance from a study investigator during skin puncture or suboptimal needle handling by the trainees may have led to the negative results [36]. However, in a recent large study conducted in women undergoing cesarean section with CSE, the authors found that US assistance improved technical performance in patients with easily palpable landmarks, but not in those with impalpable surface landmarks, and that the experience of proceduralists did not influence the first-pass success rate of CSE procedure [37]. Further studies are still needed to clarify which populations benefit the most through US assistance.

**Elderly patients**

The efficacy of US-assisted neuraxial blockade is more evident in elderly patients. In contrast to using the midline approach in obstetric patients, the paramedian approach was used in studies evaluating the utility of ultrasonography in the elderly. Lim et al. [38] compared the rate of successful dural puncture at the first attempt in patients receiving spinal anesthesia with or without preprocedural US imaging. Although the first-attempt success rate was not significantly different, shorter time was required to perform the procedure with US-assisted spinal anesthesia and patients were more satisfied compared to the manual palpation technique. Other studies showed consistent results that the number of needle passes and skin punctures were significantly decreased when using US-assisted spinal anesthesia, compared to the midline approach [39] or paramedian approach [40]. In general, neuraxial blockade is more difficult in an older population than in relatively younger obstetric patients, possibly due to degenerative changes of the lumbar spine, such as the calcified interspinous ligament and limited lumbar flexion [39]. These findings supported that preprocedural US imaging may be more beneficial in patients with difficult anatomy, as shown in a recent meta-analysis [41]. Scanning both sides and all spinal levels before selecting a puncture site for US-guided spinal anesthesia is recommended. The L5-S1 intervertebral level is a good option for neuraxial anesthesia in the elderly [42].

**Patients with difficult anatomy (obesity, scoliosis, or history of spine surgery)**

Several studies have evaluated whether US assistance improves technical performance of neuraxial blockade in patients with difficult anatomy, including moderate to severe obesity, lumbar scoliosis, ankylosing spondylitis, or history of lumbar spine surgery. Chin et al. [12] compared the first-attempt success rate of spinal anesthesia with or without US assistance in this population and found that preprocedural US imaging facilitates the performance of spinal anesthesia. Similar results were shown in obstetric patients with difficult anatomical landmarks. Wang et al. [43] reported that US scanning performed by single experienced anesthesiologist before neuraxial blockade significantly enhanced the first-attempt success rate. Another study published by Ekinci et al. [44] demonstrated that the number of skin punctures was significantly decreased when using preprocedural US imaging, but total procedure time was comparable with the conventional spinal anesthesia technique. Our recent study conducted in patients with documented lumbar scoliosis or those with history of previous spinal surgery also showed similar results that the number of needle passes and puncture attempts were significantly lower in the US group than in the control group, but total procedure time was not significantly different between the two groups [13]. Despite of US scanning time, difficulties in identifying the midline or intervertebral space in patients with abnormal vertebral anatomy would increase the procedural time in conventional palpation technique, resulting in no difference in the overall procedure time. Considering the reduced number of needle manipulations and better patient satisfaction, US neuraxial imaging should be accompanied in patients who are expected to have difficult neuraxial blockade.

**Real-time US-guided technique**

There are limited studies assessing the benefits of real-time US guidance technique. Grau et al. [45] compared real-time US-guided CSE procedure using the parasagittal
oblique view with preprocedural US scanning and conventional landmark palpation technique and found that both US-guided techniques significantly reduced the number of needle passes. The advantage of real-time US guidance was also reported in a recent study by Chong et al. [6]. They found that first-attempt success rate was significantly higher when using real-time US-guided spinal anesthesia with the parasagittal oblique view, compared to the palpation-based paramedian approach [6]. However, another study on the efficacy of real-time US-guided spinal anesthesia in patients with difficult spinal anatomy showed no advantage of real-time technique over conventional landmark technique [46]. Various approaches, including transverse [8,47] and diagonal in-plane approaches [7], have been investigated for real-time US-guided neuraxial block. Despite some results showing the advantages of real-time US guidance, there are still technical challenges to be addressed, such as visualization of a small-gauge needle around the deep target structures.

**CONCLUSION**

For better clinical practice, it is recommended to apply US guidance for neuraxial blockade. US-guided neuraxial block can facilitate successful access to the intrathecal or epidural space in patients with difficult spinal anatomy, as well as in those with easily palpable anatomical landmarks. Anesthesiologists who routinely perform lumbar neuraxial block should be familiar with the sonoanatomy of the lumbar vertebrae and US-guided techniques to improve technical performance and safety.

**CONFLICTS OF INTEREST**

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

**AUTHOR CONTRIBUTIONS**


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Ultrasound and lumbar neuraxial block

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INTRODUCTION

Placenta previa (PP) is defined as abnormal placental implantation in the lower uterine segment. The condition in which the placenta completely overlies the internal cervical os, is termed placenta previa totalis (PPT). PP occasionally combines with placenta adhesion and abnormal placental implantation, referred to as placenta accreta, which includes accreta, increta, and percreta. These conditions can cause massive peripartum hemorrhage, which increases the probability of requiring blood transfusions [1]. Thus, PP is associated with maternal morbidity and mortality [2,3]. The risk of life-saving hysterectomy after cesarean section (CS) for PP is 30 times higher than that for patients without PP, in addition to longer hospital stay after delivery [4].

Antenatal diagnosis and risk estimation for massive blood loss in parturients with PP would allow adequate preparation and multidisciplinary approaches to improve maternal morbidity and mortality. Therefore, this review focused on risk assessment and anesthetic considerations for parturients with PP in whom massive hemorrhage is expected during CS. We describe these considerations according to three categories: preoperative anesthetic management and other interventions to control bleeding in patients with previa expected to experience massive hemorrhage and require transfusion.
detecting abnormal placentation in the prenatal period. The location of the placenta (anterior, posterior, and lateral) can be identified on transvaginal US images. An anterior or previous cesarean scar were identified as independent factors for transfusion and hysterectomy in a retrospective study [5,6].

After confirming the placenta location, US findings suggesting a risk of massive blood loss and placental adhesion should be checked. Many studies have reported sonographic findings predicting placenta accreta. Lacunae space (an irregular area of low echogenicity larger than 1 cm x 1 cm in the placental parenchyma) was strongly associated with placenta accreta [6,7]. Lacunae were graded according to their appearance and number, with Grades 2 and 3 at high risk for placental invasion. Grade 2 is defined as the presence of 4-6 lacunae that tend to be larger and more irregular in shape, while Grade 3 is characterized by many large and bizarrely-shaped lacunae throughout the placenta [8]. Sponge-like findings of the cervix wall (five or more hypoechogenic areas > 5 mm in diameter), lack of retroplacental clear zone (the clear zone; sonolucent zone between the placenta and myometrium), thinning (≤ 1 mm) of the myometrium, bridging vessels from the placenta to the uterine-bladder interface, and uterine-bladder interface thinning are also suggestive of abnormal placentation [6,7,9,10] (Fig. 1). Magnetic resonance imaging (MRI) can also be used when US examination findings are inconclusive, particularly in women with abnormal placentation. In a systematic review and meta-analysis report, MRI was highly accurate for the detection of placental invasion presence, depth, and topography (Fig. 2). Further, MRI and US showed similar performance in detecting the presence of invasive placentation [11]. However, the prenatal diagnosis accuracy using US exam may be insufficient, with a sensitivity of 0.53-0.85 and a specificity of 0.71-0.89 [10-12]. US alone has limitations for the prediction of bleeding in the intra- and postpartum periods. However, the clinical characteristics should also be considered.

The cause of placental implantation in the lower uterus segment is unclear. Therefore, it has highly associated with previous endometrial damages, and uterine scarring due to myomectomy or CS, prior PP, and multiparity [13]. The clinical risk factors associated with PP and placenta adhesion have been well established, including advanced maternal age, multiparity, multiple gestations, and smoking [13,14]. A large prospective study reported that as the number of CSs increased from 1 to 2 and ≥ 3, the probability of accreta increased from 11% to 40% and ≥ 61%, respectively [15]. After CS, the layer of the decidua becomes thinner, which may fail to reconstitute the decidual basalis/endometrium. This may further promote placental accreta to a previous lower uterine segment scar [5,16]. Repeated CS, PP, especially anterior and/or CS scar, placenta adhesion, and older maternal age increased the risk of massive peripartum hemorrhage and transfusion [9,17]. The predictive factors for peripartum hysterectomy in women were prior CS (adjusted odds ratio [aOR], 23.1), major PP including partial and complete previa (aOR, 14.6), US suspicion of
placenta accreta (aOR, 42.4), and gestational age less than 34 weeks (aOR, 9.3) [18].

In clinical situations, risk estimation by combining all of these factors would be more predictable than clinical variables or imaging findings of previa and placental invasion alone. Thus, based on both clinical characteristics and imaging findings, researchers have developed prediction indexes or scoring systems to evaluate the risk of placental invasion and predict massive blood loss or the need for allogeneic blood transfusion.

**Prediction index and score**

The “Placenta Accreta Index” assigned points for ≥ 2 CSs (3.0 points), lacunae grade 2 (1.0 point) and 3 (3.5 points), sagittal smallest myometrial thickness (≤ 1 mm, > 1 but ≤ 3 mm, > 3 but ≤ 5 mm: 1.0, 0.5, and 0.25 points, respectively), anterior PP (1.0 point), and bridging vessels (0.5 points) [7]. This index indicated the probability of placental invasion; for example, > 5 points showed a 69% probability of invasion (95% confidence interval, 50–83).

Baba et al. [19] reported three independent risk factors that were associated with blood transfusion in patients with PP: a) lacunae (placental hypoechoic areas) that represented abnormal placental adhesion in imaging, b) previous CS, and c) placenta covering the previous CS scar, indicating anterior or central placenta. Kim et al. [20] developed a scoring system to predict massive postpartum transfusion that considered the following five factors: a) suspicion of placental adhesion on imaging (2 points), b) previous CS (0, 1, ≥ 2: 0, 1, and 2 points, respectively), c) gestational age below 37 weeks (1 point), d) anterior placenta (1 point), and e) sponge-like appearance of the cervix (1 point). They showed that the combination of previa, clinical features, and suspicion of placental invasion was more predictive than only a suspicion of placental adhesion, with areas under the receiver operating characteristic curve (AUC) of 0.84 and 0.67, respectively. Parturients with 4 of 7 points showed a 72% probability of massive transfusion.

Another scoring model included maternal age ≥ 35 years, fetal non-cephalic presentation, PPT, anterior placenta, uteroplacental hypervascularity, and multiple lacunae to predict postpartum massive blood loss [21]. Recently, Liu et al. [22] proposed the “Hysterectomy Index in Placenta Previa with Prior Cesarean” to predict the risk of cesarean hysterectomy. The parameters from previous studies were included in this report on the risk of placental invasion. Among parturients fulfilling all three parameters; namely, vascular lacunae on US imaging, central PP, and loss of normal hypoechoic retroplacental zone, the predicted incidence of hysterectomy was 90.4%.

Based on the scoring system or predictive model, surgeons and anesthesiologists should identify patients who are at risk for peripartum blood loss and hysterectomy to prepare multidisciplinary strategies, including massive transfusion protocols, embolization, artery ballooning, and lastly, hysterectomy. We next discuss anesthetic management.

**ANESTHETIC MANAGEMENT FOR CS**

**Anesthesia and catheterization based on a scoring system**

According to the scoring system consisting of the five factors mentioned above [20], score indexes below 3 of 7 points are considered to be at low risk of massive hemorrhage (massive transfusion probability of 44%) and, since most cases are hemodynamically stable, regional anesthesia is preferred. Score indexes over 4 points indicate a high risk of massive hemorrhage for which general anesthesia and central venous catheterization should be considered in preparation for massive transfusion, defined as the transfusion of ≥ 8 units of red blood cells [20].

**Anesthetic method**

The choice of anesthetic method for parturients with PP undergoing CS has long been controversial. Some authors have suggested the application of regional anesthesia in elective CS but not in emergencies with major hemorrhage [23]. Other authors have proposed general anesthesia over regional anesthesia for all CS patients with PP, as regional anesthesia can exacerbate hypotension and reduce sympathetic response to hypovolemia [24]. Of concern is that when massive bleeding occurs, the sympathetic blockade induced by regional anesthesia makes it difficult to maintain adequate blood pressure. However, evidence for the use of regional anesthesia in CS with PP has recently been reported [25]. Since vasoconstriction associated with sympathetic response to maintain arterial blood pressure is not possible under regional anesthesia, it has a protective effect to reduce the risk of underestimating blood loss leading to under-transfusion [26,27]. A retrospective survey re-
ported significantly reduced estimated blood loss and need for blood transfusion compared to those for general anesthesia [26,28]. Another area of concern regarding regional anesthesia is the surgery duration. In the case of CS in patients with PP, where massive bleeding is possible or has occurred, general anesthesia or conversion from regional to general anesthesia should be considered [29,30]. Although an epidural catheter can prolong anesthesia time, it can also lead to the exacerbation of hypotension and local anesthetic toxicity. In addition, to select the appropriate anesthesia between general and regional anesthesia, patient discomfort and suboptimal operating conditions should also be considered [29].

**Massive transfusion**

Massive hemorrhage is a recognized complication of PP. The optimal predelivery transfusion planning strategy requires coordination and communication among all perioperative disciplines, including anesthesiologists, obstetricians, nursing personnel, blood bank staff, and interventional radiologists. A massive transfusion protocol should be in place to address preoperative blood component preparation and intraoperative management. Although there is a report on autologous blood donation programs that have reduced the need for allogeneic blood transfusions in high risk parturients, autologous donation is not recommended because severe postpartum hemorrhage is rarely anticipated and problems such as bacterial contamination and human errors exist [31,32]. Hematology and coagulation laboratory values must be evaluated before surgery. The initial measurement of hemoglobin level is useful as a baseline measure and repeated evaluation provides information on the degree of severity of bleeding and anemia [32,33]. After analyzing risk factors by utilizing the previously described scoring system to predict massive transfusion in PP [19-22], invasive monitoring with arterial catheterization, central catheterization with a large-bore catheter, and noninvasive or minimally invasive cardiac output monitoring can be applied [34,35]. Even without proper catheterization before CS, if the bleeding is not rapidly controlled during surgery, the placement of large venous access (16 gauge or more) should be considered [32]. Permissive hypotension during the bleeding phase can be considered, aiming for a mean arterial pressure of 55–65 mmHg, with the mean arterial pressure normalized when the bleeding becomes acceptable [32]. One randomized controlled trial reported that restrictive crystalloid resuscitation (1–2 ml of crystalloid for every 1 ml of blood loss) was helpful for a low incidence of fibrinogen depletion and coagulopathy [36]. Active and early warming of the parturient to maintain normothermia is recommended to reduce a decrease in hemoglobin [37]. Vasopressors such as ephedrine and phenylephrine can help patients with hypovolemic status to maintain adequate blood pressure. Infusion or bolus of norepinephrine may be considered and have been actively introduced recently in CS [38]. The administration of tranexamic acid (1 g intravenously), an antifibrinolytic agent that reduces blood loss and blood transfusion in CS [39,40], may help reduce postpartum hemorrhage. However, the possible side effects and thromboembolic risk of tranexamic acid must be taken into account when considering its safety [32,41]. Regarding red blood cell transfusion, in most patients not accompanied by massive bleeding, the recent transfusion trigger has been gradually lowered to less than 7 g/dl and a restrictive transfusion strategy has been recommended [42,43]. However, this strategy is not applicable to massive bleeding. If massive bleeding introduced by PP develops, it is important to shift to the massive transfusion protocol to prevent the various morbidities that can be caused by severe anemia [44]. Generally, fresh frozen plasma transfusion is a part of massive transfusion protocols and should be considered if coagulopathy is suspected or confirmed by laboratory tests [45]. Likewise, platelet concentrate transfusion should be considered according to the massive transfusion protocol guided by abnormalities in platelet counts in laboratory tests or platelet function impairment as measured by various platelet function tests, including thromboelastography and rotational thromboelastometry (ROTEM) [45]. In massive hemorrhage, fibrinogen levels affect bleeding severity. The risk of severe postpartum hemorrhage increases for a fibrinogen level below 2 g/L [46]. Therefore, when severe hemorrhage occurs due to PP during CS, fibrinogen levels should be monitored early so that cryoprecipitate or fibrinogen concentrate can be administered [47]. The aforementioned ROTEM can be helpful. When FIBTEM A5 is less than 12 mm, substitution should be considered because this fibrinogen concentration corresponds to 2 g/L [48]. The benefit of the transfusion of blood components and coagulation factors according to the massive transfusion protocol is the prevention of transfusion delay and correction of coagulopathy [32].
RADIOLOGIC INTERVENTIONS

Embolization and balloon occlusion

Several attempts have been used to minimize blood loss in patients with abnormal placentation. Uterine artery embolization to control postpartum hemorrhage was first reported in 1979 [49]. This procedure is considered less invasive than arterial ligation, which has a higher failure rate of more than 50% due to the rich collateral circulation of the pelvis [50].

Uterine artery embolization has a median success rate of 89% with good clinical outcomes [51,52]. In the case of a patient with PPT and uterine myomas, uterine artery embolization was preoperatively planned and intraoperatively performed immediately after delivery of the fetus before removal of the placenta during CS [53]. Placental expulsion was performed without complications after successful uterine artery embolization using gel foam particles [53]. Another method to decrease postpartum hemorrhage induced by PP is transcatheter arterial balloon occlusion. For patients with PP suspected to have placental adhesion leading to perioperative massive hemorrhage, prophylactic transcatheter arterial balloon occlusion can be planned in both internal iliac arteries before CS. Although some studies have reported a lack of benefits or complications related to radiologic intervention [54,55], most were case reports or case studies. However, no differences in complications were observed among other large studies or prospective studies, in which prophylactic transcatheter arterial balloon occlusion can be planned in both internal iliac arteries before CS. Although some studies have reported a lack of benefits or complications related to radiologic intervention [54,55], most were case reports or case studies.

In the clinical application of the radiologic interventions mentioned above, there are various difficulties such as the catheterization timing, intervention and CS location, patient movement, anesthetic method, and fluoroscopic equipment. Therefore, to ensure patient safety and achieve successful interventions and CS, a full discussion of perioperative disciplines including interventional radiologists, anesthesiologists, and obstetricians is required.

CONCLUSION

PP can occasionally cause massive hemorrhage, leading to poor maternal and neonatal outcomes. Various studies have sought to identify the risk factors for patients with PP associated with massive hemorrhage and maternal morbidity. Based on patient information and test findings, the direction of anesthesia and surgery and whether to implement a massive transfusion protocol can be determined by cooperation and discussion among the various disciplines related to CS. In addition, radiologic interventions, such as uterine artery embolization and transcatheter arterial balloon occlusion, may be helpful for advanced anesthetic management.

CONFLICTS OF INTEREST

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

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INTRODUCTION

Intubation is a frequent procedure during general anesthesia. However, the traditionally used direct laryngoscope involves lifting the epiglottis and endotracheal tube, passing by the vocal cords, and exerting a strong stimulation to the trachea. This results in an elevated level of catecholamine and consequent increases in blood pressure (BP) and heart rate (HR), exerting a negative influence on the patients’ cardiovascular system [1,2]. Lightwand is a tool that can be utilized in patients with poor teeth conditions or difficulties in mouth opening due to temporo-mandibular joint problems. This tool allows for intubation without lifting the glottis using light wave [3]. Esmolol is a relatively cardiac-selective beta blocker with an extremely short onset and half-life [4,5]. Several studies have assessed the...
dose of esmolol required to minimize hemodynamic changes, in case of intubation through direct laryngoscope [6,7]. On the other hand, for lightwand-based intubation, there was no study identifying the appropriate dose of esmolol. Thus, the authors of this study aimed to identify the effect of different doses of esmolol on hemodynamic changes and the appropriate dose of esmolol during lightwand intubation.

**MATERIALS AND METHODS**

After obtaining study approval from the Institutional Review Board of Soonchunhyang university hospital (no. 2018-06-041-002), we recruited 140 patients of the American Society of Anesthesiologists class I and II who required general anesthesia for elective surgery.

Patients with hypertension, cardiac problems, cervical spine fracture, tumors, or polyps in the upper airway, those with expected airway difficulties, and patients currently using beta blockers were excluded from the study. Informed consent was obtained from all patients. Using a computerized random number generator (www.random.org), the patients were divided into four different groups; 35 subjects in each group. For the ‘C’ group, 20 ml of normal saline was prepared, while the ‘E0.5’, ‘E1’, and ‘E2’ groups had 20 ml of normal saline containing esmolol 0.5 mg/kg, 1 mg/kg, and 2 mg/kg, respectively.

The patients received intramuscular injections of glycopyrrolate 0.2 mg 30 min prior to entering the operation room (OR). After the patient was admitted to the OR, regular monitoring equipment including electrocardiography, non-invasive blood pressure, and pulse oximetry were attached, and baseline BP and HR were measured (T1).

The anesthesiologist performed pre-oxygenation with 100% oxygen for 3 min, followed by induction of anesthesia with intravenous (IV) propofol 2 mg/kg. Immediately before injecting propofol, 40 mg of lidocaine was injected. After the patient lost consciousness, rocuronium 0.6 mg/kg was injected, and BP and HR were measured (T1). Immediately after the injection of rocuronium, either 20 ml of normal saline or 20 ml of normal saline containing 0.5 mg/kg, 1 mg/kg, or 2 mg/kg of esmolol were injected over 15–20 s.

Two minutes after the injection of the study drug, we performed lightwand (Flexible Lighted Stylets, Bovie Medical Corporation, USA) intubation with an assistant performing jaw-lift. All lights in the OR were turned off to ensure darkness in the room, until the lightwand passed by the oral cavity and showed the brightest luminescence in the midline of the anterior neck. Using the light, an endotracheal tube was inserted into an appropriate position, and the lightwand was removed. Capnography and stethoscopes were used to confirm that the endotracheal tube was correctly inserted into the trachea. One minute after intubation, BP and HR were measured (T3). Cases involving an intubation time over 15 s or ≥ 3 attempts were considered as failures. To eliminate the differences due to technical expertise, all intubations were conducted by a single experienced anesthesiologist who performed ≥ 500 cases of intubation using the lightwand. Anesthesia was maintained using 2% sevoflurane, and medical air and oxygen were used to maintain FiO2 0.45. BP and HR were measured at 3 min (T4), 5 min (T5), and 10 min (T10) post-intubation. In addition, rate-pressure product (RPP)—an index of myocardial oxygen consumption calculated by multiplying systolic blood pressure (SBP) and HR—was calculated at each time point: Tpr T1, T4, T5, T10 and T10.

Prior to anesthesia, the investigator prepared the drug in advance. The nurse who injected the drug and anesthesiologist were not able to know the dose of esmolol for ensuring double-blinded study.

The data were compiled using SPSS 25.0 for Windows (IBM Co., USA) and were presented as mean ± standard deviation where appropriate. First, the Kolmogorov–Smirnov test was used to determine if the values showed a normal distribution. The values with a normal distribution (weight, body mass index, SBP, mean blood pressure [MBP]) were analyzed using ANOVA and age, diastolic blood pressure (DBP), HR, RPP were analyzed using the Kruskal–Wallis test. Categorical data were analyzed using the chi-square test. The probability value of < 0.05 was regarded as statistically significant.

**RESULTS**

Two patients from each the C group and E1 group were excluded from the study due to their intubation time exceeding 15 s. In the end, 136 patients were included in this study (Fig. 1). There were no noticeable differences in patient characteristics among the different groups (Table 1). Furthermore, there were no differences in the initial measurements of SBP, DBP, MBP, HR and RPP immediately after entering the OR (T0) (Table 2).

For SBP, DBP, and MBP, there were no significant differences among the groups before and after intubation (Figs. 2–4).
For HR, measurements 1 min after intubation (Tₙ) were significantly different between the C group and E1 group (100.11 vs. 85.34, P ≤ 0.001), as well as 3 min after intubation (Tₙ) (93.94 vs. 83.63, P = 0.02). Similarly, there were significant differences between the C group and E2 group 1 min after intubation (Tₙ) (100.11 vs. 87.09, P ≤ 0.001) and 3 min after intubation (Tₙ) (93.94 vs. 81.97, P ≤ 0.001) (Fig. 5).

For RPP, there were significant differences between the C group and E2 group 1 min after intubation (Tₙ) (15,003.43 vs. 11,665.40, P = 0.001) and 3 min after intubation (Tₙ) (12,162.37 vs. 9,861.89, P = 0.002) (Fig. 6).

**DISCUSSION**

The purpose of this study was to identify the effect of different doses of esmolol and the appropriate dose of esmolol on hemodynamic changes during laryngoscopy intubation. For SBP, DBP, and MBP, there were no significant differences observed between the C group and E0.5, E1, and E2 groups. However, for HR, the level of elevation immediately after intubation was suppressed in the E1 and E2 groups compared to the C group. In addition, RPP significantly decreased in the E2 group compared to the C group.
stimulation of the larynx, resulting in an elevated level of catecholamine, and consequently, increased BP, HR, and RPP [1,2]. From a hemodynamic aspect, the elevated HR results in an increased oxygen consumption, especially in the patients with ischemic heart disease. This stimulates a negative effect on the myocardial oxygen balance, leading
to possible onset of myocardial ischemia during the surgery [8]. Moreover, RPP is a known, trustworthy indicator of myocardial oxygen demand [9,10].

The lightwand can be utilized in situations involving difficult airways, where intubation using direct laryngoscope is difficult or resulted as a failure. More specifically, the lightwand is useful in patients with a hard-to-open mouth, those with a high risk of teeth damage, or excessive secretion of saliva. Since intubation using the lightwand does not involve lifting the glottis, it exerts a weaker direct stimulation to the mouth and larynx [11], resulting in less pain in the neck area after anesthesia, and results in fewer cases of hoarseness or dysphasia [12,13]. Furthermore, its simple preparation process, exceptional mobility, and easy-to-clean characteristics are additional benefits [3].

The previous study by Takahashi et al., which assessed young and healthy patients, showed no difference in changes of HR, SBP, and DBP between the lightwand and direct laryngoscope intubation [14]. Similarly, Yoon et al. [15] also demonstrated that changes in HR and MBP were similar between the two procedures when performing intubation in patients with cerebral aneurysms. Several studies have supported these findings, showing little to no difference in the trend of hemodynamic changes [12-16].

Meanwhile, Salgado et al. claimed that the lightwand blunted the elevation of MBP [17], and Nishikawa et al. [11] showed blunted elevation of SBP using the lightwand in a cohort of normal patients.

Esmolol used in this study is a beta-1-selective adrenergic receptor blocking agent, which is an anti-hypertensive drug that reaches peak blood concentration within 2 min and has an extremely short half-life of ~9 min [4]. Esmolol has existed for a long time for intubation using direct laryngoscope. The previous study by Kindler et al. [18] confirmed that the groups treated with 1 mg/kg and 2 mg/kg of esmolol exhibited blunted hemodynamic changes when using laryngoscope compared to the placebo group. A single injection of esmolol 100 mg prior to intubation using laryngoscope resulted in lesser hemodynamic changes compared to the control group [19], and the same outcome was deduced with an injection of esmolol 150 mg [20]. Furthermore, another study has shown that a bolus injection of esmolol 1 mg/kg prior to intubation and continuous infusion at 150 μg/kg/min also resulted in blunted hemodynamic changes. [21] Overall, multiple studies with various designs have been performed thus far.

As mentioned above, there have been several studies suggesting a similar level of hemodynamic changes during intubations with either a lightwand or direct laryngoscope [12,14-16]. Nonetheless, the studies of appropriate dose of esmolol usage during lightwand intubation were not found by authors. The actual results showed that 1–2 mg/kg of esmolol effectively reduced HR, while RPP blunting was most effective with 2 mg/kg of esmolol. These values are near the recommended dose of esmolol during direct laryngoscope intubation, according to the above-mentioned study by Kindler et al. [18]. These findings imply that despite using the lightwand, the level of stimulation was comparable to that of direct laryngoscope intubation. In addition, these findings can be considered that the major cause of hemodynamic changes is the direct stimulation of the trachea by the endotracheal tube rather than direct stimulation via lifting the glottis with the laryngoscope [14].

The level of hemodynamic changes from lightwand intubation will likely be associated with technical expertise. A Prolonged procedure time or repeated attempts will result in the tip of the lightwand exerting a strong stimulation to the larynx, especially in piriform recess and epiglottic vallecular. This causes blood catecholamine levels to increase even further [11]. Moreover, patients with hypertension ex-
hibit a greater increase of blood catecholamine levels with the same level of stimulation, resulting in greater hemodynamic changes [22,23]. Last, patients with difficult airway will likely exhibit a greater elevation of BP and HR due to the lengthened procedure time or repeated attempts. In this study, all procedures were performed by an expert anesthesiologist who performed lightwand intubation > 500 times. There was no case that involved more than 2 failures and only 4 cases required ≥ 15 seconds of procedure time.

When performing lightwand intubation, having an assistant to lift the patients’ mandibular angle to open their mouth will make the procedure more convenient to complete [3]. Thus, in this study, the jaw-lift method was utilized. On the other hand, a single anesthesiologist opening the patient’s mouth with one hand and manipulating the lightwand with the other hand makes it difficult to ensure neck extension. And lights may not be clearly visible due to neck folds. Consequently, the procedure may take longer and exhibit a greater chance of failure.

Although we have performed IV injections of lidocaine 40 mg—which is known to reduce the cough reflex—prior to the injection of propofol, the effect from lidocaine would have been negligible since the typical dosage for lidocaine to see its effectiveness is much greater [24].

There are a few limitations in this study. First, we did not measure blood catecholamine levels in each group. Adrenergic hormone is the key factor of BP and HR elevation, and the measurements may have provided meaningful results. Second, due to the intermittent measurement of blood pressure, the time point of maximal changes may have been undetected. For an accurate assessment, measurement of continuous arterial blood pressure should have been considered. Third, we could not assess post-intubation complications such as sore throat and hoarseness. These complications are prevalent during intubation with direct laryngoscope, and the use of a lightwand is reported to reduce these complications. However, in this study, we could not address this issue. This study was based on a cohort of healthy patients aged 18–50 years old without cardiovascular diseases. Additional studies should be performed on the patients with cardiovascular diseases, including hypertension.

In conclusion, during lightwand intubation, a single injection of 1–2 mg/kg esmolol resulted in blunted HR elevation, and 2 mg/kg of esmolol was sufficient to suppress RPP elevation.

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CONFLICTS OF INTEREST

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

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REFERENCES


Remifentanil-based propofol-supplemented vs. balanced sevoflurane-sufentanil anesthesia regimens on bispectral index recovery after cardiac surgery: a randomized controlled study

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Background: The present study was to compare the potential impact of remifentanil-based propofol-supplemented anesthesia regimen vs. conventional sevoflurane-sufentanil balanced anesthesia on postoperative recovery of consciousness indicated by bispectral index (BIS) values in patients undergoing cardiac surgery.

Methods: Patients undergoing cardiac surgery were randomly allocated to get the remifentanil-based propofol-supplemented anesthesia employing target-controlled infusion (TCI) of remifentanil and propofol (Group-PR, n = 15) or a balanced-anesthesia employing sevoflurane-inhalation and TCI-sufentanil (Group-C, n = 19). In Group-PR, plasma concentration (Cp) of TCI-remifentanil was fixed at 20 ng/ml, and the effect-site concentration of TCI-propofol was adjusted within 0.8–2.0 μg/ml to maintain BIS value of 40–60. In Group-C, sevoflurane dosage was adjusted within 1–1.5 minimum alveolar concentration to maintain BIS of 40–60, and Cp of TCI-sufentanil was fixed at 0.4 ng/ml. The inter-group difference in the time for achieving postoperative BIS > 80 (T-BIS80) in the intensive care unit was determined as the primary outcome. The inter-group difference in the extubation time was determined as the secondary outcome.

Results: T-BIS80, was shorter in Group-PR than Group-C (121.4 ± 64.9 min vs. 182.9 ± 85.1 min, respectively; the difference of means −61.5 min; 95% CI −115.7 to −7.4 min; effect size 0.812; P = 0.027). The extubation time was shorter in Group-PR than in Group-C (434.7 ± 131.3 min vs. 946.6 ± 393.3 min, respectively, P < 0.001).

Conclusions: Compared with the conventional sevoflurane-sufentanil balanced anesthesia, the remifentanil-based propofol-supplemented anesthesia showed significantly faster postoperative conscious recovery in patients undergoing cardiac surgery.

Keywords: Anesthetics; Consciousness; Propofol; Remifentanil.
INTRODUCTION

While various anesthesia regimens can be employed for cardiac anesthesia, the postoperative recovery is dependent on the time to achieve wear-off of anesthetic agents and adequate conscious recovery and spontaneous ventilation. The patient's conscious recovery speed is one of the major factors for determining overall postoperative recovery [1].

Propofol-remifentanil combination can be employed as total intravenous anesthesia (TIVA) for cardiac surgery, probably due to their shorter duration of clinical effects providing faster recovery [2,3]. Remifentanil is an ultra-short-acting with a very short context-sensitive half-life, and it has a supra-additive interaction with propofol regarding hypnotic and analgesic effects [4,5]. Administering remifentanil-based anesthesia employing a high intraoperative dosage of remifentanil, even during a prolonged period, would not compromise postoperative recovery in cardiac surgery. Likewise, administering propofol during a brief period usually does not show any dose-dependent difference in recovery speed. However, administering propofol during a prolonged period, especially in higher dosage, may compromise the patient's overall recovery, because propofol has a relatively long context-sensitive half-life and variable elimination half-life [2,3,6]. Bindra et al. [7] showed that sevoflurane could be preferred to propofol for achieving rapid emergence and cognitive recovery, even in non-cardiac surgery. Therefore, a strategy for reducing or minimizing propofol dosage would be beneficial for reducing the potential delay in postoperative recovery after applying the propofol-remifentanil combined regimen. Of course, the degree of the dosage reduction must be adjusted to avoid intraoperative awareness.

If a balanced regimen employing sevoflurane and sufentanil is used, sufentanil's longer duration of action would be a major determinant for the speed of postoperative recovery [8,9].

We assumed that the remifentanil-based regimen supplemented by the reduced dosage of propofol would provide relatively faster conscious recovery compared with the balanced sevoflurane and sufentanil regimen in patients undergoing cardiac surgery.

Intraoperative electroencephalography (EEG)-based sedation monitors, including bispectral index (BIS), have been used for assessing the depth of sedation (hypnosis) and titrating the dosage of anesthetic (hypnotic) agents. Despite controversies and its limitations [10–12], several investigations speculated the efficacy of BIS, as an objective modality for assessing the depth of sedation and managing patient sedation in the intensive care unit (ICU) [4,5,10,12]. Most of all, BIS does not require physical or auditory stimulus, which is necessarily used in assessing the depth of sedation by using other subjective modalities but interrupts the already established patients' sedation level. This feature enables objective and seamless evaluation of postoperative sedation in the ICU [4,5].

Our study compared the time of achieving the BIS value > 80 in the ICU after applying two different anesthesia regimens, a remifentanil-based propofol-supplemented regimen vs. a conventional sevoflurane-sufentanil balanced anesthesia for cardiac surgery. The extubation times of the two different anesthesia regimens were also compared, as a secondary outcome of our study.

MATERIALS AND METHODS

Population and study protocol

After obtaining the Institutional Review Board approval (no. KUH1160080), the informed consent was obtained from all patients before starting the study. This prospective, randomized, and controlled trial was registered to clinicaltrials.org (no. NCT02400879). Patients undergoing elective cardiac valve repair or replacement surgery were included in this study.

Thirty-eight patients were randomly allocated (allocation ratio 1:1) into two groups using sealed envelope method: remifentanil-based propofol-supplemented anesthesia regimen was applied in Group-PR (n = 19) and conventional sevoflurane-sufentanil balanced anesthesia regimen was applied in Group-C (n = 19). All patient was blinded to their allocation.

Preoperative and intraoperative exclusion criteria were applied. Preoperative exclusion criteria were 1) urgent or emergent surgery, 2) left ventricle ejection fraction < 50%, 3) application of intra-aortic balloon pump (IABP), 4) myocardial infarction, 5) neurologic deficit or cognitive impairment, 6) chronic or acute pulmonary disease, 7) hepatic or renal impairment, 8) cardiac pacing, 9) inotropic medication.

Intraoperative exclusion criteria were 1) cardiopulmonary bypass (CPB) application of > 300 min, 2) transfusion of packed red blood cell of > 5 units, 3) post-CPB use of...
double inotropic support for > 30 min, 4) post-CPB pacing, 5) intra- and post-operative IABP application, 6) postoperative hemodialysis, 7) number of administration of additional propofol ≥ 2, 8) postoperative use of sedatives (e.g., midazolam, propofol) before extubation, 9) excessive bleeding of > 500 ml during postoperative 6 h, 10) reoperation due to excessive bleeding.

**Anesthesia regimens**

After establishing a routine invasive arterial blood pressure and a noninvasive patient monitoring such as pulse oximetry (SpO₂), electrocardiography, BIS (BIS XP monitor, Model A2000, Aspect Medical Systems, USA) and cerebral oximetry, anesthesia was induced by two groups of anesthesiologists each consisting of two anesthesiologists (AA and BB) using different regimens: a target-controlled infusion (TCI) of propofol (effect-site concentration [Ce] of 1.0–2.0 µg/ml) and remifentanil (plasma concentration [Cp], 20 ng/ml with the time to reach target concentration of 7 min) in Group-PR (by AA); and anesthesia was induced by a bolus injection of thiopental sodium 3–4 mg/kg and TCI-sufentanil (Cp of 0.4 ng/ml) in Group-C (by BB). Tracheal intubation was facilitated by bolus rocuronium under the guidance of neuromuscular train-of-four monitoring in both groups. For anesthesia maintenance, TCI-remifentanil (fixed Cp of 20 ng/ml) and TCI-propofol (variable Ce 0.8–2.0 µg/ml to maintain BIS of 40–60) was used in Group-PR, and TCI-sufentanil (fixed Cp of 0.4 ng/ml) and sevoflurane (variable 1.0–1.5 minimum alveolar concentration [MAC]) to maintain BIS of 40–60) was used in Group-C.

Hemodynamic parameters including mean blood pressure (MBP) and heart rate were maintained within 80–120% of preoperative value in both groups. Neuromuscular block during the operation was achieved by continuous infusion of rocuronium (3 µg/kg/min) in both groups.

Controlled ventilation of O₂/air mixture (FiO₂ 0.5–0.6) was applied with the following settings: tidal volume of 6–7 ml/ideal body weight, respiratory rate maintaining the state of normocapnia (end-tidal CO₂ tension 35–40 mmHg), and inspiration to expiration ratio of 1:2. The intermittent lung-recruit maneuver was applied with constant application of positive end-expiratory pressure of 6–8 mmHg.

Pulmonary artery catheter and a probe of transesophageal echocardiography were placed after the anesthesia induction. All surgeries were performed by one surgeon and four surgical assistants. They were blinded to patient allocation and the purpose of this study. After completing a sternotomy and administering 300 units/kg of heparin, arterial and venous cannulations for CPB were performed at activated clotting time > 400–450 s and CPB was conducted using a reservoir, a membrane oxygenator, a roller pump, and a heat exchanger. CPB flow, MBP, and hemodilution were adjusted to maintain the values of cerebral oximetry within 120% of preinduction values during the CPB period.

During surgery, if the BIS value exceeded 60 for 3 min and persisted against the increased dosage of sevoflurane to 1.5 MAC in Group-C or Ce of propofol to 2.0 µg/ml in Group-PR, bolus propofol 10–20 mg was administered.

**Protocols of ventilator weaning and extubation in the ICU**

After the surgery, patients were transferred to the ICU in intubated status and received controlled or assisted ventilation till the time of extubation. For the postoperative intravenous patient-control analgesia (IV-PCA) in Group-PR, remifentanil infusion of 0.25–0.3 µg/kg/min was continued till the time of performing extubation. According to the institutional protocols, the IV-PCA of Group-PR was started at the decision of performing extubation; in contrast, it in Group-C was started at the time of the sternum closure. For the IV-PCA in Group-PR, the alfentanil-ketorolac-ondansetron combination was set to deliver alfentanil of 1.0 µg/kg/h and a bolus dose of alfentanil 1.0 µg/kg with a 10-min lockout interval. For the IV-PCA in Group-C, the fentanyl-ketorolac-ondansetron combination was set to fentanyl of 0.2 µg/kg/h and a bolus dose fentanyl 0.2 µg/kg with 15-min lockout interval.

The mode of the ventilator was converted from volume-controlled ventilation to synchronized intermittent mandatory ventilation (SIMV) when the following criteria were met: stable hemodynamics, spontaneous respiration, and the respiratory rate 10–25 breaths/min.

The decision for tracheal extubation was made when the following criteria were met: awake state (or BIS > 80), stable hemodynamics, normal airway reflex, respiratory rate of 10–25 breaths/min, SpO₂ > 95% at FiO₂ < 0.6, pH ≥ 7.3 and PaCO₂ < 55 mmHg. Exubation was performed at 20 min after the decision in all patients. In Group-PR, the IV-PCA was started at the decision for extubation, and the
remifentanil infusion was stopped immediately before the extubation.

**Measurements**

Operation time, CPB time, aortic cross-clamp (ACC) time, intraoperative fluid administration quantity, transfusion requirements, intraoperative urine output, hematocrit at admission to the ICU, preoperative and postoperative PaO\textsubscript{2}/FiO\textsubscript{2} ratio were recorded. In the ICU, patients who were not calm despite the frequent verbal instructions and who were restless or combative, excited, disoriented, and required physical restraints were regarded as "agitated." The incidences of agitation were also recorded.

As a primary outcome of this study, the duration from the end of the surgery, which is defined as the completion of skin closure, to the time of achieving the BIS value > 80 (persisting > 3 min, T-BIS80) was measured in the ICU [5,13].

The duration from the end of surgery to the time of extubation (T-extubation) and the duration from the end of surgery to the time of initiating SIMV (T-SIMV) was also measured in the ICU.

All data were collected by trained observers who did not participate in patient care and were blinded to the current study.

**Statistical analysis**

The primary outcome variable was T-BIS80. According to our pilot test results (n = 10), mean and standard deviation were 117.2 and 47.6 min for Group-C, and 69.6 and 40 min for Group-PR. Based on this pilot test result, the estimated effect size was 1.083, assuming a error probability; 0.05 (2-tailed), power; 0.80, allocation ratio; 1:1, the calculated sample size was 30.

The required sample size was 38 (19 for each group) to fulfill the study protocol assumption, considering the 20% drop out rate.

Statistical analysis was performed using Sigmasat version 3.1 (Systat Software Inc., USA). After performing the normality test using the Shapiro-Wilk test, continuous variables were analyzed using a t-test (2-tailed) or the Mann-Whitney U test. Categorical variables were analyzed by a chi-square test or a Fisher’s exact test, as applicable. The data collected were expressed as mean and standard deviation, median (1Q, 3Q), or numbers of patients (%). A P value < 0.05 was considered significant.

**RESULTS**

A total of 43 patients was evaluated for eligibility. According to the inclusion and preoperative exclusion criteria, five patients were excluded (3 declined to participate, 2 had hepatic or renal impairment), and 38 patients were included in this study. Additionally, four patients from Group-PR were withdrawn because one patient required post-CPB cardiac pacing, and three patients required post-CPB use of double inotropic support > 30 min. Thus, 34 patients (19 for Group-C and 15 for Group-PR) were included in the statistical analysis (Fig. 1).

The patients’ demographic profiles and surgical types did not show intergroup differences (Table 1). Preoperative hematocrit, PaO\textsubscript{2}/FiO\textsubscript{2}, pH, electrolyte, lactate, and glucose were comparable between the two groups (Table 2). Duration of surgery in Group-PR was significantly longer than that in Group-C (445 ± 151 min vs. 319 ± 64 min, respectively, the difference of means 126 min; 95% confidence interval [95% CI] 39–214 min; effect size 1.094; P = 0.007) (Table 3). CPB and ACC time, intraoperative fluid administration quantity, transfusion requirements, intraoperative urine output, and the number of patients who received additional propofol did not show intergroup differences.

At the time of admission to the ICU, BIS, hematocrit, PaO\textsubscript{2}/FiO\textsubscript{2}, pH, electrolyte, and lactate did not show intergroup differences. However, at the time of admission to the ICU, glucose level was significantly lower in Group-PR than in group C (109.7 ± 53.0 vs. 163.9 ± 51.7 mg/dl, respectively; differences of means –54.2 mg/dl; 95% CI –91.0 to –17.5 mg/dl; effect size 1.035; P = 0.005).

The primary outcome variable, T-BIS80, was significantly shorter in Group-PR compared to Group-C (121.4 ± 64.9 min vs. 182.9 ± 85.1 min, respectively; the difference of means –61.5 min; 95% CI –115.7 to –7.4 min; effect size 0.812; P = 0.027).

As the secondary outcome variable, T-extubation in Group-PR was significantly shorter than that in Group-C (121.4 ± 64.9 min vs. 182.9 ± 85.1 min, respectively; the difference of means –61.5 min; 95% CI –115.7 to –7.4 min; effect size 0.812; P = 0.027).

As the secondary outcome variable, T-extubation in Group-PR was significantly shorter than in Group-C (434.7 ± 131.3 min vs. 946.6 ± 393.3 min, respectively; differences of means –511.9 min; 95% CI –711.4 to –312.4 min; effect size 1.746; P < 0.001). T-SIMV did not show inter-group differences.

The incidence of agitation in the ICU did not show inter-group differences (Table 4).
Fig. 1. Flow chart. Thirty-eight patients were randomly allocated into the Group-PR or Group-C, and four patients in the Group-PR were excluded because one patient required post-CPB cardiac pacing, and 3 patients were applied post-CPB use of double inotropic support. Group-PR: remifentanil-based propofol-supplemented regimen, Group-C: combined sevoflurane-sufentanil regimen, CPB: cardiopulmonary bypass.

Table 1. Demographic Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group-PR (n = 15)</th>
<th>Group-C (n = 19)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>49.5 ± 14.8</td>
<td>47.0 ± 13.7</td>
<td>0.618</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>8/7</td>
<td>10/9</td>
<td>0.986</td>
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<tr>
<td>Height (cm)</td>
<td>162.6 ± 7.8</td>
<td>166.4 ± 8.8</td>
<td>0.201</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>55.0 (50.0, 65.0)</td>
<td>63.8 (58.0, 68.0)</td>
<td>0.058</td>
</tr>
<tr>
<td>Present illness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0 (0)</td>
<td>1 (5.3)</td>
<td>1.000</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (46.7)</td>
<td>6 (31.6)</td>
<td>0.070</td>
</tr>
<tr>
<td>Diabetes and hypertension</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>Previous medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiotensin blocker</td>
<td>5 (33.3)</td>
<td>4 (21.1)</td>
<td>0.462</td>
</tr>
<tr>
<td>ACE-inhibitor</td>
<td>4 (26.7)</td>
<td>1 (5.3)</td>
<td>0.146</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>3 (20.0)</td>
<td>0 (0)</td>
<td>0.076</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>3 (20.0)</td>
<td>3 (15.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>Statin</td>
<td>2 (13.3)</td>
<td>1 (5.3)</td>
<td>0.571</td>
</tr>
<tr>
<td>Warfarin</td>
<td>2 (13.3)</td>
<td>3 (15.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>Operation type</td>
<td></td>
<td></td>
<td>0.934</td>
</tr>
<tr>
<td>Mitral valve repair</td>
<td>6 (40.0)</td>
<td>9 (47.4)</td>
<td></td>
</tr>
<tr>
<td>Aortic valve repair</td>
<td>5 (33.3)</td>
<td>4 (21.1)</td>
<td></td>
</tr>
<tr>
<td>Double valve repair</td>
<td>4 (26.7)</td>
<td>6 (31.6)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, numbers of patients (%), or median (1Q, 3Q). Group-PR: propofol-remifentanil regimen, Group-C: sevoflurane-sufentanil regimen, ACE: angiotensin-converting enzyme, NA: not applicable.
### Table 2. Preoperative Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group-PR (n = 15)</th>
<th>Group-C (n = 19)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>38.0 (35.0, 40.0)</td>
<td>35.5 (33.0, 38.0)</td>
<td>0.081</td>
</tr>
<tr>
<td>PaO₂/FiO₂ ratio</td>
<td>362 ± 164</td>
<td>451 ± 208</td>
<td>0.182</td>
</tr>
<tr>
<td>pH</td>
<td>7.43 (7.40, 7.46)</td>
<td>7.44 (7.41, 7.45)</td>
<td>0.476</td>
</tr>
<tr>
<td>Na⁺ (mmol/L)</td>
<td>140 (138, 140)</td>
<td>140 (138, 142)</td>
<td>0.716</td>
</tr>
<tr>
<td>K⁺ (mmol/L)</td>
<td>3.8 (3.6, 4.1)</td>
<td>3.7 (3.5, 4.0)</td>
<td>0.544</td>
</tr>
<tr>
<td>Ca²⁺ (mg/dl)</td>
<td>1.1 (1.1, 1.1)</td>
<td>1.1 (1.1, 1.2)</td>
<td>0.082</td>
</tr>
<tr>
<td>Mg²⁺ (mmol/L)</td>
<td>0.5 (0.5, 0.6)</td>
<td>0.5 (0.5, 0.7)</td>
<td>0.689</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>0.7 (0.7, 1.5)</td>
<td>0.8 (0.7, 1.1)</td>
<td>0.622</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>101 (94, 119)</td>
<td>119 (100, 137)</td>
<td>0.138</td>
</tr>
</tbody>
</table>

Values are presented as median (1Q, 3Q) or mean ± SD. Values are measured just after anesthesia induction. Group-PR: propofol-remifentanil regimen, Group-C: sevoflurane-sufentanil regimen, PaO₂/FiO₂ ratio: partial pressure of O₂ in arterial blood/the fraction (percent) of inspired O₂.

### Table 3. Intraoperative Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group-PR (n = 15)</th>
<th>Group-C (n = 19)</th>
<th>Difference of means (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of surgery (min)</td>
<td>445 ± 151</td>
<td>319 ± 64</td>
<td>126 (39–214)</td>
<td>0.007</td>
</tr>
<tr>
<td>CPB time</td>
<td>155 ± 60</td>
<td>143 ± 56</td>
<td>NA</td>
<td>0.535</td>
</tr>
<tr>
<td>ACC time</td>
<td>94 ± 50</td>
<td>82 ± 41</td>
<td>NA</td>
<td>0.450</td>
</tr>
<tr>
<td>Intraoperative fluid (ml)</td>
<td>1,460 ± 409</td>
<td>1,537 ± 682</td>
<td>NA</td>
<td>0.703</td>
</tr>
<tr>
<td>Crystalloid</td>
<td>907 ± 187</td>
<td>942 ± 413</td>
<td>NA</td>
<td>0.760</td>
</tr>
<tr>
<td>Colloid</td>
<td>553 ± 302</td>
<td>595 ± 387</td>
<td>NA</td>
<td>0.736</td>
</tr>
<tr>
<td>Packed RBC (unit)</td>
<td>2.3 ± 2.2</td>
<td>1.9 ± 2.3</td>
<td>NA</td>
<td>0.621</td>
</tr>
<tr>
<td>Intraoperative urine (ml)</td>
<td>1,257 ± 496</td>
<td>1,441 ± 671</td>
<td>NA</td>
<td>0.382</td>
</tr>
<tr>
<td>Additional propofol*</td>
<td>2 (1.3)</td>
<td>1 (5.3)</td>
<td>NA</td>
<td>0.621</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or numbers of patients (%). Group-PR: propofol-remifentanil regimen, Group-C: sevoflurane-sufentanil regimen, 95% CI: 95% confidence interval, CPB: cardiopulmonary bypass, ACC: aortic cross-clamp, NA: not applicable, BIS: bispectral index.

*Number of patients required additional propofol bolus due to BIS value > 60.

### Table 4. Postoperative Variables in the Intensive Care Unit

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group-PR (n = 15)</th>
<th>Group-C (n = 19)</th>
<th>Difference of means (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At admission*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIS (0–100)</td>
<td>47 ± 5</td>
<td>44 ± 7</td>
<td>NA</td>
<td>0.176</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>29 (28, 30)</td>
<td>30 (26, 31)</td>
<td>NA</td>
<td>0.662</td>
</tr>
<tr>
<td>PaO₂/FiO₂ ratio</td>
<td>347 (181, 447)</td>
<td>352 (223, 431)</td>
<td>NA</td>
<td>0.986</td>
</tr>
<tr>
<td>pH</td>
<td>7.42 (7.39, 7.45)</td>
<td>7.43 (7.39, 7.44)</td>
<td>NA</td>
<td>0.871</td>
</tr>
<tr>
<td>Na⁺ (mmol/L)</td>
<td>145 (143, 148)</td>
<td>144 (141, 146)</td>
<td>NA</td>
<td>0.296</td>
</tr>
<tr>
<td>K⁺ (mmol/L)</td>
<td>4.1 (3.7, 4.5)</td>
<td>4.1 (4.0, 4.4)</td>
<td>NA</td>
<td>0.802</td>
</tr>
<tr>
<td>Ca²⁺ (mg/dl)</td>
<td>1.1 ± 0.1</td>
<td>1.1 ± 0.1</td>
<td>NA</td>
<td>0.413</td>
</tr>
<tr>
<td>Mg²⁺ (mmol/L)</td>
<td>0.6 ± 0.1</td>
<td>0.7 ± 0.1</td>
<td>NA</td>
<td>0.129</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>109.7 ± 53.0</td>
<td>163.9 ± 51.7</td>
<td>−54.2 (−91.0 to −17.5)</td>
<td>0.005</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>2.2 ± 1.0</td>
<td>2.8 ± 1.1</td>
<td>NA</td>
<td>0.154</td>
</tr>
<tr>
<td>Time to BIS &gt; 80 (min)</td>
<td>121.4 ± 64.9</td>
<td>182.9 ± 85.1</td>
<td>−61.5 (−115.7 to −7.4)</td>
<td>0.027</td>
</tr>
<tr>
<td>Time to SIMV (min)</td>
<td>352.8 ± 136.2</td>
<td>426.7 ± 126.7</td>
<td>NA</td>
<td>0.112</td>
</tr>
<tr>
<td>Time to extubation (min)</td>
<td>434.7 ± 131.3</td>
<td>946.6 ± 393.3</td>
<td>−511.9 (−711.4 to −312.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Agitation</td>
<td>7 (46.7)</td>
<td>6 (31.6)</td>
<td>NA</td>
<td>0.369</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, median (1Q, 3Q), or numbers of patients (%). Group-PR: propofol-remifentanil regimen, Group-C: sevoflurane-sufentanil regimen, 95% CI: 95% confidence interval, BIS: bispectral index, SIMV: synchronized intermittent mandatory ventilation, NA: not applicable. *Just after admission to the intensive care unit, PaO₂/FiO₂ ratio: partial pressure of O₂ in arterial blood/the fraction (percent) of inspired oxygen ratio.
DISCUSSION

Our result demonstrated that the remifentanil-based propofol-supplemented regimen is superior to the conventional balanced-anesthesia regimen in providing a faster time to achieve postoperative BIS > 80 in cardiac surgery. Despite the random allocation and surgery by the same surgeon, the duration of surgery was longer in Group-PR. Considering that the longer duration of surgery is a risk factor for delayed patient awakening after anesthesia [14], our result with the shorter recovery despite the longer duration of surgery in Group-PR (445 min vs. 319 min in Group-C) may be of much more significant meaning.

So far, few studies have compared postoperative conscious recovery time after applying the remifentanil-based propofol-supplemented anesthesia regimens vs. conventional sevoflurane-sufentanil balanced anesthesia regimens for cardiac surgery. According to our result, remifentanil-based propofol-supplemented TIVA can be favored, especially for patients requiring fast postoperative conscious recovery in cardiac surgery.

We employed the BIS values > 80, as the indicator of the patient’s conscious recovery in the ICU, since previous reports showed that BIS values ranging 64–80 corresponded to a transitional status from unconsciousness to consciousness [15]. BIS > 80 was comparable to the sedation status responding to the command, “open your eyes” [13]. As mentioned earlier, BIS monitoring enables a seamless and objective evaluation of the depth of sedation in the ICU [4,5]. Our result indicating the remifentanil’s superiority in providing faster BIS recovery corresponds to a previous study employing a subjective sedation scale, in which remifentanil-anesthesia provided a shallower depth of postoperative sedation than sufentanil-anesthesia did in cardiac surgery [8].

In the meantime, remifentanil or sufentanil alone cannot provide sufficient sedation, but they can potentiate the sedative effect of concomitantly administered propofol or sevoflurane, as the opioid-sedative synergism [16]. In our results, remifentanil and sufentanil could potentiate the effects and reduce the requirement concomitantly administered propofol or sevoflurane (Ce of propofol or MAC of sevoflurane) in the context of propofol-remifentanil synergy for producing intraoperative hypnosis [16]. The dosage of propofol was also guided by the BIS monitor to avoid intraoperative awareness. The reduced dosage of propofol in Group-PR, Ce of < 2.0 μg/ml, might also be beneficial in reducing or minimizing the propofol-induced myocardial depressive effect in the propofol-remifentanil combination for cardiac surgery [17,18].

In Group-PR, the increased dosage of remifentanil throughout anesthesia did not seem to produce any residual effect due to its very short plasma elimination half-life (8–10 min) and a context-sensitive half-time (3–5 min) [16]. The reduced dosage of propofol (Ce 0.8–2.0 μg/ml), which was similar to that of making patient awake (Ce 1.8 ± 0.7 μg/ml) in a previous study [19], also facilitated postoperative recovery. Only stopping of its infusion might provide immediate resolution of its effects.

Since sevoflurane has a short context-sensitive half time (< 5 min) and the time for conscious recovery (< 8 min) [20], the dosage of sufentanil in Group-C and its duration of administration might be a critical factor for producing the inter-group difference in T-BIS80. Previous reports also showed residual effects after administering opioids, including sufentanil [8,9].

However, the dosage of sufentanil in Group-C was still minimal, Cp 0.4 ng/ml, and far less than the dosage producing postoperative residual effects in previous studies [9,21]. Therefore, the dosage and the duration of administration might play an essential role in terms of achieving faster postoperative recovery. Previous studies also supported this discrepancy upon longer vs. shorter period (e.g., in non-cardiac surgeries) of sufentanil infusion: the recovery profiles were not different between remifentanil and sufentanil anesthesia for thyroidectomy [3], and the extubation time was not different between remifentanil and sufentanil anesthesia for craniotomy [2]. Measures for reducing sufentanil’s residual effect, such as earlier discontinuation of its infusion 30 min before the ending of the surgery, seem to be useful [2].

Most previous studies had focused on the contribution of respiratory recovery as an indicator of the overall postoperative recovery in evaluating anesthesia regimens [22]. The extubation time (less than 6–10 h) has been used as a typical indicator for evaluating postoperative recovery and fast-track anesthesia protocol [22]. The earlier recovery of consciousness may contribute to the earlier extubation in our study.

The shorter extubation time in the present study supports the superiority of remifentanil-based regimen to other anesthesia regimens employing sufentanil or fentanyl in providing faster postoperative respiratory recovery in cardiac surgery. The extubation time in Group-PR was signifi-
Remifentanil-based anesthesia on postoperative BIS

cantly shorter (7 h vs. 15 h in Group-C). Bhavsar et al. [23] showed that remifentanil regimen was more effective in reducing time to tracheal extubation and length of stay in the recovery area. Furthermore, the dosage of the intermediate-acting opioid (e.g., morphine, fentanyl, sufentanil) administered during the intraoperative period is also important: higher intraoperative dosage would prolong postoperative extubation time (duration of intubation, odds ratio, 1.54 per sufentanil 1 μg/kg increment) [22].

In our study, despite the significant inter-group difference in the extubation time, the time to switch to SIMV, another determinant for extubation time, was not significantly different. Lison et al. [8] showed no difference in the ventilatory weaning times after using remifentanil vs. sufentanil anesthesia cardiac surgery, although the extubation time was faster in remifentanil anesthesia. Bhavsar et al. [23] also showed that remifentanil anesthesia was not superior to a standard moderate- to high-dose sufentanil regimen in the duration of ventilatory support or ICU stay [17,21,23]. Furthermore, some reports showed that early extubation (< 6 postoperative hours) paradoxically increases ICU length of stay in cardiac patients [24,25].

This study had limitations. First, the inter-group difference in the regimens for postoperative pain control (remifentanil and alfentanil vs. fentanyl) and the start timings of the PCA might affect the degree of pain intensity as well as recovery characteristics. However, even the greater dosage of remifentanil in Group-PR (approximately 8–9 times greater than fentanyl in the equivalent-dosage calculation) provided a significantly earlier recovery. Second, we did not include the postoperative evaluation of the Ramsay score or the Riker sedation-agitation scale. These subjective sedation scales might help overcome the controversy of postoperative BIS monitoring in the ICU setting [4,5]. However, their application had the potential to annoy the sedated patients and abruptly change the stabilized BIS values. Third, since the BIS monitor only manifests cortical activity, which is mainly affected by the hypnotic agents [26], the possible sedative effect by the extra-cortical pathway (e.g., sedative effects by opioids) was not evaluated [27]. There might be an inter-group discrepancy in the BIS values indicating the conscious recovery and those corresponding to the same level of sedation/awareness. The BIS value indicating the return of consciousness in using a propofol-remifentanil combination would be higher than that in using propofol alone, as in this study. In comparing the inter-group differences in postoperative BIS values, we have to consider the variation of residual effects (or offset speed) all each anesthetic agent and BIS monitor’s capability to manifest cortical EEG activity. Finally, the possible impact of other variables on patient’s recovery and the effects of each anesthesia method on clinical outcomes, such as mortality rate, length of stay in the ICU, or length of hospital stay, were not evaluated due to the limited sample size. It may be necessary to evaluate this through further studies employing a much larger sample size.

In conclusion, the remifentanil-based propofol-supplemented regimen, which employing the relatively reduced dosage of propofol and the increased dosage of remifentanil, provided significantly faster recovery of postoperative BIS value, than balanced sevoflurane-sufentanil anesthesia regimen did in patients undergoing cardiac surgeries. It also provided significantly faster extubation time. Further investigation may be warranted to determine whether the propofol-remifentanil-ratio affects the recovery speed of postoperative consciousness in using the propofol-remifentanil anesthesia regimen for cardiac surgery.

CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS


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REFERENCES


Remifentanil-based anesthesia on postoperative BIS


INTRODUCTION

Low-flow anesthesia is economical and environmentally friendly, as it reduces the consumption of O₂ and anesthetics during inhalation anesthesia. Clinically, the method is advantageous for raising the temperature and humidity of the inspired gas in patients. Low-flow anesthesia was first introduced by Foldes et al. [1] in 1952, and it was established when minimum-flow anesthesia (0.5 L/min) was introduced by Virtue [2] in 1974. At the same time, the technologically advanced anesthetic machine facilitated safe and accurate rebreathing as well as monitoring, and the currently promoted advantage of the machine is the support for low-flow anesthesia. With the wide use of sevoflurane and desflurane in anesthesia instead of halothane with a high absorption rate, the complicated calculation of

Change of inspired oxygen concentration in low flow anesthesia

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Background: There are several advantages of low flow anesthesia including safety, economics, and eco-friendliness. However, oxygen concentration of fresh gas flow and inspired gas are large different in low flow anesthesia. This is a hurdle to access to low flow anesthesia. In this study, we aimed to investigate the change in inhaled oxygen concentration in low flow anesthesia using oxygen and medical air.

Methods: A total of 60 patients scheduled for elective surgery with an American Society of Anesthesiologist physical status I or II were enrolled and randomly allocated into two groups. Group H: Fresh gas flow rate (FGF) 4 L/min (FiO₂ 0.5). Group L: FGF 1 L/min (FiO₂ 0.5). FGF was applied 4 L/min in initial phase (10 min) after intubation. After initial phase FGF was adjusted according to groups. FGF continued at the end of surgery. Oxygen and inhalation anesthetic gas concentration were recorded for 180 min at 15 min interval.

Results: The inspired oxygen concentration decreased by 5.5% during the first 15 min in the group L. Inspired oxygen decreased by 1.5% during next 15 min. Inspired oxygen decreased by 1.4% for 30 to 60 min. The inspired oxygen of group L is 35.4 ± 4.0% in 180 min. The group H had little difference in inspired oxygen concentration over time and decreased by 1.8% for 180 min.

Conclusions: The inspired oxygen concentration is maintained at 30% or more for 180 min in patients under 90 kg. Despite some technical difficulties, low flow anesthesia may be considered.

Keywords: Balanced anesthesia; General anesthesia; Inspired oxygen; Low flow.
the anesthetic gas concentration within the anesthetic circuit during low-flow anesthesia became relatively simple [3,4]. Despite the advanced machines and the development and use of anesthetics with low absorption rates, low-flow anesthesia is still a novelty to several anesthesiologists who, due to concerns of safety, tend to resort to the use of fresh gas at a high flow of ≥ 3 L/min for anesthesia in clinical practice [5].

In this study, the latest anesthetic device and various monitoring devices were used. The fraction of inspired oxygen (FiO₂) supplied to the fresh gas was constant, while low-flow anesthesia was applied using O₂, medical air, sevoflurane, and desflurane. This study aimed to examine the changes in inspired oxygen concentration within the anesthetic circuit and their stability.

MATERIALS AND METHODS

Subjects

This study was conducted after the approval of the Institutional Review Board (no. KUGH-2019-04-14). The goals and methods of the study were explained to the patients and informed consent was obtained from each patient before the study. As a prospective intervention study based on the physical statuses I and II of the American Society of Anesthesiologists, the study recruited 60 patients aged 20–65 years scheduled to receive thyroid surgery under general anesthesia. The cases with predicted surgery duration of less than 1 h were excluded, as the duration is insufficient for monitoring the changes in oxygen saturation. Patients with preoperative pulmonary dysfunction, acute or chronic lung disease, asthma, systemic diseases, such as hypertension and diabetic kidney disease or liver disease, a history of surgery within the previous month, and a history of smoking were excluded. Patients with preoperative pulmonary dysfunction, acute or chronic lung disease, asthma, systemic diseases, such as hypertension and diabetic kidney disease or liver disease, a history of surgery within the previous month, and a history of smoking were excluded. The cases requiring inotropic or antihypertensive injection or blood transfusion were also excluded.

Methods

The Dräger Primus anesthetic machine (Dräger AG, Germany) and the standard circular respiratory circuit with a heated breathing tube (VentStar Helix heated, Dräger AG) were used. The Vapor® 2000 vaporizer (Dräger AG) was used for sevoflurane and D-Vapor® (Dräger AG) was used for desflurane. For each patient, leak tests of the ventilator and respiratory circuit were performed before anesthesia. Drägersorb Free (Dräger AG) was used for the CO₂ absorbent, and the substance was replaced with a new one every morning before the daily tasks.

During the surgery, non-invasive techniques were used to assess arterial pressure, electrocardiogram, pulse oxygen saturation, end-tidal CO₂ fraction, and body temperature. The standard monitoring procedures, including the Bispectral index score (BIS, Vista™, USA), were also performed. The measurements were taken from before the induction of anesthesia; arterial pressure was measured at 5-min intervals, and other recordings were made in real-time.

For the induction of anesthesia, 8 L/min of 100% O₂ was used for 2-min spontaneous breathing for denitrification, after which 0.2 mg glycopyrrolate was injected. At the onset of denitrification, remifentanil was initially injected at 0.2 μg/kg/min. To induce the loss of consciousness, 0.05 mg/kg midazolam and 1 mg/kg propofol were injected. As a neuromuscular agent, 0.9 mg/kg rocuronium was injected, and endotracheal intubation was performed after 90 s. An esophageal thermometer was inserted through the oral cavity.

For the continuation of anesthesia, controlled ventilation was performed while maintaining 6–8 ml/kg tidal volume, 10–15 times/min respiratory rate, and 30–40 mmHg of end-tidal CO₂ fraction. In both groups during the experiment, a minimum alveolar concentration (MAC) of ≥ 0.8 was maintained, and the bispectral index score was maintained within 40–60. Based on the blood pressure before anesthetic induction, the remifentanil injection was adjusted within a rate of 1–10 μg/min. If necessary, 5–10 mg rocuronium was intermittently used for muscular relaxation.

Following intubation, the rate of fresh gas flow was 4 L/min, whereas the inhaled anesthetics were maintained at 2.2 vol% sevoflurane and 6.0 vol% desflurane for 10 min. After 10 min, the fresh gas flow was lowered to 1 L/min in the low-flow anesthesia group (group L), for which the sevoflurane and desflurane injections were increased to 2.5 and 7.0 vol%, respectively. In the high-flow anesthesia group (group H), the fresh gas flow and anesthetic gas concentration were maintained at identical levels even after 10 min. It was planned that the patients whose inspired oxygen concentration reduced to ≤ 25% during surgery would be excluded while increasing the fresh gas flow to 4 L/min. For the cases with ≥ 20% intraoperative blood pressure in-
creases or decreases, the plan was to increase or decrease the inhaled anesthetics by 10%. The inspired oxygen, expired oxygen, inspired anesthetic, and expired anesthetic concentrations were recorded at 15-min intervals based on the elapsed time after 10 min from intubation.

SPSS 20.0 (IBM Co., USA) was used for the statistical analyses. The measured data were expressed as mean ± SD. The demographic data, such as sex, the types of anesthetic, and the American Society of Anesthesiologists classes were compared using the chi-squared test. The age, height, and weight were compared using the independent t-test. The Mann–Whitney U test was used to compare surgery duration and mean arterial pressure. The linear mixed model was used to compare the inspired oxygen concentration, inspired anesthetic concentration, end-tidal CO₂, pulse oxygen saturation, and body temperature. P < 0.05 represented statistical significance.

RESULTS

For the analyses, each experimental group contained 30 patients. The demographic statistics for group L and group H were not significantly different (Table 1). The heart rate, arterial pressure, minute ventilation, and bi-spectral index score of group L and group H were not statistically different (Table 2). The end-tidal CO₂ was maintained at 32–36 mmHg in both groups, and the bispectral index score was regulated within 40–60 range.

From the baseline of 10 min after endotracheal intubation, the inspired oxygen concentrations in group H and group L were 46.3 ± 1.0% and 45.7 ± 1.6%, respectively; they were not significantly different (P = 0.107). In group H, the difference in the time-dependent inspired oxygen concentration was small, with a 1.8% reduction within 180 min. In group L, the inspired oxygen concentration during the first 15 min was 40.2 ± 2.0%, corresponding to a 5.5% reduction (P < 0.001). After 1 h, the inspired oxygen concentration was 37.3 ± 2.6%, corresponding to a further decrease by 1.4% (P < 0.001). The concentration within 120 min after the first 60 min was reduced by only 1.9%, with a recorded value of 35.4 ± 4.0%. The change in the expired oxygen concentration was similar to that of the inspired oxygen concentration. Between the baseline of 10 min after intubation and the end-point of anesthesia, the difference between the inspired and expired oxygen concentrations were maintained at approximately 4.8–5.5% in group H and 4.9–5.7% in group L (Fig. 1).

For individual patients, the lowest inspired oxygen concentration during 180 min was 44% in group H and 26% in group L. One of the 30 patients in group L showed a reduction in the inspired oxygen concentration to < 30%, and the lowest inspired oxygen concentration for the remaining

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group H (n = 30)</th>
<th>Group L (n = 30)</th>
<th>P value</th>
</tr>
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<tr>
<td>Sex (M/F)</td>
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<td>Age (yr)</td>
<td>47.0 ± 9.8</td>
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<td>Height (cm)</td>
<td>163.4 ± 8.8</td>
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<tr>
<td>Weight (kg)</td>
<td>64.8 ± 14.0</td>
<td>69.7 ± 12.5</td>
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<tr>
<td>ASA (I/II)</td>
<td>13/17</td>
<td>12/18</td>
<td>0.793</td>
</tr>
<tr>
<td>Operative time</td>
<td>151.5 ± 37.6</td>
<td>145.5 ± 32.6</td>
<td>0.534</td>
</tr>
<tr>
<td>Inhalation agent (Sevo/Des)</td>
<td>13/17</td>
<td>13/17</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Values are presented as number or mean ± SD. Group H: fresh gas flow 4 L/min, FiO₂ 0.5, O₂ 1.5 L/min, Air 2.5 L/min; Group L: fresh gas flow 1 L/min, FiO₂ 0.5, O₂ 0.37 L/min, Air 0.63 L/min. ASA: American Society of Anesthesiologist, Sevo: Sevoflurane, Des: Desflurane. P values for differences were determined by using the chi-squares, t-test.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group H (n = 30)</th>
<th>Group L (n = 30)</th>
<th>P value</th>
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<tbody>
<tr>
<td>SBP (mmHg)</td>
<td>114.5 ± 22.4</td>
<td>110.8 ± 13.5</td>
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<tr>
<td>DBP (mmHg)</td>
<td>73 ± 14.8</td>
<td>71.2 ± 9.1</td>
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<tr>
<td>HR (beats/min)</td>
<td>85.4 ± 18.5</td>
<td>87.0 ± 14.5</td>
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<tr>
<td>MV (L/min)</td>
<td>5.8 ± 1.0</td>
<td>5.6 ± 1.0</td>
<td>0.387</td>
</tr>
<tr>
<td>BIS</td>
<td>43.8 ± 8.7</td>
<td>40.3 ± 6.9</td>
<td>0.187</td>
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</tbody>
</table>

Values are presented as mean ± SD. Group H: fresh gas flow 4 L/min, FiO₂ 0.5, O₂ 1.5 L/min, Air 2.5 L/min; Group L: fresh gas flow 1 L/min, FiO₂ 0.5, O₂ 0.37 L/min, Air 0.63 L/min. SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate, MV: minute ventilation, BIS: bispectral index score. P values for differences were determined by using the t-test.
29 patients was 32%. In both groups L and H, there was no drop-out due to a reduction in the inspired oxygen concentration to < 25%.

For the inspired concentration of inhaled anesthetics recorded at the onset of anesthesia, no significant difference was found between group H (6.0 ± 0.3 vol% desflurane and 2.2 ± 0.2 vol% sevoflurane) and group L (6.9 ± 0.7 vol% desflurane and 2.5 ± 0.2 vol% sevoflurane) (P = 0.201). The inspired concentrations of inhaled anesthetics after one hour were as follows: 5.7 ± 0.6 vol% desflurane and 2.2 ± 0.1 vol% sevoflurane in group H; 6.3 ± 0.6 vol% desflurane and 2.0 ± 0.2 vol% sevoflurane in group L (Fig. 2).

For the body temperatures, no significant difference was found between group H and group L (P = 0.248), but group L showed slightly higher temperatures with time (Fig. 3). The intraoperative temperature was 36.2 ± 0.3°C in group H and 36.3 ± 0.5°C in group L after 437
In both groups, the pulse oxygen saturation was maintained at 99–100%, with no significant difference (P = 0.215). No case of delayed postoperative recovery, difficulty breathing, or pulmonary complication until discharge was reported.

**DISCUSSION**

The benefits of low-flow anesthesia, including the reduced cost based on the reduced use of anesthetic gas, the safety of medical staff working in operation rooms, and environmental protection, are generally accepted [5]. Kim [6] claimed that the continuous monitoring of inspired oxygen concentration and oxygen saturation in low-flow anesthesia enabled the anesthesiologist to focus more on the patient and better understand the pharmacokinetics of the inhaled anesthetics; however, due to the difference between the oxygen concentration in the fresh gas injected to the anesthetic circuit and the inspired oxygen concentration measured by the monitoring device for gas concentration, the anesthesiologists could not readily apply low-flow anesthesia in clinical practice due to safety concerns [7].

The well-known previous studies on low-flow anesthesia mostly focused on the delivery of inhaled anesthetics or used N₂O and O₂. A recent study by Venkatachalapathy et al. [8] also focused on the comparison between the use of medical air and the conventional use of N₂O [1,2]. Concerns about the expansion of body cavity or nausea have reduced the use of N₂O while increasing the use of medical air [9]. No study has demonstrated the difference between low-flow anesthesia and the currently popular anesthetic methods using medical air, and this motivated the present study.

Raymond [10] reported that the relationship between FiO₂ and inspired oxygen concentration in 1 L/min fresh gas flow is linear, and the difference was maintained at approximately 20%. The study also showed that the supply of O₂ should be ≥ 0.5 L/min to maintain an inspired oxygen concentration of ≥ 30%. Virtue et al. [2] reported that when anesthesia was continued with 0.5 L/min fresh gas flow, the inspired oxygen concentration was not reduced to ≤ 30% until 60 min of anesthesia in patients weighing < 80 kg; in several patients weighing ≥ 80 kg, the inspired oxygen concentration was reduced to ≤ 20% to increase the proportion of oxygen in fresh gas [11]. Based on the previous studies, the present study determined that 1 L/min fresh gas flow was ideal for accessibility and stability in low-flow anesthesia. The study found that the inspired oxygen concentration was not reduced to ≤ 30% until 60 min of anesthesia in group L, which contained 6 patients weighing ≥ 80 kg. One patient in group L, on the other hand, showed a considerably greater reduction in inspired oxygen concentration in fresh gas flow than was predicted; the patient was 180 cm in height and 95 kg in weight, and the inspired oxygen concentration began reducing below 30% after 60 min of anesthesia, which continued to 26% until the end of surgery. The simple regression analysis based on bodyweight and inspired oxygen concentration showed that in group L, the inspired oxygen concentration decreased as body weight increased, and the negative correlation was stronger at 120 min (r = –0.16, R² = 0.41) than at 60 min (r = –0.14, R² = 0.49); in group H, the correlation was considerably weak regardless of time (60 min, r = –0.01, R² = 0.01; 120 min, r = –0.03, R² = 0.15) (Fig. 4). Considering the report of Okada et al. [12,13] on the relationship between body weight and oxygen consumption during low-flow anesthesia at 0.6 L/min (O₂, 0.3 L/min; N₂O, 0.3 L/min) and the correlation between body weight and inspired oxygen concentration found in this study, careful monitoring is required in applying 1 L/min fresh gas flow in patients weighing ≥ 90 kg (Fig. 4).

This study was not designed to analyze the inherent properties of inhaled anesthetics; however, a remark may be made on the related findings. Bailey [14] proposed that to achieve an adequate MAC concentration during low-flow anesthesia, anesthetics should be supplied with sufficient flow for ≥ 10 min after the onset of anesthesia. Due to the difference between the concentrations of the inhaled anesthetics dial and the anesthesia circuit of the vaporizer, the dial should be adjusted to a level slightly higher than the target during low-flow anesthesia [15]. Based on the findings of Bailey [14] a high flow of 4 L/min was applied for 10 min in the two groups in this study, while the concentration of inhaled anesthetics was slightly increased upon reducing the flow in group L. As the amount of inhaled anesthetics was adjusted based on the BIS and MAC levels in both groups, it is difficult to quantitatively analyze the changes in the concentration of the two inhaled anesthetics. However, it was found that the concentration was maintained at approximately 1 MAC with stability in both groups. Despite the delivery of high-flow inhaled anesthetics for 10 min, a rapid reduction in the concentration of inhaled anesthetics was observed during the first 15 min in
Further studies should obtain the concentration of inhaled anesthetics at 1-min intervals during the first 15 min of anesthesia, which is predicted to lead to a V-shaped concentration curve for inhaled anesthetics as observed by Bailey [14].

With the advancement and establishment of balanced anesthesia, the continuous injection of narcotic analgesics in addition to inhaled anesthetics and the intermittent or continuous injection of neuromuscular blocking agents have been commonly used, which consequently reduce the proportion of inhaled anesthetics for the maintenance of anesthetic depth [16–18]. During low-flow anesthesia, the relatively slow change in MAC has been pointed out as a significant drawback that inhibits adequate response to surgical stimulation; however, this may complement by the balanced anesthesia method. In this study, narcotic analgesics and neuromuscular blocking agents were used in combination, and the sudden change in the concentration of inhaled anesthetics in group L may not have been necessary.

The body temperatures of groups L and H measured in this study were not significantly different, but this may have been due to the use of a heated breathing circuit (VentStar Helix heated, Dräger AG) for maintaining the body temperature. A trend of rise in temperature by approximately 0.2°C was observed in group L 120 min after the onset of anesthesia. This was consistent with the result of Klee- mann [19], and as the current emphasis is on maintaining the perioperative body temperature of the patient, the benefits of low-flow anesthesia-related to body temperature maintenance deserves careful attention.

This study has several limitations. First, the study was designed as a pilot study to investigate the relationship between low-flow anesthesia and various patient factors. A simple regression analysis was performed to investigate the correlation between body weight and inspired oxygen saturation, and multiple regression analysis was not performed for height, age, sex, and other variables. Further studies should carry out additional correlation analyses with adequate sample sizes. Second, for the gas analyzer and the vaporizer for sevoflurane and desflurane in the anesthetic machine, deviations may have arisen despite the annual quality control, as a single device was not used for individual measurements. This is expected to be resolved by conducting a prospective randomized controlled study with appropriate sample size.

In conclusion, low-flow anesthesia with 1 L/min fresh gas flow was used to maintain the inspired oxygen concentration at ≥ 25% for up to 3 h. Considering the known advantages related to air pollution and economic issues, low-flow anesthesia should be considered in clinical practice despite one or two technological challenges, compared to the high flow anesthesia with 4 L/min fresh gas flow. Further studies should, however, investigate the possibility that 1 L/min fresh gas flow may not be sufficient for some patients when the duration of anesthesia exceeds 180 min.

**CONFLICTS OF INTEREST**

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


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REFERENCES

Effect of dexamethasone gargle, intravenous dexamethasone, and their combination on postoperative sore throat: a randomized controlled trial

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Background: Postoperative sore throat (POST) is a complication that decreases patient satisfaction and increases postoperative complaints. The present study was conducted to investigate effects of gargling with dexamethasone, intravenous dexamethasone injection and the combination of the two on the incidence and severity of POST.

Methods: Study participants were 96 patients who had undergone laparoscopic cholecystectomy, randomly allocated into three groups. Group G gargled with 0.05% dexamethasone solution and were infused intravenous 0.9% normal saline before general anesthesia; group I gargled with 0.9% normal saline and were infused intravenous 0.1 mg/kg dexamethasone; group GI gargled with 0.05% dexamethasone solution and were infused intravenous 0.1 mg/kg dexamethasone. The incidence and severity of POST, hoarseness and cough were evaluated and recorded at 1, 6, and 24 h after the surgery.

Results: There were no significant differences in the total incidence of POST up to 24 postoperative hours among Group G, Group I and Group GI (P = 0.367, Group G incidence = 34.38%, [95% confidence interval, 95% CI = 17.92–50.83], Group I incidence = 18.75%, [95% CI = 5.23–32.27], Group GI incidence = 28.13%, [95% CI = 12.55–43.70]). The other outcomes were comparable among the groups.

Conclusions: In patients who had undergone laparoscopic cholecystectomy, gargling with 0.05% dexamethasone solution demonstrated the same POST prevention effect as intravenous injection of 0.1 mg/kg dexamethasone. The incidence and severity of POST were not significantly different between the combination of gargling with 0.05% dexamethasone solution and intravenous injection of 0.1 mg/kg dexamethasone and use of each of the preventive methods alone.

Keywords: Dexamethasone; Endotracheal intubation; Laparoscopic cholecystectomy; Mouth wash; Postoperative complication; Sore throat.
INTRODUCTION

Postoperative sore throat (POST) is a commonly postoperative complication that occurs in 14.4% to 73.9% of patients who undergo general anesthesia with endotracheal intubation [1]. POST may cause patient dissatisfaction and physical discomfort during recovery [2]. Causes of POST are known to be associated with inflammation and stimulation by endotracheal intubation [3]. Various methods have been found effective in reducing POST. The methods that have been reported to be effective in reducing the incidence rate of POST include choice of a smaller endotracheal tube, meticulous manipulation of the laryngoscope, intubation after complete muscle relaxation, minimization of cuff pressure inside the endotracheal tube, smooth suction in the oropharynx, and complete contraction of the endotracheal tube cuff during the postoperative extubation [4].

The pharmacological methods that have been found to be effective in decreasing the incidence and severity of POST include preoperative gargling with ketamine and magnesium solution [5], intravenous injection of dexamethasone [6], and gargling and tube soaking with dexamethasone [7].

Many recent studies have shown that dexamethasone not only prevents postoperative nausea and vomiting but can also relieve pain or reduce general inflammatory responses [8]. The anti-inflammatory and immunosuppressant potency of orally administered dexamethasone is 26.6 times higher than that of cortisol, a natural hormone, and 6.6 times higher than that of prednisone [9]. Dexamethasone is also used to decrease side effects during chemotherapy, treat Addison’s disease and adrenal insufficiency, and facilitate fetal lung maturation in pregnant women at high risk of preterm delivery [9].

A previous meta-analysis showed that intravenous dexamethasone decreases the incidence and severity of POST at 1 h and 24 h after surgery [10]. Yang et al. [6] and Lee et al. [11] also reported reduced incidence of POST through intravenous injection of dexamethasone.

In the dental field, dexamethasone gargle is used to relieve the symptoms of burning mouth syndrome [12]. Lee et al. [7] reported that gargling with 0.05% dexamethasone solution decreased the incidence of POST.

No previous studies have been conducted to examine the effect of the combination of dexamethasone gargle and intravenous dexamethasone injection on the incidence and severity of POST. We thought that the incidence of POST differed following administration of the combination of gargling with 0.05% dexamethasone solution and intravenous injection of 0.1 mg/kg dexamethasone and use of each of the preventive methods alone. Therefore, the aim of the present study was to investigate the effects of preoperative 0.05% dexamethasone solution gargle, intravenous injection of 0.1 mg/kg dexamethasone, and combination of the two on the incidence and severity of POST, hoarseness and cough in patients undergoing laparoscopic cholecystectomy.

MATERIALS AND METHODS

The present study was conducted with patients undergoing elective laparoscopic cholecystectomy. Subjects were 96 patients between the ages of 20–70, and with American Society of Anesthesiologists physical status classification I or II. The duration of anesthesia was between 20 min and 120 min. Exclusion criteria were modified Mallampati score of 3 or higher; recent throat pain or upper respiratory infection; use of a device stimulating the oral cavity, pharynx or larynx, such as Levin tube or endoscopic nasobiliary drainage; previous experience of POST; contraindications to use of dexamethasone or allergic response to it. Additionally, cases in which intubation was attempted three times or more, in which endotracheal intubation was performed using a stylet, in which the Cormack-Lehane grade was 3 or higher were excluded.

This study was approved by the Institutional Review Board as a prospective, randomized, double-blind study (no. 19-0032), and registered with the Clinical Research Information Service (https://cris.nih.go.kr, no. KCT0004971). In the study, the patients were sufficiently informed and asked to sign a written consent prior to surgery. The patients were randomly allocated, using a computer-generated random number table, to three groups, Gargle group (Group G, n = 32), IV group (Group I, n = 32), and Gargle + IV group (Group GI, n = 32), at a ratio of 1:1:1. To blind the group allocation, the pharmacist was given a sealed envelope with a coding number written on it and asked to prepare syringes for drug injection and containers of the gargle solution. The syringes for drug injection contained either 0.9% normal saline solution 2 ml or mixed solution 2 ml (dexamethasone 0.1 mg/kg + 0.9% normal saline). The containers of the gargle solution contained either 0.9% normal saline 10 ml or 0.05% dexamethasone solution 10 ml (dexamethasone 5 mg/ml + 0.9% normal saline 9 ml) prepared asepti-
cally and passed on to the anesthesiologist on the day of surgery. In all procedures requiring the use of a syringe (Bandgold filter syringe™, Bandgold Co., Korea), a filter system was used to prevent the inflow of tiny impurities into the body. An anesthesiologist who was unaware of the group allocation, administered the drugs to the patients according to the coding number, after which anesthetic induction, endotracheal intubation and extubation were performed. After the surgery, another anesthesiologist, not the one who performed the anesthesia for the surgery, visited the patients in the ward to conduct the medical examination through an interview.

A total of 96 patients were allocated to the three groups. The patients in the gargle group (Group G) were treated with 0.05% dexamethasone solution gargle for 30 s at 10 min before general anesthesia by sufficiently tilting the head backward, followed by intravenous injection of 2 ml of 0.9% normal saline solution 5 min before general anesthesia. The patients in the intravenous injection group (Group I) were treated with 0.9% normal saline solution gargle for 30 s at 10 min before general anesthesia by sufficiently tilting the head backward, followed by intravenous injection of 0.1 mg/kg dexamethasone, mixed with 0.9% normal saline solution in a resulting volume of 2 ml, 5 min before general anesthesia. The patients in the gargle + intravenous injection group (Group GI) were treated with 0.05% dexamethasone solution gargle for 30 s at 10 min before general anesthesia by sufficiently tilting the head backward, followed by intravenous injection of 0.1 mg/kg dexamethasone, mixed with 0.9% normal saline solution in a resulting volume of 2 ml, 5 min before general anesthesia (Fig. 1).

The patients were intramuscularly injected, as premedication 30 min before the surgery, with glycopyrrolate 0.2 mg and famotidine 20 mg. Propofol (2 mg/kg) and lidocaine (1 mg/kg) were used for induction of anesthesia. Rocuronium (0.6 mg/kg) was used as a neuromuscular blocker. Endotracheal intubation was performed after verifying that the bispectral index (BIS VISTA™ Monitoring System, Covidien, Boulder, USA) was below 60 and the train-of-four TOF (TOF-Watch SX®, Organon Ltd., Ireland) count was 0 (zero) following injection of the neuromuscular blocker. The Cormack grade of all patients included in the statistical analysis was 1, and endotracheal intubation was successfully performed in two or fewer attempts in all of them. In the case of tracheal intubation in men, Macintosh # 3.5 (Briteblade pro™, Flexicare medical, USA) was used for laryngoscope and # 3 in women, and stylet was not used. The inner diameter of the silicon tube of the laryngoscope used for the endotracheal intubation was 7.5 mm (Sheridan/CF®, Teleflex Medical, USA) for the male subjects and 7.0 mm for the female subjects. An oral airway (Ace Grip Endo

![Flow diagram of study enrollment](https://www.anesth-pain-med.org)
Fix™, Ace Medical Co. Ltd., Korea) was fixed with an endotracheal tube in all study patients. Anesthesia was maintained using sevoflurane 1.5 to 2.5 vol%, 50% O2 with air, and remifentanil 0.05–0.1 μg/kg/min. The nasopharyngeal temperature, electrocardiogram, oxygen saturation, and capnogram were monitored, and an airway without the heating and humidifying functions was used. At the start and end of the surgery, a cuff pressure gauge (Mallinckrodt™ Hand Pressure Gauge, Covidien Deutschland GmbH, Germany) was used to keep the pressure at 20 to 30 cm-H2O. Ten minutes before the end of the surgery, tramadol 0.5 to 1 mg/kg and ramosetron 0.3 mg were intravenously injected to prevent postoperative pain, nausea and vomiting. After the end of the surgery, no endotracheal suction was performed but oral suction was lightly performed. Sugammadex (2–4 mg/kg) was administered to reverse the neuromuscular blocker. Extubation was carried out gently after verifying that the TOF ratio was 0.9 or higher, monitoring the patients’ recovery of consciousness, and following the anesthesiologist’s orders.

An interview regarding POST was conducted with the patients within 24 h after the surgery, considering that an acute inflammatory response usually reaches its peak in about 24 h and the incidence of POST is decreased within 24 h when dexamethasone is used [11]. In each group, an anesthesiologist who was unaware of the allocation of the patients to the groups visited the ward at 1, 6, and 24 h after the surgery to interview the patients about sore throat, hoarseness and cough. The severity of POST, hoarseness and cough was evaluated on a four-point scale (Table 1) [13]. POST was defined as discomfort at the larynx or pharynx, while resting or swallowing the saliva after the surgery [6]. The responses were categorized into cases of no sore throat (no sore throat, 0), cases in which throat pain could be felt by the patient only when the patient was asked about the presence of sore throat (minimal sore throat, 1), cases in which the patient himself or herself complained about sore throat (moderate sore throat, 2), and cases in which the patient obviously felt discomfort due to sore throat (severe sore throat, 3). Hoarseness and cough were also evaluated using the same method [13]. Patients with minimal symptoms or more (1 point or more in four-point scale) were included in incidence data estimates. Visual analog scale (VAS) scores of wound pain were recorded at the same time points. Additionally, other side effects in addition to POST were identified and specifically recorded.

To control postoperative abdominal pain, when the VAS was 5 or higher in the PACU, ketorolac tromethamine 30 mg/ml was administered and acetaminophen 1 g/100 ml was intravenously injected three times a day in the ward. When the VAS score of the pain at the surgical site was 5 or higher, intravenous injection of tramadol 0.5 mg/kg was additionally performed to control the surgical pain. If the pain continued at a VAS score of 5 or higher despite the pain control, nalbuphine 2.5 mg was intravenously injected.

The primary outcome measure was the incidence of POST. The secondary outcome measures were the incidence of hoarseness and cough, and the severity of POST, hoarseness and cough.

Considering that the incidence of POST in the group that received prophylactic dexamethasone intravenous injection was 0.69 in the study by Park et al. [13], that the POST incidence in the dexamethasone gargle group was 0.33 in Lee et al. [7], and that the POST incidence in the Gargle + IV Group would be lower than 0.33, the necessary number of subjects in each group was calculated to be 29 with a significance level of 0.05 and power of 80%. To adjust a familywise error rate, we applied $Z_{4.5}$ in sample size calculation. Taking into consideration the 10% dropout rate, the number of subjects in each group was determined to be 32.

Data was presented as mean ± SD for continuous variables, and count and percentage for categorical variables. Age, American Society of Anesthesiologists physical status classification, height, weight, anesthesia time, initial time cuff pressure, end time cuff pressure, dose of drugs administered (remifentanil, tramadol, sugammadex, acetaminophen for postoperative wound pain) and wound pain VAS.

**Table 1.** Scoring System for Sore Throat, Cough and Hoarseness [13]

<table>
<thead>
<tr>
<th>Severity score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sore throat</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>No sore throat</td>
</tr>
<tr>
<td>1</td>
<td>Minimal sore throat</td>
</tr>
<tr>
<td>2</td>
<td>Moderate sore throat</td>
</tr>
<tr>
<td>3</td>
<td>Severe sore throat</td>
</tr>
<tr>
<td><strong>Cough</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>No cough</td>
</tr>
<tr>
<td>1</td>
<td>Minimal cough</td>
</tr>
<tr>
<td>2</td>
<td>Moderate cough</td>
</tr>
<tr>
<td>3</td>
<td>Severe cough</td>
</tr>
<tr>
<td><strong>Hoarseness</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>No hoarseness</td>
</tr>
<tr>
<td>1</td>
<td>Hoarseness at the time of interview, but noted only by patient</td>
</tr>
<tr>
<td>2</td>
<td>Hoarseness that is readily apparent, but mild</td>
</tr>
<tr>
<td>3</td>
<td>Hoarseness that is readily apparent and severe</td>
</tr>
</tbody>
</table>
were compared among treatment groups using analysis of variance or Kruskal–Wallis test as appropriate. The incidence of pain, hoarseness and cough were analyzed with chi-square test. To adjust a type I error rate, we recalculated the level of significance by applying the Bonferroni method (i.e., $P (\chi^2 > 5.73) = 0.05/3 = 0.0167$). SAS macro for nonparametric analysis of factorial longitudinal data in Brunner et al. [14] was performed to compare the scores from three groups, repeated measures. Statistical analysis was conducted using SAS 9.4 (SAS Institute Inc., USA). A $P$ less than 0.05 was considered as statistically significant.

**RESULTS**

From September 2019 to April 2020, 96 patients were screened and enrolled in the study. These patients were randomly allocated to three groups. The evaluation was performed with the 96 patients who satisfied the inclusion criteria, and all patients completed the study with no drop-outs. No significant differences were found in the sex ratio, age, anesthesia time, American Society of Anesthesiologists physical status classification, height, weight, initial time endotracheal tube cuff pressure and end time endotracheal tube cuff pressure. The total doses of drugs administered (remifentanil, tramadol, and sugammadex in the perioperative period, acetaminophen for postoperative pain control) and wound pain VAS scores were comparable among Group G, Group I, and Group GI (Table 2).

The sore throat incidence and severity over time did not show a significant difference among Group G, Group I, and Group GI at 1 h, 6 h and 24 h in resting and swallowing (Table 3, resting POST group * time $P = 0.558$, swallowing POST group * time $P = 0.751$, total POST incidence $P = 0.367$, group G incidence = 46.88%, [95% confidence interval, 95% CI = 32.68–67.32]).

The hoarseness incidence and severity did not show a significant difference among the groups at 1 h, 6 h and 24 h after the surgery (Table 4, hoarseness group * time $P = 0.654$, total hoarseness incidence $P = 0.415$, group G incidence = 34.38%, [95% confidence interval, 95% CI = 29.58–32.27], group GI incidence = 28.13%, [95% CI = 12.55–43.70]).

Table 2. Patient Characteristics, Perioperative and Postoperative Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group G (n = 32)</th>
<th>Group I (n = 32)</th>
<th>Group GI (n = 32)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>0.840</td>
</tr>
<tr>
<td>M</td>
<td>14 (44)</td>
<td>12 (38)</td>
<td>12 (38)</td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>18 (56)</td>
<td>20 (62)</td>
<td>20 (62)</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>46.9 ± 12.6</td>
<td>48.8 ± 13.1</td>
<td>47.0 ± 14.5</td>
<td>0.780</td>
</tr>
<tr>
<td>ASA I</td>
<td>21 (66)</td>
<td>24 (75)</td>
<td>18 (56)</td>
<td>0.287</td>
</tr>
<tr>
<td>I</td>
<td>11 (34)</td>
<td>8 (25)</td>
<td>14 (44)</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.0 ± 8.3</td>
<td>162.8 ± 7.8</td>
<td>162.4 ± 9.7</td>
<td>0.339</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.0 ± 10.6</td>
<td>65.1 ± 11.5</td>
<td>65.3 ± 13.0</td>
<td>0.380</td>
</tr>
<tr>
<td>Anesthesia time (min)</td>
<td>51.3 ± 10</td>
<td>53.6 ± 13.8</td>
<td>52.8 ± 10.0</td>
<td>0.708</td>
</tr>
<tr>
<td>Initial time cuff pressure (cmH₂O)</td>
<td>27.9 ± 0.6</td>
<td>27.9 ± 0.6</td>
<td>28.0 ± 0.7</td>
<td>0.835</td>
</tr>
<tr>
<td>End time cuff pressure (cmH₂O)</td>
<td>27.2 ± 0.8</td>
<td>27.3 ± 0.6</td>
<td>27.4 ± 0.8</td>
<td>0.608</td>
</tr>
<tr>
<td>Dose of remifentanil administered (μg)</td>
<td>195.3 ± 63.5</td>
<td>201.2 ± 77.8</td>
<td>199.5 ± 87.6</td>
<td>0.902</td>
</tr>
<tr>
<td>Dose of tramadol administered (mg)</td>
<td>47.8 ± 4.2</td>
<td>46.9 ± 4.7</td>
<td>45.9 ± 5.0</td>
<td>0.274</td>
</tr>
<tr>
<td>Dose of sugammadex administered (mg)</td>
<td>192.2 ± 18.5</td>
<td>184.4 ± 23.6</td>
<td>190.63 ± 19.8</td>
<td>0.282</td>
</tr>
<tr>
<td>Dose of acetaminophen administered (g)</td>
<td>2.8 ± 0.4</td>
<td>28.9 ± 0.4</td>
<td>2.8 ± 0.37</td>
<td>0.932</td>
</tr>
<tr>
<td>Wound pain VAS (0–10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 h</td>
<td>3 (2, 3)</td>
<td>2 (2, 3)</td>
<td>3 (2, 3)</td>
<td>0.951</td>
</tr>
<tr>
<td>6 h</td>
<td>3 (2, 3)</td>
<td>2 (2, 3)</td>
<td>3 (2, 3)</td>
<td>0.959</td>
</tr>
<tr>
<td>24 h</td>
<td>3 (2, 3)</td>
<td>2 (2, 3)</td>
<td>3 (2, 3)</td>
<td>0.880</td>
</tr>
</tbody>
</table>

Data presented as number of patients, mean ± SD, or median (1Q, 3Q). Group G: gargle with 0.05% dexamethasone solution, intravenous injection with 0.9% normal saline 2 ml, Group I: gargle with 0.9% normal saline, intravenous injection with mixed solution 2 ml (dexamethasone 0.1 mg/kg + 0.9% normal saline), Group GI: gargle with 0.05% dexamethasone solution, intravenous injection with mixed solution 2 ml (dexamethasone 0.1 mg/kg + 0.9% normal saline). ASA: American Society of Anesthesiologists physical status classification, VAS: Visual Analog Scale.
severity did not show a significant difference among the groups at 1 h, 6 h and 24 h after the surgery (Table 5, cough group * time P = 0.388, total hoarseness incidence P = 0.541, group G incidence = 0.00%, group I incidence = 6.25%, [95% CI = 0.00–14.64], group GI incidence = 6.25%, [95% CI = 0.00–14.64]).

No postoperative complication, except sore throat, cough and hoarseness, was found in any of the patients in the three groups.

DISCUSSION

We predicted that combined gargle and intravenous injection of dexamethasone would lead to a lower incidence of POST than use of each of the preventive methods alone, but our findings revealed no difference between the combined or single applications with respect to POST.

According to the experimental results of the present study, the POST-preventing effect of gargling with 0.05% dexamethasone solution alone and that of intravenous injection of 0.1 mg/kg dexamethasone solution alone were equivalent to the effect of the combination of gargling with 0.05% dexamethasone solution and subsequent intravenous injection of 0.1 mg/kg dexamethasone.

The combined gargle and intravenous injection of dexamethasone did not demonstrate a better POST-preventing effect than the single use of each method, probably because the topical application of dexamethasone gargle did not result in any increase in the plasma drug concentration over that caused by the intravenous injection.

---

**Table 3. Incidence and Severity of Sore Throat among the Groups after Tracheal Extubation**

<table>
<thead>
<tr>
<th>Post operation time (severity score)</th>
<th>Group G (n = 32)</th>
<th>Group I (n = 32)</th>
<th>Group GI (n = 32)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 h (0/1/2/3)</td>
<td>26/6/0/0</td>
<td>29/3/0/0</td>
<td>29/3/0/0</td>
<td>0.258</td>
</tr>
<tr>
<td>6 h (0/1/2/3)</td>
<td>30/2/0/0</td>
<td>30/2/0/0</td>
<td>32/0/0/0</td>
<td>0.006</td>
</tr>
<tr>
<td>24 h (0/1/2/3)</td>
<td>31/1/0/0</td>
<td>32/0/0/0</td>
<td>32/0/0/0</td>
<td>0.558</td>
</tr>
</tbody>
</table>

**Table 4. Incidence and Severity of Hoarseness among the Groups after Tracheal Extubation**

<table>
<thead>
<tr>
<th>Post operation time (severity score)</th>
<th>Group G (n = 32)</th>
<th>Group I (n = 32)</th>
<th>Group GI (n = 32)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 h (0/1/2/3)</td>
<td>15/17/0/0</td>
<td>20/12/0/0</td>
<td>24/8/0/0</td>
<td>0.062</td>
</tr>
<tr>
<td>6 h (0/1/2/3)</td>
<td>19/13/0/0</td>
<td>24/8/0/0</td>
<td>23/9/0/0</td>
<td>0.000</td>
</tr>
<tr>
<td>24 h (0/1/2/3)</td>
<td>26/6/0/0</td>
<td>31/1/0/0</td>
<td>30/2/0/0</td>
<td>0.654</td>
</tr>
</tbody>
</table>

**Table 5. Incidence and Severity of Cough among the Groups after Tracheal Extubation**

<table>
<thead>
<tr>
<th>Post operation time (severity score)</th>
<th>Group G (n = 32)</th>
<th>Group I (n = 32)</th>
<th>Group GI (n = 32)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 h (0/1/2/3)</td>
<td>32/0/0/0</td>
<td>30/2/0/0</td>
<td>31/1/0/0</td>
<td>0.141</td>
</tr>
<tr>
<td>6 h (0/1/2/3)</td>
<td>32/0/0/0</td>
<td>31/1/0/0</td>
<td>31/1/0/0</td>
<td>0.157</td>
</tr>
<tr>
<td>24 h (0/1/2/3)</td>
<td>32/0/0/0</td>
<td>32/0/0/0</td>
<td>30/2/0/0</td>
<td>0.388</td>
</tr>
</tbody>
</table>

Data are presented as number of patients. Severity of sore throat was assessed using 4 scoring system: 0, no sore throat; 1, mild sore throat; 2, moderate sore throat; 3, severe sore throat. The statistical significance was accepted with P values less than 0.05 for primary comparison among groups.

Data are presented as number of patients. Severity of cough was assessed using 4 scoring system: 0, no cough; 1, mild cough; 2, moderate cough; 3, severe cough. The statistical significance was accepted with P values less than 0.05 for primary comparison among groups.
De Oliveira et al. [15] reported that the incidence and severity of POST showed a decrease when dexamethasone 0.1 mg/kg was administered intravenously than when dexamethasone 0.05 mg/kg was administered by the same method. Park et al. [2] reported that the intravenous injection of dexamethasone 0.2 mg/kg was more effective in reducing the incidence and severity of POST than the intravenous injection of dexamethasone 0.1 mg/kg. The explanation for these findings may be that the plasma drug concentration was increased as the dose of dexamethasone administered by intravenous injection was increased. Gargling with dexamethasone did not increase the effect, because it may have not increased the plasma drug concentration. Therefore, we suspect that the combination of gargling with 0.05% dexamethasone solution and intravenous injection of 0.1 mg/kg dexamethasone did not increase the concentration of dexamethasone in the blood, resulting in no better effect on incidence of POST.

The incidence of POST was investigated at 1 h, 6 h, and 24 h postoperatively because the complaint of pain within one hour after the surgery may be decreased by the analgesic used for the general anesthesia [3]. As reported by Hung et al. [3], the incidence of POST was highest at 6 h postoperative.

In the present study, among the patients who received dexamethasone 0.1 mg/kg intravenous injection, the proportion of those who complained of sore throat during swallowing was 12% at 1 h after the surgery, 25% at 6 h after the surgery, and 6% at 24 h after the surgery. Lee et al. [11] reported that among the patients in their study who were intravenously injected with dexamethasone 0.1 mg/kg, the proportion of those who complained of throat pain was 40% at 1 h after the surgery, 17% at 6 h after the surgery, and 4% at 24 h after the surgery. The difference between the two studies may be the result of the change in the patient’s position required for the lumbar spine surgery in the study by Lee et al. [11]; that change may have resulted in a change in the endotracheal tube cuff pressure and an abnormality in the tube location [16].

POST is caused by endotracheal intubation, which results in a mucosal injury or vocal cord injury in the trachea [17]. The intubation to the posterior pharynx, larynx and airway, the expansion of the cuff, and the direct manipulation of the laryngoscope cause the stimulation and inflammation [6].

Various interventions have been attempted to reduce the incidence of POST but none of them was capable of completely removing the complication. Steroid has been often used to prevent sore throat, and systemic dexamethasone is the most widely studied drug for POST [18]. A wide spectrum of methods may be used for the delivery of steroid, such as soaking the endotracheal tube with triamcinolone [19], gargling with dexamethasone or soaking a endotracheal tube in it [7], or intravenously injecting dexamethasone [6]. Intravenous injection of dexamethasone showed significant effect on the prevention of postoperative nausea and vomiting [20], and intraperitoneal administration of dexamethasone showed a significantly greater decrease in nausea in comparison with the intravenous injection [21].

Corticosteroid binds to annexin proteins and thus generates Ca2+-dependent phospholipids to inhibit phospholipase A2 and decrease the synthesis of inflammatory mediator, prostaglandins, and leukotriene [22]. In addition, corticosteroid suppresses the transport of leukocytes to inflammatory sites, inhibits the release of cytokine by maintaining cellular integrity, and causes anti-inflammatory responses by inhibiting the growth of fibroblasts [23].

Local use of dexamethasone for the reduction of postoperative pain includes its addition in ultrasound-guided transverse abdominis plane block [24] and oral gargling [7]. In the patient undergoing unilateral inguinal hernia repair, the addition of dexamethasone during ultrasound-guided transverse abdominis plane block decreased the numerical rating scale score more than the administration of levobupivacaine alone [24].

Dexamethasone gargle was effective on the oral mucosa to prevent POST [7]. Gargling for prevention of postoperative sore throat showed an effect on the local nociceptors rather than a systemic effect [5]. In the present study, the total incidence of POST within 24 h of dexamethasone 0.05% gargle was 34.4%, similar to the findings of Lee et al. [7] that the total incidence within 24 h of dexamethasone 0.05% gargle was 33.3%. The oral mucosa has a thin horny layer and many blood vessels and is capable of allowing a larger amount of drug to reach vessels, compared to the skin. Drugs that can be administered through application are selected in oral mucosal diseases because they can penetrate into the level of the basement membrane and remain effective for a longer period in comparison with intravenous drug administration [25]. There is no commercially available dexamethasone gargle solution product in Korea. However, solutions at a concentration of 0.01% to 0.06% are prepared by mixing dexamethasone powder or liquid with normal saline solution or distilled water, and
used for patients in the departments of otolaryngology, dentistry, and hemato-oncology (burning mouth syndrome, oral lichen planus, intraoral ulcer) [26]. In the present study, as in that reported by Lee et al. [7], dexamethasone 5 mg/ml was mixed with normal saline 9 ml to prepare a 0.05% solution, which was used for gargling for 30 s with the head sufficiently tilted backward.

Dexamethasone gargle is considered to allow the drug to function directly on the mucosa of the pharynx and larynx where POST is caused. Gargling with dexamethasone has advantages because it can be simply performed before a elective surgery and its effect is observed within several minutes [27]. According to Park et al. [26], patients who received dexamethasone gargle to treat oral manifestations of chronic graft versus host disease (cGVHD) had decreased cGVHD severity and pain scores.

In the present study, the incidence of POST during swallowing in patients treated with the combination of 0.05% dexamethasone solution gargle and intravenous injection of dexamethasone 0.1 mg/kg was 13% at 1 h, 13% at 6 h, and 0% at 24 h postoperatively, indicating that the POST-preventing effect of the combination was not significantly different from the use of either dexamethasone gargle or dexamethasone intravenous injection alone. This finding indicates that the topical application of dexamethasone gargle has an effect equivalent to that of dexamethasone intravenous injection, and suggests that the combination of the two administration methods does not provide a superior outcome in the prevention of POST.

As mentioned at the beginning of the discussion, we think that the combined use of dexamethasone gargle and intravenous injection did not increase the concentration of dexamethasone in the blood, resulting in no better effect on incidence of POST.

In this experiment, using only dexamethasone did not bring a better effect on incidence of POST, in contrast, the combination of dexamethasone with other drugs was found more effective in reducing POST than the use of a single drug. Safavi et al. [28] reported that incidence of POST at postoperative 0 h, 2 h, 4 h, 8 h and 24 h was lower in the group in which gargling with a 30 ml solution containing 40 mg ketamine was used in combination with intravenous injection of dexamethasone 0.2 mg/kg than in the other two groups in which only one of the two methods was used. The combination of intravenous injection of dexamethasone and ketamine gargle reduced the incidence of POST in comparison with the single use of each administration method. This result may be due to a synergic effect caused by the anti-hyperalgesic effect of ketamine and the anti-inflammatory effect of dexamethasone [28]. According to Cho et al. [29], the incidence of POST within 24 postoperative hours was lower in the group that received dexamethasone 8 mg/kg intravenous injection in combination with lidocaine 1.5 mg/kg than in the group that received only dexamethasone 8 mg/kg intravenous injection. In this case, a synergic effect might have been the result of the suppression of the airway reflex, reduced bronchial hyper-reactivity, and pain relief caused by lidocaine, and the anti-inflammatory effect of dexamethasone [29].

Therefore, the use of drugs with different mechanisms seems to be more effective than use of a single drug in the prevention of POST.

The present study has the following limitations.

First, the plasma dexamethasone concentration was not measured in the cases of dexamethasone intravenous injection, dexamethasone gargle, and their combination. Even the use of a single dose of steroid has the risk of increasing postoperative infection, hemorrhage and inflammation [30]. Although such problems did not occur within 24 postoperative hours in the present study, the possibility of systemic side effects thereafter was not predicted. Second, the incidence and severity of POST were investigated in the present study by applying the dexamethasone administration methods only to patients undergoing laparoscopic cholecystectomy, which requires a relatively short surgical time. In comparison with laparotomy, the incidence of POST may be higher in patients undergoing laparoscopic surgery because the cuff pressure of the endotracheal tube is higher owing to pneumoperitoneum and the Trendelenburg position. Since the duration of anesthesia for the laparoscopic cholecystectomy in the present study was about 50 min, further studies may need to be conducted to investigate the incidence and severity of POST in cases in which the surgical duration is longer. Third, the dose of dexamethasone for the intravenous injection was 0.1 mg/kg in the present study. The dose of the dexamethasone for the intravenous injection, tested with respect to POST, was fixed or varied on the basis of the weight (0.1–0.2 mg/kg). Further studies may need to be conducted on the POST-preventing effect of dexamethasone depending on the dose [10,18]. Fourth, the evaluation of POST, hoarseness and cough was performed in the present study based on patient’s subjective responses obtained through inter-
view. Therefore, the individual patients might have expressed their symptoms differently depending on their experiences and psychological state.

In conclusion, in the patients who had undergone laparoscopic cholecystectomy, gargling with 0.05% dexamethasone solution showed the same POST-preventing effect as the intravenous injection of 0.1 mg/kg dexamethasone. The incidence and severity of POST were not significantly different between the combination of 0.05% dexamethasone solution gargle and 0.1 mg/kg dexamethasone intravenous injection and the use of each of the two preventive methods alone.

CONFLICTS OF INTEREST

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

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REFERENCES


Clinically relevant concentrations of dexmedetomidine may reduce oxytocin-induced myometrium contractions in pregnant rats

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Background: Recently, there have been some trials to use dexmedetomidine in the obstetric field but concerns regarding the drug include changes in uterine contractions after labor. We aimed to evaluate the effects of dexmedetomidine on the myometrial contractions of pregnant rats.

Methods: In a pilot study, the contraction of the myometrial strips of pregnant Sprague-Dawley rats in an organ bath with oxytocin at 1 mU/ml was assessed by adding dexmedetomidine from $10^{-6}$ to $10^{-2}$ M accumulatively every 20 min, and active tension and the number of contractions were evaluated. Then, changes in myometrial contractions were evaluated from high doses of dexmedetomidine ($1.0 \times 10^{-4}$ to $1.2 \times 10^{-3}$ M). The effective concentrations (EC) for changes in uterine contractions were calculated using a probit model.

Results: Active tension and the number of contractions were significantly decreased at $10^{-3}$ M and $10^{-4}$ M dexmedetomidine, respectively (P < 0.05). A complete loss of contractions was seen at $10^{-2}$ M. Dexmedetomidine ($1.0 \times 10^{-4}$ to $1.2 \times 10^{-3}$ M) decreased active tension and the number of contractions in a concentration-dependent manner. The EC₉₅ of dexmedetomidine for inhibiting active tension and the number of contractions was $5.16 \times 10^{-2}$ M and $2.55 \times 10^{-5}$ M, respectively.

Conclusions: Active tension of the myometrium showed a significant decrease at concentrations of dexmedetomidine higher than $10^{-3}$ M. Thus, clinical concentrations of dexmedetomidine may inhibit uterine contractions. Further research is needed for the safe use of dexmedetomidine in the obstetrics field.

Keywords: Adrenergic alpha-agonists; Alpha 2 adrenergic receptors; Dexmedetomidine; Rat; Relaxation; Smooth muscle; Uterine contraction; Uterus.

INTRODUCTION

Dexmedetomidine is a highly selective $\alpha_2$ adrenergic receptor (AR) agonist which has been in the spotlight be-
medetomidine, such as anxiolysis, reducing anesthetic requirement when used as an adjuvant, and cardiovascular stability, can be attractive factors when considering the use of dexmedetomidine in pregnant women [2]. Several trials of dexmedetomidine have been conducted in the obstetrics field, such as application as an adjuvant analgesic with remifentanil during labor [3], as an adjuvant during general anesthesia for cesarean sections in normal pregnancies [4], in a parturient with preeclampsia [5], or as the sole sedative during cesarean section under spinal anesthesia [6]. However, there are some concerns for the use of dexmedetomidine for obstetric anesthesia, such as changes in uterine contractions after labor and fetal effects by placental transfer [2]. Although some human and animal studies reported that dexmedetomidine increased spontaneous contractions of the myometrium [7–9], the studies used relatively low concentrations of dexmedetomidine in vitro, which seem insufficient in clinical use [10]. Also, there are some conflicting reports that clonidine, a non-selective $\alpha_2$ AR agonist, did not affect uterine contractions and that $\alpha_2$ AR does not participate in the contractile response of the myometrium [11].

In this study, we evaluated the effects of dexmedetomidine on oxytocin-induced contractions of the myometrium in pregnant rats. We also calculated the effective concentration for changes in the contractile profiles and compared them with the clinical concentration of dexmedetomidine used for sedation.

**MATERIALS AND METHODS**

**Animals**

After approval by the Animal Care and Use Committee (no. CIACUC2018-S0043), the current study was conducted following Animal Research: Reporting of In Vivo Experiments guidelines [12]. A total of 10 specific-pathogen-free Sprague-Dawley pregnant rats (weighing 200–250 g) were used for the study (pilot study, n = 2; concentration-response study, n = 8). The rats were purchased from Damul Science (Korea) and brought to the laboratory on the 17th day of pregnancy. The pregnant rats were housed for one day in cages with free access to water and food located in a room maintained with a light/dark cycle of 12:12 and constant temperature (20 to 23°C).

**Tissue preparation**

The study was performed from 9:00 a.m. to 5:00 p.m. in the laboratory. The pregnant rats were euthanized by an infusion of carbon dioxide into the chamber on the 18th day of pregnancy, which is comparable to about 31–32 weeks of pregnancy in humans [13]. Immediately, the abdomen of the rat was incised, and the pregnant uterus was isolated. The uterus was transferred to a petri dish filled with Krebs solution (118.3 mM NaCl, 4.7 mM KCl, 2.5 mM CaCl$_2$, 25 mM NaHCO$_3$, 1.2 mM KH$_2$PO$_4$, 1.2 mM MgCl$_2$, and 11.1 mM glucose) [14]. The dissected uterus was carefully trimmed of fat and connective tissue and cut in the longitudinal direction. Myometrial strips were prepared in approximately 5 mm × 10 mm sections. Then, a myometrial strip was mounted in an organ bath, which was filled with Krebs solution. The bath consisted of double walls and had a capacity of 25 ml. Heated water was circulated in the space between the two walls of the bath to maintain a temperature of 37°C. The end of the strip was anchored with a triangular clip and both ends were connected to a hook on the base of the organ bath and lever arm of a force-displacement transducer (Isometric Transducer; Harvard App Ltd., USA). The Krebs solution in the bath was maintained at a pH of approximately 7.4 by continuous aeration with a gas mixture of 95% oxygen and 5% carbon dioxide.

**Drug preparation**

Dexmedetomidine powder (purity ≥ 98%, CAS Number 145108-58-3, C$_{13}$H$_{16}$N$_2$·HCl, molecular weight 236.74 g/mol) was purchased from Sigma-Aldrich (USA) and was prepared by dissolving in distilled water (20 mg/ml). Then, the dexmedetomidine solution was diluted to varying concentrations for the concentration-response study; $10^{-6}$ to $10^{-2}$ M for the pilot study, and $1.0 \times 10^{-4}$ to $1.2 \times 10^{-3}$ M for the concentration-response study.

**Measurement of isometric tension**

After the myometrial strips were mounted, the isometric tension of the strips was assessed using a force-displacement transducer. The default value for isometric tension was determined using a 2.0 g weight and an initial resting tension of 2.0 g was applied to the myometrial strips for 60 min for equilibration by flushing fresh Krebs solution in
the organ bath every 20 min. During the equilibration, rhythmic spontaneous contractions of the myometrial strips developed, and 1 mU/ml of oxytocin (Sigma-Aldrich) was added to the organ bath [9]. During the equilibration with oxytocin for a further 60 min, the myometrial strips developed strong, regular contractions. Then, the isometric tension was measured over the 20 min and used as control values. The measured data were traced with an i-WORX 118 system (USA) and recorded by Labscribe software (Windows ver. 2.0; iWorx Systems Inc.).

**Quantitative measurement of changes in myometrial strip contractions**

Changes in myometrial strip contractions during the time interval were calculated by data quantitatively measured by the force-displacement transducer. Active tension was calculated as the difference between the peak tension and the resting tension during contractions of the myometrial strip. The number of contractions was expressed as the number of contractions for 20 min of each concentration of dexmedetomidine.

**Pilot study**

To evaluate the concentration-response of dexmedetomidine on pregnant myometrial strips and determine concentrations for the probit analysis, a pilot study was conducted (n = 2). Dexmedetomidine concentrations from $10^{-6}$ to $10^{-5}$ M were added to the organ bath accumulatively. Changes in the contractions of the myometrial strip at each concentration of dexmedetomidine were observed.

**Concentration-response study**

According to the results of a pilot study, the concentrations used to evaluate the concentration-response curve by probit analysis were: $1.0 \times 10^{-4}$ M, $3.0 \times 10^{-4}$ M, $6.0 \times 10^{-4}$ M, $9.0 \times 10^{-4}$ M, and $1.2 \times 10^{-3}$ M. In the pilot study, varying concentrations of dexmedetomidine were added accumulatively to the organ bath every 20 min and changes in contractions of the myometrial strip were observed (n = 8).

**Statistical analysis**

The data are expressed as mean ± standard deviation. The effects of dexmedetomidine at each concentration were compared to the control data, and changes in active tension and number of contractions were described as a percentage. Shapiro-Wilk tests were used to analyze the normality of distribution of the data, and one-way analysis of variance or the Kruskal–Wallis test using SPSS (Windows ver. 21.0, IBM Co., USA) were performed for comparisons with the control. A post-hoc test was followed by Mann–Whitney U test with Scheffes’s method. A P value of less than 0.05 was considered statistically significant. Probit analysis was performed to analyze the effective concentration (EC) of dexmedetomidine on the changes in active tension and the number of contractions of the myometrial strips [15]. The calculated EC data are described as concentrations and 95% confidence intervals (CI) according to the percentage of change as EC$_5$, EC$_{25}$, EC$_{50}$, EC$_{75}$, and EC$_{95}$.

**RESULTS**

**Pilot study**

No significant effect on myometrial contractions was induced by oxytocin in dexmedetomidine concentrations from $10^{-6}$ to $10^{-5}$ M (Fig. 1). However, higher concentrations of dexmedetomidine decreased the active tension and number of contractions. The active tension and number of contractions were compared to the control data, and changes in active tension and number of contractions were described as a percentage. Shapiro-Wilk tests were used to analyze the normality of distribution of the data, and one-way analysis of variance or the Kruskal–Wallis test using SPSS (Windows ver. 21.0, IBM Co., USA) were performed for comparisons with the control. A post-hoc test was followed by Mann–Whitney U test with Scheffes’s method. A P value of less than 0.05 was considered statistically significant. Probit analysis was performed to analyze the effective concentration (EC) of dexmedetomidine on the changes in active tension and the number of contractions of the myometrial strips [15]. The calculated EC data are described as concentrations and 95% confidence intervals (CI) according to the percentage of change as EC$_5$, EC$_{25}$, EC$_{50}$, EC$_{75}$, and EC$_{95}$.

**Fig. 1.** A pilot study on the changes in myometrial contractions caused by dexmedetomidine. There was no significant effect of dexmedetomidine concentrations from $10^{-6}$ to $10^{-5}$ M on myometrial contractions. Active tension and the number of contractions were significantly decreased by dexmedetomidine concentrations of $10^{-3}$ M and $10^{-4}$ M, respectively. Both active tension and the number of contractions disappeared at $10^{-3}$ M. The box plot represents active tension. Data are expressed as median (1Q, 3Q). The black dots represent the number of contractions. Data are expressed as mean. *p < 0.05 compared to the control active tension. †p < 0.05 compared to the control number of contractions.
contractions were significantly decreased from dexmedetomidine concentrations of 10⁻³ M and 10⁻⁴ M, respectively (P < 0.05). Complete relaxation and a loss of myometrial strip contractions were found at 10⁻² M dexmedetomidine.

**Concentration-response study**

As the concentration of the dexmedetomidine increased (1.0 × 10⁻⁴ to 1.2 × 10⁻³ M), the active tension and number of contractions decreased in a concentration-dependent manner (Table 1). Both active tension and the number of contractions were significantly decreased by 1.0 × 10⁻¹ M dexmedetomidine (P < 0.05).

The EC₉₀ and EC₉₅ of dexmedetomidine to inhibit the active tension of the myometrial strip were 4.88 × 10⁻⁵ M (95% CI [2.29 × 10⁻⁵ M, 1.39 × 10⁻⁴ M]) and 5.16 × 10⁻² M (95% CI [5.67 × 10⁻³ M, 5.28 × 10⁻⁰ M]), respectively (Table 2, Fig. 2). The EC₉₀ and EC₉₅ of dexmedetomidine to inhibit the number of myometrial strip contractions were 2.55 × 10⁻³ M (95% CI [1.41 × 10⁻³ M, 5.04 × 10⁻³ M]) and 2.08 × 10⁻² M (95% CI [3.76 × 10⁻² M, 4.45 × 10⁻¹ M]), respectively (Table 2, Fig. 3).

**DISCUSSION**

Dexmedetomidine is a unique drug that regulates the release of neurotransmitters with highly selective α₂ AR agonism. The α AR is located at both presynaptic and postsynaptic sites [16], but clinical interest in dexmedetomidine is focused on the presynaptic α₂ AR, which controls the release of adenosine triphosphate (ATP) and norepinephrine by negative feedback [17]. The effects of dexmedetomidine via α₂ AR are mediated by a second messenger system or ion channel through guanine-nucleotide regulatory binding protein activation [17].

Previously, the stimulation of α₂ AR was shown to cause increases in the contractile force of the myometrium via the influx of extracellular Ca²⁺ through the G protein signal transduction pathway. Kitazawa et al. [18] reported that clonidine increased the contractile force of porcine myometrium by increasing intracellular Ca²⁺ without changing 3,5-cyclic adenosine monophosphate (cAMP) levels. However, there is a possibility that α₂ stimulation by dexmedetomidine may increase uterine contractility by reducing cAMP formation by inhibiting adenylate cyclase [17]. In contrast, there is also a possibility that dexmedetomi- dine-induced α₂ stimulation may decrease uterine contractility by reducing the ATP, norepinephrine, and intracellular conductance of calcium by negative feedback [17,19]. Thus, we aimed to evaluate the effects of dexmedetomidine on the contractility of rat myometrium.

In the current study, we first conducted a pilot study to investigate differences in the contractile profile of the myometrium according to dexmedetomidine concentrations and determine the concentrations for the probit analysis, in which the concentration-response of dexmedetomidine on pregnant myometrial strips was evaluated. The results

**Table 1.** Effects of Dexmedetomidine on Active Tension and the Number of Contractions in the Uterine Smooth Muscle of Pregnant Rats

<table>
<thead>
<tr>
<th>Concentration (M)</th>
<th>Active tension (g)</th>
<th>Inhibition (%) of active tension</th>
<th>P value</th>
<th>Number of contractions (n)</th>
<th>Inhibition (%) of number of contractions</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>3.74 ± 0.22</td>
<td>-</td>
<td>-</td>
<td>33.70 ± 2.50</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1.0 × 10⁻⁴</td>
<td>3.45 ± 0.14</td>
<td>7.36 ± 6.65</td>
<td>0.003</td>
<td>28.30 ± 2.31</td>
<td>15.68 ± 8.51</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>3.0 × 10⁻⁴</td>
<td>3.10 ± 0.08</td>
<td>16.75 ± 6.15</td>
<td>&lt; 0.001</td>
<td>22.70 ± 1.83</td>
<td>32.25 ± 8.47</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>6.0 × 10⁻⁴</td>
<td>2.85 ± 0.27</td>
<td>23.38 ± 11.26</td>
<td>&lt; 0.001</td>
<td>21.80 ± 1.87</td>
<td>34.91 ± 8.16</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>9.0 × 10⁻⁴</td>
<td>1.16 ± 0.18</td>
<td>68.39 ± 4.07</td>
<td>&lt; 0.001</td>
<td>14.30 ± 1.64</td>
<td>57.47 ± 5.47</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>1.2 × 10⁻³</td>
<td>0.89 ± 0.29</td>
<td>75.97 ± 7.80</td>
<td>&lt; 0.001</td>
<td>3.90 ± 1.20</td>
<td>88.39 ± 3.74</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

The data are expressed as mean ± SD. P values are compared to the control, n = 8.

**Table 2.** Estimated Effective Concentrations (M) of Dexmedetomidine to Inhibit Active Tension and the Number of Contractions in the Uterine Smooth Muscle of Pregnant Rats

<table>
<thead>
<tr>
<th>Myometrial contractions</th>
<th>EC₉₀</th>
<th>EC₉₅</th>
<th>EC₅₀</th>
<th>EC₅₅</th>
<th>EC₂₀</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active tension (g)</td>
<td>(4.63 × 10⁻⁴)</td>
<td>(2.81 × 10⁻⁶)</td>
<td>(4.88 × 10⁻⁵)</td>
<td>(8.49 × 10⁻⁴)</td>
<td>(5.16 × 10⁻²)</td>
</tr>
<tr>
<td>Number of contractions (n)</td>
<td>(2.16 × 10⁻⁶, 1.40 × 10⁻⁴)</td>
<td>(1.60 × 10⁻⁵, 3.42 × 10⁻⁴)</td>
<td>(1.41 × 10⁻⁵, 5.04 × 10⁻⁴)</td>
<td>(1.62 × 10⁻⁴, 1.80 × 10⁻³)</td>
<td>(3.76 × 10⁻⁴, 4.45 × 10⁻²)</td>
</tr>
</tbody>
</table>

The data are expressed as estimated value (95% confidence interval), EC: effective concentration of % inhibition. n = 8.
Fig. 2. Probability of inhibiting active tension of the myometrium of a pregnant rat according to the concentration of dexmedetomidine (M). The horizontal bars represent the concentration of dexmedetomidine calculated to inhibit the active tension of myometrial strips with 50% and 95% probabilities (EC$_{50}$ and EC$_{95}$), respectively, and a 95% confidence interval. EC: effective concentration.

Fig. 3. Probability of inhibiting the number of myometrial contractions of a pregnant rat according to the concentration of dexmedetomidine (M). The horizontal bars represent the concentration of dexmedetomidine calculated to inhibit the number of myometrial strip contractions with 50% and 95% probabilities (EC$_{50}$ and EC$_{95}$), respectively, and a 95% confidence interval. EC: effective concentration.
of the pilot study showed that the contractile profile of myometrium induced by oxytocin did not change significantly at dexmedetomidine concentrations from $10^{-6}$ to $10^{-5}$ M. A significant decrease was seen in active tension at $10^{-3}$ M and the number of contractions at $10^{-4}$ M. Interestingly, a complete loss of contractions was found at $10^{-2}$ M. These results suggest that the $\alpha_2$ AR of the myometrium may display biphasic effects according to the concentration of dexmedetomidine.

According to previous studies, dexmedetomidine increased the contractility of rat myometrium at concentrations of $10^{-9}$ M to $10^{-5}$ M [7], and in a human myometrial strip at clinical plasma concentrations of $10^{-9}$ g/ml, which were calculated as $2.53 \times 10^{-5}$ M in vitro [8]. Our results, which showed no significant changes in contractions at concentrations of $10^{-4}$ to $10^{-3}$ M, were inconsistent with the results of the previous studies. Previous studies differed from the current study in that they did not use oxytocin to stimulate the myometrium. Myometrial contractions are regulated by depolarization triggered by intracellular Ca$^{2+}$ influx and calcium plays a key role in this mechanism [20]. Ocal et al. [9] reported that dexmedetomidine increased spontaneous contraction forces in a dose-dependent manner, but there was no change in late-term pregnancy rats when Ca$^{2+}$-free solution was used. Oxytocin increases intracellular Ca$^{2+}$ influx, which is a major mechanism of uterine contractions [20]. After labor, increased oxytocin stimulates uterine contractions, and we used oxytocin to create a similar biological environment [21]. Without oxytocin, the baseline contractility is decreased compared to when oxytocin is used, and this could be the reason for the discrepant results. Moreover, we evaluated changes in uterine contractility at higher concentrations of dexmedetomidine. The maximal concentrations of dexmedetomidine in previous studies were $10^{-5}$ M [7] and $10^{-4}$ M [9]. However, we found a significant decrease in active tension at $10^{-4}$ M dexmedetomidine. Specifically, both the contractile force and the number of contractions disappeared at $10^{-2}$ M dexmedetomidine. These results suggest that an occupation of the $\alpha_2$ AR of the myometrium above a certain level may relax the uterus.

Several hypotheses could explain how dexmedetomidine decreases myometrial contractility. First, the excessive stimulation of $\alpha_2$ AR may produce uterine relaxation by inhibiting $\alpha_2$ ARs. Kyozuka et al. [22] found that postsynaptic $\alpha_2$ AR may exist on the plasma membrane of rat myometrial smooth muscles and has no contractile function. However, they suggested that occupancy by a selective $\alpha_2$ agonist could competitively interact by occupying sites of the $\alpha_2$ AR with contractile functions. Second, dexmedetomidine may produce uterine relaxation because of its higher affinity for $\alpha_{2A}$ and $\alpha_{2C}$ AR subtypes [23]. In pregnant rats, $\alpha_{2A}$ and $\alpha_{2C}$ AR decrease myometrial contractions, whereas $\alpha_{2B}$ AR increases them [24]. Moreover, the expression of $\alpha_2$ AR subtypes is related to gestational hormones and affected by the levels of progesterone. In the non-pregnant uterus, an $\alpha_2$ AR agonist did not cause myometrial contractions [24]. Haja-gos-Toth et al. [25] suggested the use of $\alpha_{2C}$ agonists and $\alpha_{2B}$ antagonists with progesterone for reducing uterine contraction in the treatment of preterm labor. These results indicate that dexmedetomidine may produce uterine relaxation by the stimulation of $\alpha_{2A}$ and $\alpha_{2C}$ AR subtypes.

In the current study, we also compare the calculated concentration from the in vitro study with the clinical concentration of dexmedetomidine for the sedation. According to clinical research on the pharmacokinetics and pharmacodynamics of dexmedetomidine, dexmedetomidine showed a significant sedative effect when the plasma concentrations were maintained between 0.2 and 0.3 ng/ml [10]. This plasma concentration was about $8.45 \times 10^{-1}$ M to $1.27 \times 10^{-2}$ M, given that the molecular weight of the dexmedetomidine is 236.74 g/mol. The effective concentrations are $5.07 \times 10^{-2}$ M to $7.69 \times 10^{-2}$ M in vitro because the protein binding of dexmedetomidine is 94% [10]. These concentrations are similar to the EC$_{50}$ of dexmedetomidine to inhibit active tension ($5.16 \times 10^{-3}$ M) and the number of myometrial contractions ($2.08 \times 10^{-2}$ M) in the current study. Thus, there is a possibility that uterine contractility might be decreased when dexmedetomidine is used for sedation in pregnant women, which may cause problems after delivery. However, we cannot be sure whether those hypotheses can be applied to clinical situations because there are significant differences between species.

There were several limitations to our study. We did not evaluate the responses after the simultaneous stimulation or inhibition of adrenergic receptors. It is possible that interactions between the receptors could regulate uterine contractions. Also, there would be interactions and feedback mechanisms between $\alpha$ AR and other physiologic receptors. The results of the current study were not validated in humans. Thus, a well-designed clinical study is needed for the safe use of dexmedetomidine in pregnant women.

In conclusion, active tension of the myometrium did not change at concentrations of dexmedetomidine less than
10^{-4} M but showed a significant decrease at concentrations higher than 10^{-3} M. The EC_{95} of dexmedetomidine to inhibit active tension and the number of contractions was 4.88 \times 10^{-5} M and 2.55 \times 10^{-5} M, respectively. The use of dexmedetomidine at clinical concentrations in pregnant women has the potential to relax uterine muscles, so further research is needed for the safe use of dexmedetomidine in the obstetrics field.

ACKNOWLEDGEMENTS

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CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

Conceptualization: Ki Tae Jung. Experiment conduction: Young Joon Ki, Bo Hyun Jang, Seongcheol Kim, Ki Tae Jung. Data acquisition: Dong Joon Kim, Ki Tae Jung. Formal analysis: Sang Hun Kim, Ki Tae Jung. Funding: Ki Tae Jung. Supervision: Ki Tae Jung. Writing—original draft: Dong Joon Kim, Ki Tae Jung. Writing—review & editing: Sang Hun Kim, Ki Tae Jung.

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Comparing hemostatic resuscitation management of intraoperative massive bleeding with traumatic massive bleeding: a computer simulation

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Background: Appropriate blood component transfusion might differ between intraoperative massive bleeding and traumatic massive bleeding in the emergency department because trauma patients initially bleed undiluted blood and replacement typically lags behind blood loss. We compared these two blood loss scenarios, intraoperative and traumatic, using a computer simulation.

Methods: We modified the multi-compartment dynamic model developed by Hirshberg and implemented it using STELLA 9.0. In this model, blood pressure changes as blood volume fluctuates as bleeding rate and transcapillary refill rate are controlled by blood pressure. Using this simulation, we compared the intraoperative bleeding scenario with the traumatic bleeding scenario. In both scenarios, patients started to bleed at a rate of 50 ml/min. In the intraoperative bleeding scenario, fluid was administered to maintain isovolemic status; however, in the traumatic bleeding scenario, no fluid was supplied for up to 30 min and no blood was supplied for up to 50 min. Each unit of packed red blood cells (PRBC) was given when the hematocrit decreased to 27%, fresh frozen plasma (FFP) was transfused when plasma was diluted to 30%, and platelet concentrate (PC) was transfused when platelet count became 50,000/ml.

Results: In both scenarios, the appropriate ratio of PRBC:FFP was 1:0.47 before PC transfusion, and the ratio of PRBC:FFP:platelets was 1:0.35:0.39 after initiation of PC transfusion.

Conclusion: The ratio of transfused blood component did not differ between the intraoperative bleeding and traumatic bleeding scenarios.

Keywords: Blood coagulation disorder; Blood component transfusion; Computer simulation; Hemorrhage.
and acidosis [2–4]. Coagulopathy-related diffuse bleeding is difficult to manage. The causes of coagulopathy are multifactorial and interrelated, including consumption and dilution of coagulation factors and platelets, dysfunction of platelets and the coagulation system, increased fibrinolysis, compromise of coagulation by the infusion of colloids, hypocalcemia, and disseminated intravascular coagulation-like syndrome [5–7].

Although the extreme circumstances of massive hemorrhage do not allow prospective controlled trials, computer modeling offers an interesting alternative. A computer simulation can capture the interactions between bleeding, hemodynamics, hemodilution, and replacement as they unfold during severe hemorrhage. Various replacement options can then be applied to the model to evaluate effectiveness in preventing or correcting dilutional coagulopathy [8].

In this study, we focused on dilutional coagulopathy in both intraoperative bleeding and traumatic bleeding scenarios. Prior to the era of blood component transfusion, the transfusion of large volumes of stored blank blood did not result in hemorrhagic diathesis in young and previously healthy soldiers wounded during the Vietnam war [9]. However, recent resuscitation with crystalloids, colloids, and/or packed red blood cells (PRBCs) can result in dilutional coagulopathy. Because trauma patients bleed undiluted blood initially and replacement typically lags behind blood loss, it was hypothesized that there would be differences between patients who bleed during surgery and patients who receive emergent resuscitation after a period of traumatic massive bleeding. Furthermore, in trauma patients, shock, tissue hypoxia, acidosis, and hypothermia can aggravate bleeding tendency.

To date, no consensus has been reached regarding what, when, how much fluid, and what blood component should be given during massive transfusion [10]. Appropriate blood component therapy during hemostatic resuscitation might be different between intraoperative bleeding and traumatic bleeding. We therefore compared when and how much of each blood component should be given in both of these scenarios using computer simulation.

**MATERIALS AND METHODS**

We modified the multi-compartment dynamic model developed by Hirshberg [8] and implemented it using a graphical modeling tool STELLA 9.0 (High Performance Systems, USA). In this model, blood pressure changed as blood volume fluctuated, and bleeding rate and transcapillary refill rate were controlled by blood pressure. With ongoing bleeding and transfusion, hematocrit and dilution of clotting factors and platelets were calculated.

Blood volume consists of three compartments: red cells, plasma, and virtual intravascular water. Intravascular water accepts crystalloid infusion and exchanges free water with interstitial spaces (Fig. 1). Equations for the fraction of infused crystalloids that is retained in circulation during massive hemorrhage [11], transcapillary refill rate [12–14], and the pressure-volume relationship of circulation [12,15] are the same as in the Hirshberg model. Fibrinogen dilution was assumed to be directly proportional to hemodilution [7,9]. Correcting function was used in calculating platelet level [8]. The entire set of model equations is given in the Supplementary Materials.

**Blood components**

Information on blood components was obtained from the Korea Center for Disease Control and Prevention 2013 transfusion guidelines (Table 1). The average volume of PRBCs derived from 400 ml of whole blood was 243.12 ±

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**Table 1.** Blood Compartment Information in the Transfusion Guidelines, Korea Center for Disease Control and Prevention, 2013

<table>
<thead>
<tr>
<th>Blood Component</th>
<th>FFP</th>
<th>Platelets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume (ml)</td>
<td>243.12 ± 13.48</td>
<td>155.03 ± 12.11</td>
</tr>
<tr>
<td>Hematocrit (%)</td>
<td>70.31 ± 4.16</td>
<td>66.7 ± 11.7</td>
</tr>
<tr>
<td>Count (× 10^6/unit)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. PRBC: packed red blood cells, FFP: fresh frozen plasma.
Hematocrit was 70.31% on average. As a result, red blood cell volume was at an average of 170 ml. We assumed all PRBCs were derived from 400 ml of whole blood for convenience. In the manufacturing blood compartment, 56 ml of citrate-phosphate-dextrose with adenine (CPDA-1) solution was added. Plasma volume in PRBCs was 243 - 170 = 73 ml, which includes some amount of CPDA-1 solution. Total plasma volume in whole blood including CPDA-1 solution was 73 + 155 + 51 = 279 ml. Volume of CPDA-1 solution in PRBCs was 73 × 56 / 279 = 15 ml. Calculated real plasma volume contained in PRBCs was 73 - 15 = 58 ml, which excluded the volume of CPDA-1 solution.

The average volume of plasma derived from 400 ml whole blood was 155.03 ± 12.11 ml. Except for the volume of CPDA-1 solution, each fresh frozen plasma (FFP) was assumed to contain 124 ml of plasma. The average volume of platelet concentrate (PC) derived from 400 ml whole blood was 50.85 ± 1.90 ml. Except for the volume of CPDA-1 solution, each unit of PC contained 41 ml of plasma and 6.67 × 10^10 platelets on average, of which one third underwent splenic sequestration when transfused [16].

**The reference scenario**

We generated an intraoperative bleeding scenario and a trauma bleeding scenario. Both scenarios included a 70 kg person whose blood volume, hematocrit, fibrinogen concentration, and platelets of 4.9 L, 42%, 3 g/L, and 230,000/ml was assumed, respectively. In both scenarios, patients started to bleed at a rate of 50 ml/min.

The intraoperative bleeding scenario was based on a washout equation by designing the normovolemic status to be maintained by administering fluid. As bleeding continued, the blood pressure was assumed to be unchanged. If hematocrit decreased to 27%, one unit of PRBCs was given for 10 min. FFP was transfused for 10 min when plasma was diluted to 30% of the original plasma. Each unit of PC was transfused for 5 min when platelet count became 50,000/ml. FFP and PC starting time followed the practice guidelines for perioperative blood transfusion and adjuvant therapies [17].

In the traumatic bleeding scenario, the patient was set to bleed for 30 min without fluid supply until arrival at the emergency room (ER). The traumatic bleeding scenario was not only based on a washout equation, but also adopted a pressure-volume relationship concept. Using the pressure-volume equation, the amount of bleeding per minute reduced as blood pressure decreased due to a loss of blood. From arrival in the ER, crystalloid was administered via an intravenous line at the rate of 300 ml/min until the patient recovered to isovolemic status. After 50 min of trauma, blood components were prepared and each unit of PRBCs was given when hematocrit decreased to 27%. FFP was transfused when plasma was diluted to 30%, and PC was transfused when platelet count became 50,000/ml. The infusion of each blood component was same as in the intraoperative bleeding scenario.

**RESULTS**

In the intraoperative bleeding scenario (Fig. 2), bleeding during operation began at time 0 and PRBC administration started at 43 min when the bleeding volume was 0.44 times total blood volume (Table 2). In the traumatic bleeding scenario (Fig. 3), the patient lost 1,175 ml of blood volume and transcapillary refill volume was 449 ml until arrival in the ER when the systolic blood pressure was 84 mmHg. PRBC administration was started at 52 min when bleeding volume was 0.42 times total blood volume. In the intraoperative bleeding scenario, FFP administration started at 164 min when bleeding volume was 1.67 times the total blood volume. In the traumatic bleeding scenario, FFP administration started at 170 min when bleeding volume was 1.67 times the total blood volume. In the intraoperative bleeding scenario, FFP administration started at 164 min when bleeding volume was 1.67 times the total blood volume. In the traumatic bleeding scenario, FFP administration started at 170 min when bleeding volume was 1.63 times the total blood volume. During FFP transfusion, the appropriate PRBC:FFP ratio was 1:0.47 in both scenarios.

PC administration was started at 219 min when bleeding volume was 2.24 times the total blood volume in the intraoperative bleeding scenario and at 225 min when bleeding volume was 2.20 times the total blood volume in the traumatic bleeding scenario. After the start of PC transfusion, the appropriate PRBC:FFP:PC ratio was 1:0.35:0.39 in both scenarios.

**DISCUSSION**

Computer simulations regarding dilutional coagulopathy have been previously studied [8,9,16]. Here, we designed two separate scenarios and compared them. In the traumatic bleeding scenario, the amount of bleeding per minute reduced due to decreased blood pressure compared to intraoperative scenario; as a consequence, the onset of dilutional coagulopathy was delayed. Similar results have been
shown by Hirshberg et al. [8,18].

The key Hirshberg model equations and parameters were not complete as is, and did not work when entered into the STELLA program. Therefore, we modified some parts of the equation to implement the model and attempt to reproduce the results of the Hirshberg study. As such, our results have some differences when compared with Hirshberg, which suggest two options for giving FFP before the prothrombin time (PT) crossover time. PT crossover time means the point during a simulation when a clotting test first crosses its respective threshold. In other words, the time when the plasma fraction goes below 30% of the original plasma fraction. The first option is to use an aggressive lower PRBC/FFP replacement ratio such as 3:2 and the second option is to give two units of FFP concurrently with the first units of PRBCs at the beginning of the operation. This suggestion by Hirshberg et al. [8,18] is a much lower PRBC/FFP ratio than the 5:2 to 5:3 ratio used in many massive transfusion protocols and also much lower than our simulation results of 1:0.47 = 5:2.35 ratio

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**Table 2. The Outcome of Two Scenarios**

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Intraoperative bleeding scenario</th>
<th>Traumatic bleeding scenario</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRBC:FFP</td>
<td>10.47</td>
<td>10.47</td>
</tr>
<tr>
<td>PRBC:FFP:PC</td>
<td>10.35:0.39</td>
<td>10.35:0.39</td>
</tr>
<tr>
<td>Time of PRBC administration after initiation of bleeding (min)</td>
<td>43</td>
<td>52</td>
</tr>
<tr>
<td>Time of FFP administration after initiation of bleeding (min)</td>
<td>164</td>
<td>170</td>
</tr>
<tr>
<td>Time of PC administration after initiation of bleeding (min)</td>
<td>219</td>
<td>225</td>
</tr>
<tr>
<td>Bleeding fraction at initiation of PRBC transfusion</td>
<td>0.44</td>
<td>0.42</td>
</tr>
<tr>
<td>Bleeding fraction at initiation of FFP transfusion</td>
<td>1.67</td>
<td>1.63</td>
</tr>
<tr>
<td>Bleeding fraction at initiation of PC transfusion</td>
<td>2.24</td>
<td>2.2</td>
</tr>
</tbody>
</table>

In the Hirschberg model, patient initial bleeding rate was 135 ml/min with 3,297 ml lost and 67% of the estimated blood volume at the beginning of the operation. However, in our traumatic bleeding scenario, initial bleeding rate was 50 ml/min with 1,175 ml lost and 41% of the estimated blood volume, and FFP transfusion was started during the 11th PRBC transfusion. We think the reason why this difference occurred was because the increased massive bleeding without hemodilution incurred a greater loss of clotting factor. Comparing our intraoperative bleeding scenario (FFP transfusion started at 1.67 blood volume loss) with the trauma scenario (FFP transfusion started at 1.63 blood volume loss), dilutional coagulopathy began at less blood loss. Early FFP transfusion in the Hirshberg model could be due to early massive blood loss in that scenario [8].

Hirshberg ignored plasma contained in PRBCs and PC. PRBCs contain a small amount of plasma (30–60 ml) as does PC (approximately 80 ml) [20]. In our model, we assumed PRBCs contain 58 ml of plasma and PC contains 41 ml of plasma, both without CPDA-1 solution, by using information of the blood compartment obtained in the 2013 transfusion guidelines. These are not negligible volumes compared with 124 ml of plasma contained in FFP without CPDA-1 solution. If plasma contained PRBCs and PC is not considered, the calculated PRBC/FFP ratio will decrease. Therefore, the Hirshberg 3:2 PRBC/FFP ratio could be underestimated.

The Pragmatic, Randomized Optimal Platelet and Plasma Ratios trial was designed to address the effectiveness and safety of transfusing PRBC, FFP, PLT in a 1:1:1 ratio compared with a 2:1:1 ratio in patients with trauma who were predicted to receive a massive transfusion. Among patients with severe trauma and major bleeding, early administration of PRBC, FFP, PLT in a 1:1:1 ratio compared with a 2:1:1 ratio did not result in significant differences in mortality at 24 h or 30 days. However, more patients in the 1:1:1 group achieved hemostasis and fewer experienced death due to exsanguination by 24 h. Even though there was an increased use of FFP and PLT transfused in the 1:1:1
group, no other safety differences were identified between the two groups [21]. Conversely, other studies have reported beneficial outcomes across a wider range of blood product ratios or goal-directed approaches [22,23].

Our simulation shows a 1:0.47 ratio for PRBC:FFP and a 1:0.35:0.39 ratio for PRBC:FFP:PC, if dilutional coagulopathy is assumed to occur when plasma dilution is < 30%, fibrinogen is < 0.8 g/L, and platelets are < 50,000/ml. Interpreting this result requires circumspection; however, patients generally have a wide range of coagulation problems such as dysfunction of platelets and the coagulation system, increased fibrinolysis, compromise of coagulation by the infusion of colloids, hypocalcemia, disseminated intravascular coagulation-like syndrome, acidosis, hyperthermia, and the destruction of clotting factor in stored FFP [24,25]. In the massive transfusion scenario, avoiding the above listed problems is not easy and computer simulations will not perfectly imitate the conditions of the real body. So, our results can be used only as reference and not indication. Careful observation of operation in the field, communication with surgeons, and repetitive coagulation tests are the most important variables in preventing coagulopathy.

The results of this simulation show that coagulopathy can occur at less blood loss due to the loss of undiluted blood if fluids are not infused after the start of bleeding. In addition, it must be noted that the coagulopathy and transfusion start times were delayed because low blood pressure reduces hemorrhage. Restricting fluid infusion seems to delay dilutional coagulopathy but it can generate circulatory problems and can bring about more disastrous consequences to the patient. Therefore, restricting fluid technique to delay reduction of hemorrhage and dilutional coagulopathy must be done cautiously. In addition, the difference in the time when coagulopathy occurred between the two scenarios was negligible in our study. More than likely, the amount of hemorrhage (about 20% of total blood volume) was too small to make a difference and transcapillary refill could have attributed to make the difference even less negligible.

Massive transfusion protocols are widely various among hospitals, with replacement ratios ranging between 10:1 and 5:3 for PRBC:FFP and between 10:6 and 10:12 for PRBC:PLT [26,27]. Clinical suitability and justification of the various massive transfusion practices in trauma or operations is clearly required. Due to the limitations of computer modeling when compared with a biologic system or clinical trial data, our findings surely need validation and further assessment. However, computer simulation models can uncover new predictions and generate data that can be used in place of harmful clinical trials that would be against medical ethics; as such, increased need for computer simulations in clinical experiments is apparent.

In conclusion, according to computer simulation, the appropriate blood component ratio might be a 1:0.47 ratio for PRBC:FFP and a 1:0.35:0.39 ratio for PRBC:FFP:PC, which did not differ between the intraoperative bleeding and traumatic bleeding scenarios.

SUPPLEMENTARY MATERIALS

Supplementary data including key model equations and parameters can be found online at https://doi.org/10.17085/apm.20042.

CONFLICTS OF INTEREST

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

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REFERENCES

Management of massive bleeding

95.


Liver transplantation in an adult patient with hepatocellular carcinoma following liver cirrhosis as a complication of the Fontan procedure -A case report-

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Background: Fontan-associated liver disease (FALD) is a hepatic disorder caused by hemodynamic changes and systemic venous congestion following the Fontan procedure. FALD includes liver cirrhosis and hepatocellular carcinoma (HCC), both of which may require liver transplantation (LT). However, the Fontan circulation, characterized by elevated central venous pressure and reduced cardiac output, is a challenging issue for surgeons and anesthesiologists.

Case: We report a living-donor LT for the treatment of HCC. The patient was a 24-year-old male who underwent the Fontan procedure for pulmonary atresia and right ventricle hypoplasia. We focused on maintaining enough blood volume for cardiac output without causing pulmonary edema, as the patient is not well adapted to changes in volume. Owing to a multidisciplinary approach, the surgery was successfully performed without fatal adverse events.

Conclusions: To our knowledge, this is the first case of isolated LT in a recipient who became an adult after having undergone the Fontan procedure.

Keywords: Fontan procedure; Hepatocellular carcinoma; Liver cirrhosis; Liver transplantation.
The etiology of FALD is a complex one, including both chronic congestive venous overflow and systemic hypoxia secondary to left ventricular dysfunction and diffuse pulmonary veno-venous shunts [5]. In patients with end-stage liver disease, the use of liver transplantation in the treatment of both HCC and LC has been well established. However, the Fontan circulation, characterized by elevated central venous pressure (CVP) and reduced cardiac output, is a challenging issue for both transplant surgeons and anesthesiologists. Moreover, as patients treated with the Fontan procedure represent a growing population that can survive well into adulthood, and the incidence of both LC and HCC increases with the duration of the Fontan circulation, the number of patients who need liver transplantation due to FALD will most likely continue to increase [1,2]. Therefore, it is important to understand the physiology of patients with FALD to determine the appropriate intraoperative management.

The first case series to discuss the development of HCC after the Fontan procedure was published in 2013. To the best of our knowledge, only 18 cases have been reported in the literature, with just a few patients for whom curative treatment with modalities such as hepatectomy was suitable [1]. Herein, we report a case of successful isolated living-donor liver transplantation for the treatment of HCC in a 24-year-old male patient who survived after a Fontan procedure for pulmonary atresia and severe right ventricular hypoplasia. Written informed consent was obtained from the patient for publication of this case report.

**CASE REPORT**

**Patient history**

The patient was prenatally diagnosed with both pulmonary atresia with an intact ventricular septum and severe right ventricular hypoplasia. He showed cyanosis due to congenital heart disease immediately after birth. At the time of birth, his oxygen saturation level was 75–80%, requiring oxygen supply. Prostaglandin was continuously administered for patent ductus arteriosus. On the fifth day after birth, right-modified Blalock-Taussig shunt and right ventricular outflow tract widening were performed simultaneously to enhance pulmonary flow. When he was 6 months old, bidirectional cavo-pulmonary shunt and right pulmonary artery angioplasty were performed as a bridging therapy for congenital heart disease. One year after his most recent surgery, he underwent a Fontan operation with adjustable fenestration (Fig. 1). After the Fontan procedure, his oxygen saturation level improved to 90–95% without oxygen supply, and he lived without inconvenience in his daily life for 17 years. However, when he was 18 years old, dyspnea developed during exercise. Significant narrowing and diffuse hypoplasia were identified in the left pulmonary artery, for which a stent was inserted. During the workup, liver magnetic resonance imaging showed multiple HCCs in S3 and S7. Transcatheter arterial chemoembolization and radiation therapy for HCC were performed for 1 month with the expectation of cancer down-staging. For curative therapy, he was placed on the waiting list for liver transplantation.

When he was 24 years old, living-donor liver transplantation was planned. During the preoperative workup, his oxygen saturation was 80–85% on room air; however, after administering 3 L/min of oxygen via nasal cannula, oxygen saturation was maintained at 87–92%. A laboratory evaluation revealed the following results: a hemoglobin concentration of 20.2 g/dl, platelet count of 133 K/µl, creatinine level of 0.7 mg/dl, bilirubin level of 3.2 mg/dl, international normalized ratio level of 1.12, and sodium concentration of 139 mmol/L. Left ventricle (LV) cavity size, LV function, and conduit function were all normal upon preoperative examination using echocardiography. Flow in the left pulmonary arterial stent was sluggish, and fenestration flow was patent, with a peak velocity of 1.0 m/sec in the former.

![Fig. 1. Patient’s cardiac anomaly status after the Fontan operation.](www.anesth-pain-med.org)
Since the baffle between the inferior vena cava and the pulmonary artery had a small leakage, a right-to-left shunt was observed in the patient. The ejection fraction was 74%, and regional wall motion abnormality was not observed.

**Operative procedure and management**

The donor was a 55-year-old female (weight, 75.6 kg; height, 173 cm; body mass index, 25 kg/m²) and the patient’s mother. She was not found to have any comorbidities. The height and weight of the recipient were 158.7 cm and 49.6 kg, respectively. Computed tomography volumetric analysis of the donor’s liver showed an adequate right liver volume, and the calculated graft-to-recipient weight ratio was 0.87. She was deemed to be a suitable single donor. Preoperatively, an 11.5 Fr I-J catheter was inserted into the right internal jugular vein by a radiologist. The distal tip of the catheter was positioned on the superior vena cava. An air filter was applied to his intravenous line to prevent the entrance of air via the right-left shunt. Before induction, nasogastric tube insertion was attempted for esophageal varix; however, the patient did not cooperate owing to discomfort. His oxygen saturation before induction was 88% on room air. After pre-oxygenation with 100% oxygen via a facial mask, general anesthesia was induced with etomidate (14 mg), midazolam (2 mg), and rocuronium (80 mg). Before the application of the surgical retractor, anesthesia was maintained with sevoflurane and 50–100% oxygen (88% on room air). After pre-oxygenation with 100% oxygen, general anesthesia was induced with sevoflurane and remifentanil, and cisatracurium. The initial CVP was 15 mmHg and was maintained between 10 and 25 mmHg. CVP was monitored via a central venous catheter inserted into the internal jugular vein. The EV1000 clinical platform (Edwards Lifesciences, USA) was used to monitor hemodynamic parameters, such as CO, SV, systemic vascular resistance, and stroke volume variation (SVV). Pulse pressure variation (PPV) was monitored via femoral arterial cannulation. CVP, SVV, and PPV were used to ensure an adequate volume status. Cardiac output was maintained between 6 and 10 L/min, and oxygen saturation was maintained between 88% and 98% (Table 1). The target SpO₂ was above 90% at a FiO₂ of 0.5. Isoflurane was maintained between 1 and 1.5 MAC.

After his liver was explanted, a porto-caval shunt was performed. The mean hepatic duration was 125 min. After portal vein anastomosis, the graft was reperfused by consecutively unclamping the hepatic and portal veins. Hypotension was observed in the patient, whose mean arterial blood pressure was 50 mmHg. As treatment for hypotension, 0.1 μg/kg/min of norepinephrine was continuously infused. Hepatic artery anastomosis was performed after reperfusion, after which biliary anastomosis was performed and a porto-caval shunt was ligated. The patient was transferred to the surgical intensive care unit (ICU) and administered 0.1 μg/kg/min of norepinephrine. The transfer was uneventful.

The total operating time was 516 min. The cold and

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**Table 1. Hemodynamic Changes & Oxygenation Status During Liver Transplantation**

<table>
<thead>
<tr>
<th>Event</th>
<th>Preanhepatic phase (I)</th>
<th>Anhepatic phase (II)</th>
<th>Post-reperfusion phase (III)</th>
<th>POD 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+0 min</td>
<td>+60 min</td>
<td>+120 min</td>
<td></td>
</tr>
<tr>
<td>MBP (mmHg)</td>
<td>76</td>
<td>97</td>
<td>82</td>
<td></td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>17</td>
<td>17</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>5.4</td>
<td>7.3</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>SV (%)</td>
<td>4</td>
<td>3</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>PPV</td>
<td>9</td>
<td>5</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>19.4</td>
<td>19.9</td>
<td>19.3</td>
<td></td>
</tr>
<tr>
<td>PaO₂ (mmHg)</td>
<td>74</td>
<td>79.1</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Oxygen saturation (%)</td>
<td>92</td>
<td>92</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>FiO₂</td>
<td>0.53</td>
<td>0.53</td>
<td>0.50</td>
<td></td>
</tr>
</tbody>
</table>

POD: postoperative day, MBP: mean blood pressure, CVP: central venous pressure, CO: cardiac output, SV: stroke volume variation, PPV: pulse pressure variation, Hb: Hemoglobin, PaO₂: arterial partial pressure of oxygen, FiO₂: fraction of inspired oxygen.
warm ischemic times were 141 and 64 min, respectively, and there were few ascites. The estimated blood loss (expressed as lost red blood cell mass) was 450 ml, and 300 ml of salvaged blood was transfused without allogeneic red blood cells [6]. During the operation, 7,610 ml of crystalloid without colloid was infused. The total urine output was 910 ml.

**Post-liver transplantation**

On the day of the operation, the patient was returned to the operating room for bleeding control. Active bleeding from the hepatic artery anastomosis site was controlled, and he was discharged to the ICU again. The patient was extubated on postoperative day (POD) 1. His vital signs were stable, and his liver function had improved. His heart function was stable during the regular checks with trans-thoracic echocardiography (ejection fraction 49.1–58.5%). On POD 5, he was transferred to the general ward. In the ward, 3 L/h of oxygen was applied via the nasal cannula, and his oxygen saturation was maintained at 88–90%. On POD 10, he underwent reoperation for bleeding control, but surgeons could not find a specific focus of bleeding. The mid-portion of the wound was maintained in an open state, and gauze packing was applied while a penrose drain was inserted. The wound site exuded for 18 days after the surgery, and the patient was discharged on POD 27 because of delayed wound repair.

**DISCUSSION**

Fontan circulation affects the dual blood supply of the liver and is responsible for the injury pattern commonly seen in FALD. In the Fontan circulation, the hepatic veins drain directly into the Fontan circuit, and the liver is therefore particularly susceptible to the effects of central venous hypertension [3]. Cirrhosis is the single most important risk factor for the development of HCC [7], which has been recognized as an uncommon complication of FALD in some reports. Cirrhosis may develop approximately 11–15 years after the Fontan procedure, and there are both case series and reports of HCC having complicated cirrhosis in FALD patients [8–11]. However, there is limited evidence regarding the optimal treatment strategy for HCC complicated by FALD. Liver transplantation might be considered in patients with early stage HCC; however, the circulatory characteristics of the Fontan circulation limits the use of this method. Hence, previous studies have recommended heart-liver transplantation for these patients. Evidence of the effectiveness or safety of isolated liver transplantation in adult patients with severe congenital heart disease is limited. Conversely, liver transplantation has been successfully performed in children with congenital heart disease, and a successful case of pediatric liver transplantation has been reported following a Fontan procedure in left isomerism combined with biliary atresia [12]. Most adult patients with failed Fontan procedures have significantly elevated right atrial pressure. In some hospitals, isolated liver transplantation is considered a relative contraindication when patients have right atrial pressure greater than 15 mmHg [5]. A high CVP may also increase bleeding risk during surgery, and a decrease in systemic vascular resistance after reperfusion may lead to further intra-cardiac shunting (right to left) and hypoxia [13]. However, in the present case, the Fontan circulation was relatively well preserved, right atrial pressure was 14–17 mmHg, and the ejection fraction was 74%; therefore, isolated liver transplantation was decided upon following a multidisciplinary discussion.

In patients with Fontan circulation, the most challenging issue during liver transplantation is maintaining sufficient blood volume for cardiac output without causing pulmonary edema. This is owing to the documented cases of patients not being able to adapt to volume changes [5]. To achieve a successful outcome, there are several important principles to consider. First, from an anesthesiologist’s perspective, it is of paramount importance that cardiac contractility and a high CVP be preserved. However, it is challenging to maintain such a state because a high CVP may lead to excessive bleeding during surgery. Hence, volume management with crystalloid, colloid, and blood products should be adjusted carefully. The use of an inodilator may be an option for patients with Fontan circulation if the CVP or arterial blood pressure has not been adequately maintained during surgery, especially after reperfusion. One such inodilator, Milrinone, is a phosphodiesterase type III inhibitor that works to increase the heart’s contractility and decrease pulmonary vascular resistance. Second, the potential for air embolism, which can lead to either pulmonary embolism or paradoxical emboli and cerebral infarction, needs to be considered [14,15]. Moreover, in patients with Fontan circulation, the risk of thromboembolism is higher because the pulmonary blood flow remains non-pulsatile as venous flow takes place without the right
ventricle. Therefore, the use of an air filter and close observation with TEE can be useful. However, because patients who undergo the Fontan procedure usually have severe esophageal varix, the decision to use TEE should be preceded by a thorough risk-benefit assessment. Third, from the surgeon’s standpoint, meticulous surgery to reduce blood loss is mandatory. At our institution, we attempted to minimally clamp the inferior vena cava during the anhepatic phase while also monitoring femoral vein pressure, the latter of which represents inferior vena cava pressure and helps to maintain CVP. The creation of a transient porto-caval shunt can be an effective method to reduce temporal portal hypertension during the anhepatic phase and increase central venous volume.

In our case, the patient suffered wound problems and underwent additional operations for bleeding control after the liver transplantation, which led to a prolonged hospital stay. Delayed wound healing could potentially be the result of hypoxia caused by the Fontan circulation.

In conclusion, a living-donor liver transplant was used to successfully treat HCC in a 24-year-old male patient who survived a Fontan procedure for pulmonary atresia and severe right ventricular hypoplasia. To the best of our knowledge, this is the first case of isolated liver transplantation where the recipient became an adult after the Fontan procedure. In addition to a comprehensive understanding of the physiology of patients with FALD, a multidisciplinary approach should be used to assess successful outcomes in these patients.

CONFLICTS OF INTEREST

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

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www.anesth-pain-med.org
Liver transplantation: Fontan procedure


Familial amyloid polyneuropathy (FAP) is a rare form of amyloidosis that is predominantly found in Portugal, Japan, and Scandinavia [1]. It is characterized by a progressive sensory-motor polyneuropathy with often severe autonomic neuropathy due to amyloid deposition [2]. Transthyretin (TTR) is a transport protein produced mainly by the liver that carries retinol-binding protein and thyroxine. Misfolding of TTR monomers causes aggregation which results in the formation of amyloid fibrils. TTR gene mutation makes the protein more prone to the dissociation to monomers from its natural tetramer forms; thus, formation and aggregation of amyloid fibrils are accelerated and its accumulation causes various impairments in the organ [3]. Thus, liver transplantation (LT) is required to stop its progression [4]. However, undergoing major surgical operations puts the patient at risk for various anesthetic complications due to various organ impairments caused by amyloid deposition.

Domino LT was first proposed in 1995 [5]. The liver of an FAP patient is fully functional, except for the production of mutant TTR. Since the clinical manifestation of amyloid deposition takes years to develop [6], it is reasonable to make use of the explanted liver for patients with hepatic failure or cancer who are in need of urgent LT.

Here, we present a series of living donor LTs (LDLTs; i.e., a domino LT), first performed in Korea. Institutional Review Board approval was obtained prior to the operation. Written informed consent was obtained from the donor and the patient. The patient received domino LT according to domino liver transplantation protocol [18]. The patient was transferred to the ICU for postoperative resuscitation due to cardiopulmonary arrest. The patient died on postoperative day 1. It is not clear why the patient died, but further investigation is needed to prevent and better manage postoperative morbidity and mortality.
Board approved the study (no. 2020-06-087) and waived the requirement for informed consent for all three patients.

**CASE REPORT**

Demographics of three patients are presented in Table 1, and timeline of operation is presented in Fig. 1.

**Case 1. First donor**

A 24-year-old man presented as a living donor for LT. Preoperative evaluation revealed a 2.5-pack-year smoking history without any other past medical history or abnormal laboratory/imaging findings.

Spinal and general anesthesia was planned, and 2 mg of midazolam was administered intravenously as a sedative. Spinal anesthesia was performed using 27 G Whitacre needle with a midline approach at L4-5. Morphine sulfate (400 μg) was injected intrathecally without any acute complications. Intravenous thiopental (350 mg) was administered as an induction agent and vecuronium (8 mg) was used as a neuromuscular blocking agent. Continuous remifentanil infusion beginning at 0.2 μg/kg/min was administered to control pain, as well as to manage discomfort caused by intubation. After mask ventilation with 100% oxygen and isoflurane for 3 min, intubation was performed with ease. The arterial catheter was placed in the right radial artery for monitoring.

Anesthesia was maintained with isoflurane and continuous infusions of both vecuronium and remifentanil. Plasma solution A® was used for hydration at a rate of 200 ml/h. The Pringle maneuver was applied for 17 min 40 s without significant hemodynamic instability. Four hours after induction, 5,000 units of heparin were administered intravenously and the graft was harvested. Hydroxyethyl starch solution (500 ml) was infused following the harvest, and isoflurane was changed to desflurane. Pyridostigmine (15 mg) paired with glycopyrrolate (0.4 mg) was given as a reversal agent, and 25 mg of pethidine was given as well. Total urine output was 130 ml and the estimated blood loss (expressed as lost red blood cell [RBC] mass was) 463 ml [7]. The donor was transferred to the post-anesthesia care unit after surgery and was discharged on the 10th postoperative day (POD) without any complications; no transfusions were required.

**Case 2. First recipient (second donor)**

A 59-year-old woman presented for living donor LT and

**Table 1. Summary of Cases of Domino LT**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>M</td>
<td>F</td>
<td>M</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>24</td>
<td>59</td>
<td>64</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21,67</td>
<td>20,88</td>
<td>28,96</td>
</tr>
<tr>
<td>Blood type</td>
<td>B+</td>
<td>B+</td>
<td>B+</td>
</tr>
<tr>
<td>MELD</td>
<td>-</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Graft type</td>
<td>Right hemiliver</td>
<td>Extended right hemiliver</td>
<td>-</td>
</tr>
<tr>
<td>Graft size (g)</td>
<td>630</td>
<td>605</td>
<td>-</td>
</tr>
<tr>
<td>GRWR</td>
<td>-</td>
<td>1.15</td>
<td>0.8</td>
</tr>
</tbody>
</table>

BMI: body mass index, MELD: model for end-stage liver disease, GRWR: graft recipient weight ratio.
as a liver donor for domino LT. She presented with symptoms of edema and paresthesia of both lower extremities 7 years ago and was found to have cardiomegaly on chest radiography. She was diagnosed with amyloidosis 1 year previously while undergoing a pericardial window operation for pericardial effusion.

Airway examination showed macroglossia. Laboratory findings showed a decrease in hemoglobin concentration (10.1 g/dl); prolongation of prothrombin time (PT) expressed as an international normalized ratio (INR) of 1.13; and elevated cardiac markers (troponin I 0.131 ng/ml [reference range: < 0.04 ng/ml], NT-proBNP 2,739 pg/ml [reference range: < 222 pg/ml]). Chest radiography was consistent with previous findings of cardiomegaly without active lung lesions. Sinus rhythm with atrial premature complexes and left ventricular hypertrophy were found in electrocardiogram. An echocardiogram showed increased left ventricle (LV) wall thickness, diastolic dysfunction (grade 2) with increased LV filling pressure, both atrial enlargement, and a moderate amount of pericardial effusion. The LV ejection fraction was 60.5% without regional wall motion abnormality. The right ventricle cavity size and systolic function were normal. These findings were an improvement compared to echocardiogram findings from 4 months previously. During consultations, cardiologists agreed that the patient’s cardiac condition had improved and that she would be able to undergo the operation. Nerve conduction study results were suggestive of amyloidosis-associated polyneuropathy with abnormal electrophysiology. Autonomic nerve function tests showed severe sudomotor, adrenergic, cardiovagal autonomic dysfunction. After consulting with cardiologists, we decided to proceed without inserting a temporary pacemaker. Instead, an external patch was incidentally removed but was not reattached because the patient’s vital signs were stable.

The arterial line was acquired with administration of loxidine (10.1 g/dl); prolongation of prothrombin time (PT) expressed as an international normalized ratio (INR) of 1.13; and elevated cardiac markers (troponin I 0.131 ng/ml [reference range: < 0.04 ng/ml], NT-proBNP 2,739 pg/ml [reference range: < 222 pg/ml]). Chest radiography was consistent with previous findings of cardiomegaly without active lung lesions. Sinus rhythm with atrial premature complexes and left ventricular hypertrophy were found in electrocardiogram. An echocardiogram showed increased left ventricle (LV) wall thickness, diastolic dysfunction (grade 2) with increased LV filling pressure, both atrial enlargement, and a moderate amount of pericardial effusion. The LV ejection fraction was 60.5% without regional wall motion abnormality. The right ventricle cavity size and systolic function were normal. These findings were an improvement compared to echocardiogram findings from 4 months previously. During consultations, cardiologists agreed that the patient’s cardiac condition had improved and that she would be able to undergo the operation. Nerve conduction study results were suggestive of amyloidosis-associated polyneuropathy with abnormal electrophysiology. Autonomic nerve function tests showed severe sudomotor, adrenergic, cardiovagal autonomic dysfunction. After consulting with cardiologists, we decided to proceed without inserting a temporary pacemaker. Instead, an external patch was incidentally removed but was not reattached because the patient’s vital signs were stable.

The arterial line was acquired with administration of local anesthesia before induction in order to monitor arterial blood pressure during induction. Induction was successfully done with 16 mg of etomidate, 8 mg of vecuronium, and isoflurane. Intubation was easily performed with a Macintosh blade #3. Macroglossia with nodules due to amyloidosis was noted, but the vocal cord was spared for infiltration. An additional arterial line at the right femoral artery was acquired. The central venous line was also placed in the right femoral and right internal jugular veins. A multifunction pulmonary artery catheter was inserted to monitor cardiac output, pulmonary arterial pressure, pulmonary artery occlusion pressure, and mixed venous oxygen saturation. During these procedures, the patient’s heart rate did not change in response to the stimuli, such as intubation or line insertion. Instead, the heart rate slowly but continuously decreased to 48 beats/min. Isoproterenol (1 μg/min) was administered and the heart rate increased to 80 beats/min. Isoproterenol was tapered to 0.5 μg/min and the infusion rate was maintained. Remifentanil and norepinephrine were used appropriately to control blood pressure, and vecuronium was infused continuously to ensure adequate neuromuscular blockade.

Blood flow to and from the left lobe was kept intact to minimize the changes in hemodynamics throughout the procedures. Post-reperfusion syndrome was noted with a decrease in mean arterial pressure from 75 to 36 mmHg without a change in heart rate (92 beats/min). Pulmonary arterial pressure decreased from 18 to 13 mmHg. Phenylephrine (50 μg) was administered and the continuous infusion rate of norepinephrine was increased; autologous blood from Cell Saver was transfused to normalize the blood pressure. Hemodynamic parameters remained stable after the intervention with a vasopressor; thus, TEE was not used throughout the procedure.

The total urine output was 685 ml, and the estimated lost RBC mass was 641 ml [7]. One unit of pre-leukocyte-reduced RBC (PLRBC) and 471 ml of autologous blood from Cell Saver was transfused and the operation commenced uneventfully. The patient was transferred to the intensive care unit (ICU) while intubated after removal of the pulmonary artery catheter. Continuous isoproterenol infusion was maintained during the transfer to the ICU. During the transfer from the operation table to the hospital bed, the external patch was incidentally removed but was not reattached because the patient’s vital signs were stable.

Postoperative laboratory values were as follows: hemoglobin 9.6 g/dl, platelet counts 114 × 10^3 /μl, PT INR 1.62, and fibrinogen 180 mg/dl. Five hours later, continuous infusion of vasopressin (0.03 unit/min) was added to maintain blood pressure, and isoproterenol infusion was stopped due to sinus tachycardia (120 beats/min). On the 1st POD, the patient showed stable vital signs and alert mental status thus, the patient was weaned off the ventila-
Case of LDLT of a FAP patient

A 64-year-old man agreed to undergo domino LT. He was diagnosed with liver cirrhosis due to hepatitis B virus infection and had undergone multiple transarterial chemo-embolization due to hepatocellular carcinoma. Without a living donor and with a low model for end-stage liver disease score of 9, he was not eligible for LDLT or deceased donor LT (DDLT). He agreed to undergo domino LT with a liver graft from a FAP patient.

The patient was on medication for hypertension and diabetes mellitus II. Laboratory findings were consistent with cirrhotic liver and chronic illness showing a hemoglobin of 8.6 g/dl, platelet count of 89 × 10^3 /μl, and a prolonged prothrombin time (INR) of 1.34. All other test results were within the normal range. Upper and lower gastrointestinal endoscopy was performed and no active bleeding lesions were found, but esophageal and gastric varices were found.

Induction was performed with thiopental (325 mg), atracurium (40 mg), and sevoflurane. Intubation was performed with ease and without complications. Arterial and central lines were placed with a multifunction pulmonary artery catheter. Anesthesia was maintained with isoflurane and continuous infusion of atracurium. The liver was uneventfully extracted. At the start of the anhepatic phase, Hepabig 10,000 IU mixed with 200 ml of 5% dextrose solution was infused. Dopamine and norepinephrine were given at rates of 3 μg/kg/min and 0.05 μg/kg/min, respectively, to maintain blood pressure. The total urine output was 1,100 ml, and the estimated lost RBC mass was 874 ml. Three packs of PLRBC and 100 ml of blood from Cell Saver were transfused. The patient was transferred to the ICU while still intubated. He was moved to the general ward on the 6th POD without any complications and was discharged 2 weeks later.

**DISCUSSION**

FAP is the hereditary form of TTR-related amyloidosis which is caused by mutations in the TTR gene, which alters the secondary and tertiary structure to alter metabolism and amyloid fibril formation [2]. LT is the only treatment option that can stop its progression; however, it presents various challenges for anesthetic management of these patients. Meanwhile, explanted liver from FAP patients is fully functional, except for the production of the mutated amyloids, which becomes a clinical problem in the years following the transplant to a non-FAP patient. Thus, as in our case, it can be a possible treatment option for those who may not be candidates for either LDLT or DDLT. Since domino LT is possible, with the presence of a structurally and functionally normal liver of FAP patients, FAP patients are important for a successful operation.

Various intraoperative anesthetic management techniques should be considered for patients with FAP. Peripheral vasodilation, cardiac autonomic denervation, and restrictive cardiomyopathy secondary to amyloid infiltration contribute to hypotension [8,9]. Intraoperative TEE is a useful modality to differentiate the cause of hypotension [10]. Although TEE was prepared in case it was needed to identify the cause of hypotension during the procedure, there was no incidence of unstable hemodynamic changes that were not already expected during the LDLT procedures. There was an event of PRS; however, it was quickly corrected with vasopressor interventions. If there was an

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event that was not expected during regular LDLT procedures, TEE could provide additional information that would be useful for differentiation of hypotension.

The patient had cardiac denervation, which was presented as bradycardia in this case. Therefore, the patient did not manifest dramatic increases in heart rate or blood pressure, despite preparing the patient for the operation (e.g., intubation, position change). Cardiac autonomic denervation in FAP does not alter cardiac beta-receptor responsiveness to catecholamine, thus isoproterenol is used to increase heart rate while atropine may be ineffective [8].

Isoflurane is known to decrease arterial pressure mainly by reducing systemic vascular resistance with minimal effect on cardiac output compared with other volatile anesthetics [11]. Use of isoflurane for patients with FAP for resolution of sinus dysrhythmia has also been reported, thus indicating that it is a good choice for maintaining anesthesia [12]. Researchers speculate that isoflurane decreases the rate of phase 4 depolarization of sinoatrial node cells [13].

There are discrepancies in implementation of preoperative pacemaker insertion in FAP patients with cardiac involvement who are undergoing LT [14]. After in-depth discussion with cardiologists and surgeons, we decided to omit temporary pacemaker insertion and proceeded with the procedure using an external patch. It was thought to give the same benefit as the pacemaker without the patient having to go through another meticulous procedure. Implementation of a pacemaker could provide stable rhythm control compared to an external patch. However, undergoing the procedure may burden the FAP patient. In addition, the placed wire can interfere with the pulmonary arterial catheter introduced during induction, causing complications such as arrhythmia. If the pacemaker wire was introduced via femoral access, the position could be altered during inferior vena cava clamping during the operation.

Despite timely CPR management in the ICU, the patient was not resuscitated. Autonomic denervation of the FAP patient’s heart makes it resistant to inotropic and chronotropic actions that we routinely use in the cycles of CPR. It would have been more beneficial if isoproterenol was used. There are reports of sudden unexpected death of patients with cardiac amyloidosis which may be a result of arrhythmias or disturbances of conduction [15]. The patient’s heart was functionally at risk for conduction failure; it would thus have been helpful if the external patch or pacemaker was in place post-operatively.

Notably, this is the first case of domino LT in Korea and anesthetic management was successfully performed without complications during the operation. However, there are still challenges in managing patients with FAP post-operatively, which would dramatically alter the course of the patient.

CONFLICTS OF INTEREST

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

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Antinociceptive effects of intrathecal cimifugin treatment: a preliminary rat study based on formalin test

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Background: Cimifugin is one of the components of the root of Saposhnikovia divaricata. The extract derived from S. divaricata is traditionally used as an analgesic. This study was conducted to evaluate the analgesic effect of intrathecal cimifugin in the formalin test.

Methods: Male Sprague–Dawley rats (n = 20) were randomized into four groups for intrathecal administration of 70% dimethylsulfoxide and various doses of cimifugin (100 μg, 300 μg, and 1,000 μg). The typical flinch response after the injection of 5% formalin into the hind paw was assessed in two distinct phases: phase 1 until 10 min, and phase 2 from 10 min to 60 min. ED₅₀ values were calculated via linear regression.

Results: Intrathecal cimifugin significantly reduced the flinch response in both phases of the formalin test. Significant antinociceptive effects of cimifugin were found with the dose of 300 μg in phase 1 and the dose of 100 μg in phase 2. The ED₅₀ value (95% confidence intervals) of intrathecal cimifugin was 696.1 (360.8–1,342.8) μg during phase 1 and 1,242.8 (42.0–48,292.5) μg during phase 2.

Conclusions: Intrathecal cimifugin has an antinociceptive effect against formalin-induced pain. Cimifugin has an anti-inflammatory effect at low concentrations, and non-inflammatory analgesic effect at higher concentrations.

Keywords: Analgesia; Apiaceae; Chromones; Cimifugin; Nociception; Pain measurement.
treat fever, rheumatism, neuralgia, and headache [4]. Bioactive substances derived from ‘Bangpung’ showed anti-oxidant [5] and anti-inflammatory effects [6,7]. These properties of ‘Bangpung’ suggested potential pharmaceutical candidates [2]. Compounds isolated from *S. divaricata*, including sec-O-glucosylhamaudol (SOG), hamaudol, ledabouriellol, divaricatol, isofofraxidin, and cimifugin showed an analgesic effect [8]. We previously demonstrated the strong antinociceptive effect of intrathecal SOG, which is one of the constituents of *P. japonicum* Thunb. via opioid receptors [9]. Recent studies showed anti-inflammatory effects of cimifugin, a chromone (1,4-benzo-pyran, Fig. 1), which is one of the bioactive substances derived from *S. divaricata* [10,11]. Thus, we hypothesized that the anti-inflammatory effect of cimifugin may result in an analgesic effect. Thus, we conducted a preliminary study to determine the antinociceptive effect of intrathecal cimifugin using a formalin test to confirm the analgesic effect of cimifugin mediated via anti-inflammatory effect. The primary outcome of the study was to the concentration-dependent analgesic effect of cimifugin based on a formalin test. The secondary outcome was calculating the effective dose (ED) of cimifugin required for the analgesia.

**MATERIALS AND METHODS**

**Animal preparation**

The animal study was approved by the Institutional Animal Care and Use Committee (no. CIACUC 2018-S0042). We followed the guidelines and ethical standards stipulated by the International Association for the Study of Pain [12] and ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines (https://www.nc3rs.org.uk/arrive-guidelines) for the investigation of experimental pain in animals. Specific pathogen-free male Sprague-Dawley rats were purchased from Damul Science (Korea), and those weighing 225–250 g each were used in the study (*n* = 20). The rats were housed in the cage located in a room maintained at a constant temperature (20 to 23°C), with free access to water and food under a light/dark cycle of 12:12.

**Intrathecal catheterization**

The intrathecal catheter was implanted after the anesthesia with isoflurane. After a sterile dressing of the surgical field, the head of the rat at the level of the atlanto-occipital membrane was incised and the cisterna magna was opened. A polyethylene-5 catheter was inserted into the intrathecal space for drug administration [13]. The inserted catheter was placed at the end of the intrathecal catheter at the lumbar enlargement by carefully advancing it into the caudal region about 8.5 cm from the incision site. The catheter location was confirmed by the leakage of cerebrospinal fluid (CSF) through the tip of the catheter. The catheter tip was pulled out through the skin in the frontal area of the head and fixed with a 3-O silk. The tip of the catheter was plugged with a 30-gauge stainless steel wire to inhibit CSF leakage. After the intrathecal catheterization procedure, the rats were allowed to recover from the anesthesia in the individual cages. Ambulatory function was observed after full recovery from anesthesia. Only the rats without motor or sensory deficits were used in the study. The rats with motor or sensory deficits were euthanized immediately with an overdose of volatile anesthetics.

**Drug preparation and grouping**

Cimifugin (purity ≥ 98%) was purchased from ChemFaces (China). Cimifugin powder was dissolved in 70% dimethylsulfoxide (DMSO). The dissolved solutions were diluted to 100, 300, and 1,000 μg levels. Cimifugin powder was fully dissolved by DMSO at a concentration greater than 70%. The maximal concentration of cimifugin powder required to dissolve in 70% DMSO was 1,000 μg/10 μl. The concentration of cimifugin was determined by a pilot study (data not shown).

The rats were randomized into four groups (each *n* = 5) using a computerized random number according to the study protocol (Fig. 2). The rats in the vehicle-treated group were administered 70% DMSO intrathecally as a control during the formalin test. The rats in the different test groups were treated with intrathecal cimifugin at concentrations of 100, 300, and 1,000 μg, respectively, during the formalin test.
Flinch response

The formalin test was conducted from 9:00 a.m. to 12:00 p.m. by two researchers. One investigator administered formalin injection and intrathecal drug treatment, and another investigator carried out the behavioral test. After adaptation in a restrained cylinder for 20 min, different doses of cimifugin or vehicle (DMSO 70%) were administered in a volume of 10 μl solution intrathecally using a gear-operated Hamilton syringe pump, and 10 μl of saline was flushed additionally. After 10 min, 5% formalin (50 μl) was subcutaneously injected into the center of the hind paw with a 30 gauge needle. The flinch responses were assessed by counting the number of flinches per minute. Phase 1 response (initial acute phase, 0–9 min) was measured at 1 and 5 min after the formalin injection, while phase 2 response (10–60 min) was measured every 5 min until an hour after the formalin injection [14].

Statistical analysis

The sample size was calculated using G*Power 3.1 software. The calculated effect size was 1.12 based on the results of a previous study, which showed significant antinociceptive effect when the total flinch count was decreased to 60.2% compared with the control [9]. The total sample size in the three groups was calculated as 16 with α = 0.05 and 95% power for 13 consecutive flinches based on repeated measures analysis of variance. We decided the total sample size as 20 given the drop-out rate of 20%.

Dose-responsiveness of cimifugin was calculated as the percentage of control in the two phases as follows.

\[
\text{% of control} = \frac{\text{sum of phase 1 or 2 flinch count with cimifugin}}{\text{sum of control phase 1 or 2 flinch count}} \times 100
\]

The ED<sub>50</sub> was defined as a dose of cimifugin that resulted in a 50% inhibition of flinch count compared with the control. The ED<sub>50</sub> was calculated via standard linear regression analysis according to the method of Tallarida [15]. ED<sub>50</sub> values and confidence intervals (CIs) in each phase were calculated.

The time-response or the dose-response data of flinch responses are expressed as the number of flinches or the percentage of control. All data are expressed as mean ± SEM. The flinch responses in phases 1 and 2 were analyzed separately because of the distinct biphasic response of the formalin test. One-way analysis of variance followed by post-hoc test with Turkey’s test for multiple comparisons was used for the statistical analysis of the flinch responses. P values less than 0.05 were considered statistically significant.

RESULTS

Typical biphasic flinch responses to the formalin test were observed in all rats following intrathecal administr-
tion of vehicle (DMSO 70%) (Fig. 3).

Pre-treatment with intrathecal cimifugin decreased the flinch response triggered by formalin injection significantly in both phases (Figs. 3, 4). During phase 1, a statistically significant reduction in flinch response was found using the dose of 300 μg, and the maximal reduction in flinch response was observed at a dose of 1,000 μg (41.0% of control, P < 0.001, Figs. 4, 5, and Table 1). During phase 2, a statistically significant reduction of flinch response was found at a dose of 100 μg (65.5% of control, P = 0.011), and the maximal reduction in flinch response occurred at a dose of 1,000 μg (50.6% of control, P = 0.003, Figs. 4, 5, and Table 1).

The ED_{50} (95% CIs) values of intrathecal cimifugin were 696.1 (360.8–1,342.8) μg during phase 1 and 1,242.8 (42.0–48,292.5) μg during phase 2.

**Fig. 3.** Time course data showing the antinociceptive effects of cimifugin after formalin injection. Intrathecal cimifugin significantly decreased the formalin-induced flinch response during both phases. DMSO: dimethylsulfoxide. Each line represents the mean ± SEM of 5 rats/group.

**Fig. 4.** Antinociceptive effects of intrathecal cimifugin are presented as dose-response data. Intrathecal cimifugin decreased the formalin-induced flinch response significantly during phase 1 (A) and phase 2 (B). In phase 1, a statistically significant reduction in flinch response was found with the dose of 300 μg and the maximal reduction in flinch response occurred at a dose of 1,000 μg. In phase 2, a statistically significant reduction in flinch response was found at the dose of 100 μg. The maximal reduction in flinch response occurred at a dose of 1,000 μg. Data are expressed as mean ± SEM. *P < 0.001 vs. control.
DISCUSSION

As mentioned above, ‘Bangpung’ was traditionally used to treat fever and pain. The anti-inflammatory and antioxidant activity of the bioactive substances derived from *S. divaricata* may correspond to those effects [5–7]. According to the phytochemical studies, Prim-O-glucosylcimifugin is the main chromone present in *S. divaricata*, with antipyretic, anti-inflammatory, and analgesic properties [4]. Cimifugin is an aglycone of prim-O-glucosylcimifugin, synthesized during blood absorption [4]. According to Li et al. [16] cimifugin showed the highest concentration in plasma of rats treated with the extracts of *S. divaricata* orally. They concluded that cimifugin is the potential pharmacodynamic component of *S. divaricata* formed via biotransformation in vivo even though prim-O-glucosylcimifugin is the major constituent [4,16].

As far as we know, only one study reported the analgesic effect of cimifugin. Okuyama et al. [8] reported that oral administration of 80 mg/kg of cimifugin showed significant analgesia in mice during acetic acid-induced writhing test. The results suggested that the analgesic potency of chromones may be attributed to the non-glycosylated dihydro-pyran-type C-ring. Chromones are an important class of natural products that exhibit antibacterial, anticoagulant, anti-inflammatory, antioxidant, and anticancer activities [3]. Several types of compounds in chromones targeting multiple inflammatory pathways have been reported. The anti-inflammatory effects of chromones are mediated not only via inhibition of the COX pathway but also by neutrophil-dependent superoxide anion generation [3]. A recent study involving RAW264.7 cells showed that cimifugin inhibits the activities of mitogen-activated protein kinase and NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) signaling pathways and suppresses the release of inflammatory factors [11]. Another study of reported that cimifugin significantly attenuated allergic inflammation by reducing thymic stromal lymphopoietin and IL-33 synthesis [10].

These studies suggest that cimifugin has an anti-inflammatory role resulting in an analgesic effect via inhibition of the inflammatory process. Neuroinflammation plays an important role in the generation and modulation of pain [17], so the anti-inflammatory effect of cimifugin was thought to decrease the induction of inflammatory pain. Thus, we conducted the formalin test as a preliminary

![Fig. 5. Dose-response data indicate the antinociceptive effects of intrathecal cimifugin. *P < 0.001 vs. control.](image)

![Table 1. Antinociceptive Effects of Intrathecal Cimifugin: Dose-response Data](table)
study to evaluate the analgesic effect of intrathecal cimifugin and its relation to inflammation. In the current study, we confirmed that intrathecal administration of cimifugin decreased the flinch response to formalin injection in both phases. The two phases in the formalin test indicate different nociceptive mechanisms [18]. The flinch response in phase 1 is due to a direct effect on the nociceptors, while the phase 2 response represents both inflammatory pain in the peripheral tissue and functional changes in the dorsal horn mediated via inflammatory reaction in the spinal cord. Thus, the inflammatory pathway mediated by prostaglandins does not play an important role during the early phase but the latent phase. However, some nonsteroidal anti-inflammatory drugs such as paracetamol show analgesic effects in both phases, suggesting effects against non-inflammatory pain. In the current study, cimifugin reduced the flinch response in both phases; however, significant antinociceptive effects were observed upon treatment with 300 μg in phase 1 (70.8% of control) and 100 μg in phase 2 (65.5% of control). However, its maximal antinociceptive effect with the 1,000 μg dose was more effective in phase 1 (phase 1: 41.0% of control vs. phase 2: 50.6% of control). These results are consistent with a previous study reporting the anti-inflammatory effects of isolated compounds from P. japonicum Thunb., which showed a relatively weak inhibitory activity of cimifugin against both COX-1 and COX-2 [7]. Therefore, it is suggested that cimifugin has an antinociceptive effect mediated via anti-inflammatory effect at low concentrations and via other non-inflammatory analgesic effects at high concentration.

Other hypotheses have been proposed to explain the mechanisms of action. First, derivatives of natural products display analgesic effect via multiple mechanisms. For example, eugenol, the bioactive compound derived from clove, carries not only anti-inflammatory and antioxidant potential but also analgesic effects mediated via α2-adrenergic and opioid receptors [19]. Our previous study investigating SOG, and other extracts derived from S. divaricata, showed that SOG exhibits analgesic effect against incisal pain via the μ-opioid receptor [20]. Thus, other targets may modulate acute peripheral nociception. Second, the antioxidant effect may mediate the formalin-induced pain response. According to the study evaluating the analgesic effect of antioxidants in the formalin test, the pro-oxidant may play an important role in the pain induced by tissue injury and intrathecal administration of an antioxidant (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxy) effectively reduced the response in both phases [21]. Hong et al. [22] suggested that antioxidants such as vitamin E induce antinociceptive effects by not only decreasing the central sensitization but also scavenging the reactive oxygen species in the peripheral tissue.

Although the current study showed an analgesic effect of cimifugin in both phases of the formalin test, there were several limitations. First, we merely evaluated the pharmacological effect of different doses of cimifugin in the formalin test in this preliminary study, without elucidating the mechanisms of action. Further studies using different routes of administration using antagonists of specific receptors and methods other than formalin test, as well as other molecular studies are needed to determine the exact site of action of cimifugin. Second, a higher dose of cimifugin (> 1,000 μg) may yield a more potent analgesic effect, but the maximal dose of the current study was 1,000 μg. Higher concentrations of cimifugin could not be administered in this study because of technical difficulties and inability to dissolve higher concentrations of cimifugin (> 1,000 μg/10 μl of 70% DMSO). Thus, we used 1,000 μg of cimifugin as the maximal dose for the intrathecal administration. Moreover, cimifugin powder was only dissolved in DMSO at a concentration greater than 70%. Even though the control dose of DMSO alone had no analgesic effect, DMSO showed some reducing effects in the formalin test [23]. The high concentration of DMSO used for drug preparation may affect the study results. Third, the CI of the ED50 values in phase 2 was large according to the linear regression (42.0 to 48,292.5 μg), which was considered as computational limitation due to the inability to use higher concentrations of cimifugin. Such a large CI limits further evaluation because of difficulty associated with the intrathecal administration. Further studies investigating the side effects of treatment with large doses are needed. Fourth, further investigations using biological markers are needed for objective results.

In conclusion, intrathecal cimifugin had antinociceptive effects in both phases of the formalin test, suggesting that cimifugin has an anti-inflammatory effect at low concentrations and non-inflammatory analgesic effects at higher concentrations. Further studies are required to investigate the actual mechanisms of cimifugin.

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CONFLICTS OF INTEREST

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

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Incidence of inadvertent intercostal or epidural spread during thoracic sympathetic ganglion block

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Background: Sympathetic blocks (SBs) have been used widely to relieve the symptoms of sympathetically maintained pain (SMP). The thoracic sympathetic ganglion is not separated from somatic nerves by muscles and connective tissue. The upper thoracic ganglion runs along the posterior surface of the vertebral column in close proximity to the adjacent epidural region. This anatomical difference leads to frequent epidural and intercostal spread in cases of thoracic SBs. The purpose of this study was to investigate the incidence of inadvertent intercostal and epidural injections during thoracic SBs.

Methods: Twenty-two patients who were suffering from complex regional pain syndrome or lymphedema after breast cancer surgery were managed with two or three times of thoracic SBs. Therefore, injections of 63 thoracic SBs from 22 patients were enrolled in this study. An investigator who did not attend the procedure evaluated the occurrence of intercostal or epidural spread using anteroposterior fluoroscopic images.

Results: The overall incidence of inadvertent intercostal or epidural spread of contrast was 47.5%. Among the inadvertent injections, intercostal spread (34.9%) was more frequent than epidural spread (12.6%). Only 52.5% of the thoracic SBs demonstrated successful contrast spread without any inadvertent spread. The mean difference in skin temperature between the blocked and unblocked sides was 2.5 ± 1.8ºC. Fifty-nine (93.6%) injections demonstrated more than 1.5ºC difference.

Conclusions: Thoracic SBs showed a high incidence (47.5%) of inadvertent epidural or intercostal injection. Thus, special attention is required for the diagnosis of SMP or the injection of any neurolytic agent around sympathetic ganglion.

Keywords: Anatomical difference; Inadvertent injection; Injection, epidural, intercostal; Skin temperature; Sympathetic blocks; Sympathetically maintained pain; Thoracic sympathetic ganglion.
trunk, extending from the base of the skull to the coccyx, presents bilaterally. It divides into the cervical, thoracic, lumbar and sacral segments [1–3].

Certain neuropathic pain conditions are referred to as sympathetically maintained pain (SMP). Although the mechanism of SMP is still unclear, abnormal coupling between the sympathetic and the somatosensory nervous system has been suggested. This coupling occurs as a result of neurogenic inflammation following a lesion in the peripheral nerve or the dorsal root ganglion [4–6].

Clinically, sympathetic blocks (SB) have been widely used to relieve the symptoms of SMP or to differentiate between SMP and sympathetically-independent pain. For an SB to provide a diagnostic value, the sympathetic activity should be successfully disturbed for a proper duration of time [7–9]. For the diagnosis of SMP using an SB, complete interruption of sympathetic activity must be achieved, while preserving sensory and motor function. The sympathetic trunk at the lumbar region runs on the anterolateral surface of the vertebral column from the L1 to L4 levels and deep to the medial aspect of the psoas major muscle [10]. Therefore, it is hard to find epidural contrast spread during lumbar SB due to the anterior location of lumbar sympathetic ganglion to the vertebral body. Our previous study demonstrated frequent psoas muscle injection due to the close proximity of lumbar sympathetic ganglion [11].

In contrast to the lumbar sympathetic ganglion, the thoracic sympathetic ganglion is not separated from somatic nerves by muscles and connective tissue. Moreover, the upper thoracic ganglion runs along the posterior surface of the vertebral column in close proximity to adjacent epidural region [12]. These anatomical differences in the thoracic sympathetic ganglion lead to frequent epidural and intercostal spread when performing thoracic SBs. Spread to the epidural and intercostal space lowers the diagnostic and therapeutic value of thoracic SBs. In addition, serious adverse outcomes can be encountered if a neurolytic agent such as alcohol is injected into the epidural or intercostal space inadvertently during the procedure of thoracic SB. Considering the diagnostic and therapeutic value and safety of thoracic SBs, evaluation of the actual incidence of intercostal and epidural spread is important.

The conventional target point of a thoracic SB in lateral fluoroscopic images is the anterior edge of the costovertebral articulation, where the needle tip contacts the posterior one-third of the lateral vertebral body [9,13].

The purpose of this study was to evaluate the incidence of intercostal and epidural spread when the needle tip was located at the conventional target point.

MATERIALS AND METHODS

Patients

This prospective randomized study was approved by the Institutional Review Board (no. 05-028-004) of our institution. All participants were explained about potential benefits and risks of the trial and they were provided with written informed consent. This trial was registered prior to patient enrollment at ClinicalTrials.gov (no. NCT03995576, Date of registration: 06/20/2019).

From June to August 2019, 22 patients who were managed with two or three times of thoracic SBs were enrolled. The inclusion criteria in this study were patients who demonstrated severe unilateral arm pain or edema due to complex regional pain syndrome (CRPS) or lymphedema after breast cancer surgery. The enrolled patients were intractable to conservative therapy, including pain medication and physical therapy. Patients who had known allergies to contrast or local anesthetics, or who had coagulopathies or spine infections, were excluded. Therefore, the ultimate enrolled number of the thoracic SBs was 63 injections. All procedures were performed by one pain physician who had more than 15-years of experience with pain intervention using fluoroscopy.

Procedure

In the thoracic SB procedure, the patient was laid on the fluoroscopic bed in a prone position and the upper back of the target vertebra was sterilized. To facilitate needle insertion, fluoroscopy was rotated ipsilaterally by 15–20°. After local infiltration with 1% lidocaine, a 10-cm long, 23-gauge spinal needle was inserted medially toward the lateral margin of the second or third thoracic vertebra. Strict attention was paid to insert the needle within a 3-cm distance from the spinous process of the targeted vertebra to minimize the risk of pneumothorax. A right or left side injection was determined according to the symptomatic side of pain or edema.

A spinal needle was inserted using a tunnel view technique under oblique view. After the needle touched the lateral vertebral body, it was slightly advanced to the posterior one-third of the vertebral body. The final location of
the needle tip was confirmed using anteroposterior (AP) and lateral fluoroscopic views. After the needle tip was located successfully, 3 ml of contrast medium (omnipaque 300, GE Healthcare, UK) was injected slowly. All AP and lateral images were saved to the hard disc of the fluoroscopic machine and were transmitted to a picture archiving and communication system (INFINITT Healthcare, Korea).

**Outcome measurements**

Age, sex, diagnosis of patient, and skin temperature of both hands before and after thoracic SB were collected from the medical record. Temperature was measured for 20 min at 5-min intervals using a round-shaped skin temperature sensor attached to the volar side of both thumbs (carescape monitor B650, GE Healthcare). If the temperature difference between the two fingertips was more than 1.5°C, the sympathetic block was considered successful [14].

An investigator who did not attend the procedure evaluated the occurrence of intercostal or epidural spread using the AP images which were saved in a picture archiving and communication system. This investigator had more than 10-years of experience with pain intervention using fluoroscopy. Patterns of spread were divided into successful thoracic SBs without any inadvertent spread (Fig. 1A), thoracic SBs with intercostal spread (Fig. 1B), thoracic SBs with epidural spread (Fig. 1C) and failed SBs.

**Statistical analysis**

Our study is a simple observational study to report the incidence of epidural or intercostal spread. Therefore, we did not perform any power analysis to calculate the sample size. We obtained the incidence of inadvertent injections from 63 injections of thoracic SBs. Continuous numerical data were expressed as mean and standard deviation (for normally distributed data). Categorical data were expressed as frequencies and percentages. Chi-square or Fisher’s exact test was used for the categorical variables. All data were analyzed using SPSS version 18.0 (IBM Co., USA) and a P value < 0.05 was considered statistically significant.

**RESULTS**

This study included 63 thoracic SBs performed on 22 patients with a mean age of 42.5 ± 6.5 years. Among 22 patients enrolled, 18 patients had CRPS and 4 patients had lymphedema (Table 1). Thoracic SBs were performed at T2 or T3 levels. Thir-

<table>
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<th>Table 1. Demographic Data</th>
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<tr>
<td>Variable</td>
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<td>Body mass index (kg/m²)</td>
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Values are presented as mean ± SD or number of patients.

**Fig. 1.** Patterns of thoracic sympathetic block (SB) showing successful SB without any inadvertent spread (A), thoracic SB with intercostal spread (B), and thoracic SB with epidural spread (C). White arrows in (B) and (C) indicates intercostal and epidural spreads, respectively.
ty-one injections were made on the right side and 32 injections were made on the left side.

The overall incidence of inadvertent intercostal or epidural spread of contrast was 47.5%. Among the inadvertent injections, intercostal spread (34.9%) was more frequent than epidural spread (12.6%). Only 52.5% of the thoracic SBs demonstrated successful contrast spread without any inadvertent spread (Table 2). There was no failed SB.

The right and left side thoracic SBs showed 15/31 (48.3%) and 7/32 (21.8%) inadvertent intercostal injections, respectively. Skin temperature was measured at both thumbs to assess the block efficacy (Fig. 2). The mean difference in skin temperature between the blocked and unblocked sides was 2.5 ± 1.8°C. Fifty-nine (93.6%) injections demonstrated more than 1.5°C difference.

**DISCUSSION**

In this study, about half (47.5%) of thoracic SBs showed inadvertent intercostal or epidural spread. Among the inadvertent injections, the intercostal spread of contrast was more frequent than epidural spread. When sympathetic blocks were performed at the lumbar area, the incidence of psoas muscle spread was 21.3% [11]. It is thought that the reason of more frequent inadvertent injection of thoracic SB than lumbar SB comes from the anatomical difference of the thoracic sympathetic ganglion. The upper thoracic ganglion runs along the posterior surface of the vertebral column in close proximity to the adjacent epidural region [12]. Due to this posterior location, thoracic SBs performed in this study targeted a final needle location at the posterior one-third of vertebral body.

During thoracic SB, the communicating ramus is the key structure by which injected medicine is delivered to the intercostal nerve. White and gray communicating rami are located between intercostal nerve and thoracic sympathetic ganglion. The types of communicating rami of the thoracic sympathetic ganglion include transverse or oblique rami connecting to the intercostal nerve of the same level, ascending rami to the intercostal nerve of the higher level and descending rami to the intercostal nerve of the lower level [12,15]. The second thoracic sympathetic ganglion presents a diverse way of giving off its communicating rami. The incidence of ascending or descending rami arising from the second thoracic sympathetic ganglion was 66.7% and this incidence decreased below T3 level. In addition, T2 showed much stronger anatomical variation compared to T3 or T4 [15]. Considering this anatomical variation and the diverse way of giving off ascending or descending rami at T2 sympathetic level, a significant inadvertent incidence of T2 would be expected. However, this study did not show any significant differences between T2 and T3 levels.

Right-side thoracic SBs showed an increased incidence of inadvertent injections compared to the left side in this study. According to a recent cadaver study, the number of rami of the upper thoracic sympathetic chain was significantly greater on the right side. Also, the horizontal distance between the sympathetic chain and union of the rami on the intercostal nerves was significantly greater on the right side [15]. This anatomical difference of the upper
thoracic sympathetic chain might contribute to the slightly increased inadvertent injections on right-side thoracic SBs.

Primary palmar hyperhidrosis is a debilitating disorder characterized by excessive sweating. The communicating rami of the upper thoracic sympathetic ganglion are frequently involved in essential palmar hyperhidrosis. A surgical method of dividing the sympathetic communicating rami, while preserving the thoracic sympathetic ganglia and nerve chain, has been introduced to address this disorder [16]. Percutaneous ethanol or alcohol sympatholysis is another treatment modality for primary hyperhidrosis. According to a recent study, 39 consecutive patients with primary hyperhidrosis received percutaneous sympatholysis with a technical success rate of 100%. However, major complications were encountered, including severe intercostal neuralgia and pneumothorax [17]. Therefore, if chemical neurolysis will be performed using alcohol or ethanol, instead of a surgical approach, special attention should be paid to minimize inadvertent spread.

A stellate ganglion block is the most commonly used simple technique to interrupt the sympathetic innervation of the upper extremity [8]. However, clinical and anatomical studies have suggested that this may not be the best method for upper extremity sympathetic block [7,9,18]. Complex regional pain syndrome treated by thoracic SB showed reduced pain intensity with improved depression and quality of life [7,9]. Frequent occurrences of epidural and intercostal injections during thoracic SBs, leading to an unwanted somatic blockade, might affect the therapeutic outcome of complex regional pain syndrome.

This study included patients with lymphedema after breast cancer surgery. Our pain clinic performs thoracic SBs to manage an intractable upper limb edema occurring after breast surgery. A previous study showed reductions in arm circumferences with improved lymphedema and breast cancer questionnaire scores after thoracic SBs [19].

Our study had several limitations. In this study, skin temperature difference was measured to determine the property of thoracic SBs. However, the association between thoracic SBs, with or without inadvertent spread and skin temperature differences, was not evaluated. Further study is needed to determine whether the appearance of inadvertent spread during thoracic SB affects skin temperature or therapeutic outcome.

In addition, we did not present any technical method to reduce high incidence of inadvertent injection of thoracic SBs. Future studies on thoracic SBs, comparing new and conventional approaches, are required. Lastly, our study has some limitations due to small sample size. Further multicenter study with enough cases of thoracic SBs might present new method and has a higher impact.

In conclusion, inadvertent intercostal and epidural spreads, which lead to somatic blockade, were observed in half of the thoracic SB injections. Considering such a high incidence of inadvertent injections, injecting any neurolytic agent or diagnosing SMP should be performed cautiously.

CONFLICTS OF INTEREST

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

AUTHOR CONTRIBUTIONS

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Inadvertent spread during thoracic sympathetic ganglion block


Pneumocephalus is an extremely rare complication of dural punctures. Early diagnosis, correct management, and patient counseling promote a successful management [1]. Unlike previous blind epidural block procedures, the recent introduction of fluoroscopy has made performing epidural block safer. The need for epidural steroid injections is increasing with the growing elderly population. The development of safe interventions for pain control is especially important in elderly patients because of the high risk of complications due to multiple underlying diseases as well as generalized frailty. Herein, we report two cases of pneumocephalus following unintentional dural puncture in two elderly patients during a fluoroscopy-aided interlaminar lumbar steroid injection.

**Case Report**

We obtained written informed consent from the patients’ guardians.

**Case 1**

An 82-years-old woman (height 157 cm, weight 56 kg) presented with bilateral buttock pain. Three years prior, she received multiple injections for epidural block. Magnetic resonance imaging (MRI) of the lumbar spine revealed spondylolytic spondylolisthesis, a bulging disc, ligamentum flavum (LF) thickening, and moderate central stenosis at L4/5 (Fig. 1). On presentation, a fluoroscopy-guided epidural steroid injection was scheduled. In the prone position...
position, the injection site was disinfected and 1% lidocaine was injected. The L4/5 interspace was identified under fluoroscopy, and an 18-gauge Tuohy needle was advanced into the interlaminar space under an anterior-posterior (AP) fluoroscopic view. The needle was advanced into the epidural space under lateral fluoroscopy using the loss of resistance (LOR) technique with a 1.0 ml air-filled syringe. After checking for the negative aspiration of cerebrospinal fluid (CSF), 0.5 ml of contrast agent (Pamiray 250 Injection®, Dong Kook Pharm. Co., Korea) was injected. After examining the AP and lateral fluoroscopic images, a mixture of 0.125% ropivacaine (6 ml) and 10 mg triamcinolone was injected (Fig. 2). In the recovery room, the patient’s blood pressure was 140/60 mmHg, and her heart rate (HR) was 77 beats/min. Thirty minutes later, her blood pressure declined to 82/53 mmHg, and her HR increased to 88 beats/min. Supplement oxygen was administered using a facial mask with reservoir and intravenous fluids were started, and ephedrine (5 mg) was injected. The patient exhibited intense perspiration, and complained of a severe occipital headache (numerical rating scale [NRS] 7), dizziness and nausea. Her body temperature decreased to 35°C. The hypothermia improved 1 h after oxygen therapy was initiated and warming intervention were applied. The patient was referred to a neurologist. Neurological examinations revealed no deficits; however, pneumocephalus was suspected. Brain computed tomography (CT) scans revealed multiple locules of air in the cranial cavity and air at the velum interpositum, anterior and posterior interhemispheric fissure, supracerebellar cistern and right sylvian fissures (Fig. 3). The patient was admitted to the hospital and oxygen was administered (5 L/min) using a facial mask with a reservoir. Her headache was reduced by 50% after 24 h and she was discharged the next day. Five days after discharge, her headache had completely resolved. Subsequent physical examination at follow-up was negative for pneumocephalus.

Case 2

An 88-years-old woman (height 146 cm, weight 50 kg) presented with complaints of low back and bilateral buttock

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**Fig. 1.** Lumbar MRI of patient (case 1) shows spondylolytic spondylolisthesis, bulging disc, ligamentum flavum thickening, and moderate central stenosis in L4/5. MRI: magnetic resonance imaging.

**Fig. 2.** Fluoroscopic image of patient (case 1). (A) AP post-contrast image. (B) Lateral post-contrast image. Two images show intrathecal injection. AP: anterior-posterior.
pain as well as numbness in both lower extremities. The patient was suffering from a gait disorder which severely restricted her mobility without a wheelchair. A history of congestive heart failure and cerebral infarction was reported. The patient also had a 5-year history of lumbar nerve root and epidural blocks to manage her symptoms. MRI revealed multiple old compression fractures (T10–12, L2–4), vertebroplasty at T7, 10, 11, and L4 and spinal canal stenosis (severe central stenosis L1/2, bilateral mild foraminal stenosis T10–L1) (Fig. 4). On presentation, a fluoroscopy-guided epidural steroid injection was scheduled. In the prone position, the injection site was disinfected and 1% lidocaine was injected. The L5/S1 interspace was identified by fluoroscopy, and an 18-gauge Tuohy needle was advanced into the interlaminar space under an AP fluoroscopic view. The needle was advanced into the epidural space using the LOR technique with a 1-ml air-filled syringe though the LF and a location where the syringe would not rebound. However, CSF aspirated, and on injecting 0.5 ml of the contrast, a dural puncture was confirmed through the fluoroscopic AP and lateral images (Fig. 5). The procedure was aborted immediately. After explaining the occurrence of the dural puncture to the patient, she was sent to the recovery room. Her blood pressure was 103/61 mmHg, HR was 87 beats/min and oxygen saturation was 96%. Normal saline was infused intravenously and oxygen (5 L/min) was administered using a facial

**Fig. 3.** Axial cranial CT scan (case 1) revealing multiple locules of air in the cranial cavity and air at velum interpositum (black arrow), posterior interhemispheric fissure (black dotted arrow) suprachiasmatic cistern (white dotted arrow) and right sylvian fissure (white arrow). CT: computed tomography.

**Fig. 4.** Lumbar MRI of patient (case 2) shows multiple old compression fractures (T10–12, L2–4), vertebroplasty at T7, 10, 11, and L4 and spinal canal stenosis (severe central stenosis L1/2, bilateral mild foraminal stenosis T10–L1). MRI: magnetic resonance imaging.

**Fig. 5.** Fluoroscopic image of patient (case 2). (A) AP post-contrast image suggesting intrathecal injection. (B) Lateral post-contrast image suggesting intrathecal injection. AP: anterior-posterior.
mask with a reservoir. One hour later, she complained of severe (NRS score 5–6) bilateral temporal headache and pain on the top of her head that persisted regardless of posture changes. Tramadol administration did not reduce her headache. A case of pneumocephalus was suspected. Brain CT examination showed the presence of air at the ventricular frontal horn, anterior interhemispheric fissure, right ambient cistern, and around bilateral cavernous sinuses. The patient was admitted to the hospital after an explanation was provided to her and her guardian. After the admission, oxygen (5 L/min) was administered. Twenty-two hours later, the headache was reduced by 70%. Follow-up brain CT confirmed the reduction of the pneumocephalus. Therefore, she was discharged the next day. Follow-up 2 weeks after discharge, indicated complete resolution with no complaint of headache. Her physical examination was negative for pneumocephalus.

**DISCUSSION**

In both cases, the elderly patients described each received, a fluoroscopy-guided lumbar epidural block. However, pneumocephalus occurred following a dural puncture in each case and was resolved only after oxygen therapy. Pneumocephalus is the presence of air in the intracranial compartments such as the intraventricular, intraparenchymal, subarachnoid, subdural and epidural space of the brain. Headache due to the presence of intrathecal air, following pneumoencephalography is well reported. This procedure was widely performed between 1919 and 1970. In pneumoencephalography, CSF is aspirated by dural puncture of the lumbar spine and 35–50 ml of air is injected to visualize the ventricles and cortical status. A wide range of side effects have been reported in association with pneumoencephalography, including headache, vomiting, pyrexia, tachycardia, changes in blood pressure neck stiffness, mental confusion, and temperature disorders. Resolution of pneumocephalus after injection of a large volume of air (20–50 ml) requires 1–2 weeks.

Conservative treatments for pneumocephalus include hydration, bed rest, use of analgesics and 100% oxygen therapy. Concentrated oxygen therapy decreases the partial pressure of nitrogen in the blood with an increase in the concentration gradient. This hastens the diffusion of intracranial air into the bloodstream. The two patients described improvement with oxygen therapy.

To assess LOR, air or fluid is routinely used. Saline, a local anesthetic, and contrast are usually used in the LOR technique for epidural block. Use of air LOR (ALOR) was prevalent until the 1980s; however, because there are reported side effects associated with ALOR such as dural puncture with or without postdural puncture headache (PDPH), pneumocephalus, spinal cord and nerve root compression subcutaneous emphysema and paresthesia, practitioners prefer saline over the alternatives. However, a systematic review or randomized controlled trial have reported no difference in safety between the use of air and saline during epidural block for gynecological cases. The use of saline with LOR for epidural block in patients with chronic pain exhibited a lower incidence of pneumocephalus than ALOR; no large-scale studies have been conducted to confirm these findings.
conducted recently [4].

Verdun et al. [1] recommended the use of saline to prevent pneumocephalus. For a clinician more familiar with air injection, the study recommended using a mixture of 1–2 ml saline and 1–2 ml air. The use of saline and contrast to increase positivity has been suggested. For severe cases of central canal stenosis in the lumbar epidural block area, interlaminar (or at other levels) or bilateral transformaminal injections may be recommended. In the first case, the dural puncture occurred due to the advancement of the needle into a region with severe central canal stenosis. Because no CSF was aspirated, the practitioner did not carefully scrutinize the fluoroscopy images and continued with the procedure. In the second case, the procedure was aborted due to the confirmation of pneumocephalus. It is important to carefully observe an intrathecal injection during fluoroscopy-guided epidural block. The contrast pattern of intrathecal injection rapidly descends in the CSF with gravity and outlines the excited nerve roots on the lateral view.

There are two types of headache seen after penetration of the dura mater; CSF leakage and pneumoencephalopathy due to intrathecal air. Headaches caused by pneumocephalus, reportedly, occur s few hours after the treatment and usually continue for a few days. The patient usually recovers naturally. The headache may even occur when the patient is supine. In case of PDPH, the headache may occur 24–48 h after dural puncture, and an epidural blood patch is sometimes required. PDPH worsens depending on the sitting position [1].

Fluoroscopy-guided epidural block was attempted and failed in both patients. In normal adults, in the lumbar area, the epidural space is the largest, the LF is the thickest, and the midline gap is the smallest, enabling an easier epidural block. Zaki [5] reported the structural difference of the LF in the cadavers of older adults. Reduction of the elastic to collagen area ratio affected the spinal ligament and particularly lumbar LF ossification. Other obstacles including, increased vasculature, absence of the midline gaps, and fragmentation and rupture of the elastic fibers are reported to have occurred. Hogan [6] reported that, due to lumbar degenerative changes, loss of intervertebral disc height occurs causing buckling of the LF. This reduces the space between the posterior elements, causing the spurious process to stick together. This in turn causes needle insertion to be difficult during an epidural block. The patients in this study were above 80 years in age. The treatment was initiated at the lower level of the severe degenerative lesion of the lumbar spine. Nonetheless, due to the severe degenerative changes, pneumocephalus developed.

In elderly patients, even with the aid of fluoroscopy, dural punctures are inevitable during epidural block owing to anatomical changes in the spine. Thus, a blind epidural block for should be avoided in elderly patients. According to Table 1 [7–12], which contains reported cases of pneumocephalus, some Korean practitioners have performed blind epidural blocks. Although the practitioner may be very familiar with the technique, in blind epidural block, 30–40% of blocks are performed incorrectly [13]. We would like to emphasize that, careful identification of the location of the epidural space is strongly recommended to ensure safety. This is particularly true in elderly patients, during an epidural block using the LOR technique guided by fluoroscopy and contrast injection [14]. In addition, even when CSF is not aspirated when performing epidural blocks,

Table 1. Pneumocephalus Cases Resulting from Epidural Block for Pain Control in the Korean Literatures

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year of publication</th>
<th>Age of patient</th>
<th>Epidural LOR technique (air or saline/volume)</th>
<th>Procedure level (cervical/thoracic/lumbar)</th>
<th>Fluoroscopy or blind</th>
<th>Symptom/onset time</th>
<th>Pneumocephalus resolution in CT</th>
<th>Duration of symptom resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Han et al. [7]</td>
<td>1996</td>
<td>38</td>
<td>Air/9 ml</td>
<td>Lumbar 3/4 interlaminar</td>
<td>Blind</td>
<td>Headache/1 h</td>
<td>Unknown</td>
<td>4 days</td>
</tr>
<tr>
<td>Ahn et al. [8]</td>
<td>2012</td>
<td>70</td>
<td>Unknown/unknown</td>
<td>Lumbar 3/4 interlaminar</td>
<td>Unknown</td>
<td>Headache, nausea/</td>
<td>5 days</td>
<td>3 days</td>
</tr>
<tr>
<td>Kim et al. [9]</td>
<td>2012</td>
<td>68</td>
<td>Air/8 ml</td>
<td>Lumbar 4/5 interlaminar</td>
<td>Blind</td>
<td>immediately after</td>
<td>Unknown</td>
<td>1 day</td>
</tr>
<tr>
<td>Kim et al. [11]</td>
<td>2015</td>
<td>54</td>
<td>Air/1 ml</td>
<td>Lumbar 4/5 interlaminar</td>
<td>Fluoroscopy</td>
<td>Headache/4 h</td>
<td>16 days</td>
<td>21 days</td>
</tr>
<tr>
<td>Chung et al. [12]</td>
<td>2017</td>
<td>58</td>
<td>Air/unknown</td>
<td>Lumbar 4/5 interlaminar</td>
<td>Blind</td>
<td>Headache and seizure/5 min</td>
<td>Unknown</td>
<td>11 days</td>
</tr>
</tbody>
</table>

LOR: loss-of-resistance, CT: computed tomography.
contrast injection should be used to confirm the subdural or subarachnoid injection, intravascular injection, and facet injection [15].

In conclusion, lumbar epidural block should be performed under fluoroscopic guidance in elderly patients with severe lumbar degenerative changes. The physician should be aware of the increased possibility of dural punctures due to anatomical changes. The use of saline is recommended for the LOR technique, and contrast injections should be used together with the LOR technique locate epidural space. If a dural puncture does occur, the patient should be carefully monitored to determine whether pneumocephalus has developed.

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CONFLICTS OF INTEREST

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

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In December 2019, a novel coronavirus was first identified in Wuhan, China, and the number of infected individuals has since exponentially increased worldwide [1]. The first case in South Korea was reported on January 20, 2020 [2]. The coronavirus disease 2019 (COVID-19) is characterized by a wide range of symptoms, from asymptomatic presentation to mild symptoms, including fever and cough, to severe symptoms, such as acute respiratory distress syndrome, septic shock, and death [1,2]. Studies have shown that ventilatory care is required for 2.3–4.0% of patients with COVID-19 [3,4]. Patients with severe disease are likely to become “super-spreaders,” who shed higher viral loads of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3]. The exact route of transmission is still unclear, although COVID-19 is known to be transmitted through respiratory droplets and contact transmission. Moreover, a large number of secondary infections have been observed in the hospital setting, similar to those seen with the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [1].

Therefore, when a COVID-19 patient requires surgery, not only are the medical staff required to wear personal protective equipment (PPE), but also additional facilities, such as a negative-pressure operating room, must be available. During general anesthesia of the intubated patient, the risk of aerosol propagation is increased during the con-
necting and disconnecting of the anesthetic breathing system to the patient’s endotracheal tube as well as with endotracheal suctioning. Furthermore, the infectious material can spread through the endotracheal tube during transportation; thus, special care must be taken for infection control during anesthesia and when transporting the patient.

To date, there are only a few reports on the anesthetic management of patients with severe COVID-19. Herein, we report our experience with anesthetic management and infection control for a COVID-19 patient under ventilatory care who underwent an exploratory laparotomy for a suspected duodenal ulcer perforation. Written informed consent for publication was obtained from the legal guardian of the patient.

**CASE REPORT**

A 73-year-old man who was confirmed to have COVID-19 was hospitalized for treatment. The patient had underlying comorbidities, including hypertension and diabetes mellitus, had undergone percutaneous coronary intervention (PCI) two years earlier, and had been taking 100 mg aspirin daily. The patient tested positive for SARS-CoV-2 by real-time reverse transcription polymerase reaction (RT-PCR) on February 27, 2020, and was admitted to the Pohang Medical Center. At admission, the patient presented with a fever of 37.7°C and cough, which are typical symptoms of COVID-19, and chest radiography revealed ill-defined, hazy, and streaky density in both the lungs (Fig. 1A). Therefore, oral hydroxychloroquine treatment was initiated; however, due to symptoms of pneumonia accompanied by hypotension and melena, the patient was transferred to the Samsung Medical Center for further management. After his vital signs had been stabilized, the patient remained under observation without additional treatment. However, on Day 1 of admission at the Samsung Medical Center, the patient expelled a large quantity of melena and developed hypotension and tachycardia along with a peripheral oxygen saturation (SpO₂) of approximately 80%, and his hemoglobin level had decreased to 6.3 mg/dl.

The patient underwent blood transfusion and endotracheal intubation as well as the insertion of arterial catheter and central venous catheter. The patient was evaluated using esophagogastroduodenoscopy (EGD), which revealed a duodenal ulcer without active bleeding. The patient was at risk of re-bleeding; however, computed tomography (CT) and embolization for COVID-19 patients were not possible at the Samsung Medical Center at the time. Therefore, the patient was transferred to our hospital where a COVID-19 patient care environment had been prepared. As the patient was at a high risk of re-bleeding, the patient immediately underwent endoscopic hemoclipping and embolization. Surgery was considered; however, given the patient's condition and the stress of invasive surgery for the patient, we decided to first perform endoscopy and embolization.

One day after hemoclipping and embolization, the patient complained of abdominal pain, and the follow-up
chest X-ray revealed subphrenic free air, an indication of pneumoperitoneum. Based on his endoscopic findings, perforation of the duodenal ulcer was suspected, and emergency surgery was planned. Despite a fever of 37.8°C, the patient’s preoperative vital signs were stable; electrocardiography (ECG) showed a normal sinus rhythm, and chest radiography revealed peripheral lung consolidation, which suggested aggravated pneumonia (Fig. 1B). Blood analysis revealed hemoglobin and C-reactive protein levels of 11.1 mg/dl and 103 mg/L, respectively. Arterial blood gas analysis revealed the following: pH, 7.48; pCO₂, 33.0 mmHg; pO₂, 173 mmHg; bicarbonate, 24.7 mmol/L; and saturation, 99.4% under mechanical ventilation of synchronized intermittent mandatory ventilation mode with a fraction of inspired oxygen of 0.35. The patient was on a continuous infusion of remifentanil for sedation and intravenous antibiotics, such as tazobactam and piperacillin, to treat the pneumonia.

The patient tested positive for SARS-CoV-2 again when RT-PCR of his nasopharyngeal and oropharyngeal swabs was performed on March 3, 2020. Since the patient presented with severe pneumonia symptoms and persistent detection of the SARS-CoV-2 virus, the risk of nosocomial transmission to the medical staff during endotracheal intubation and mechanical ventilation was high. Therefore, the medical staff who participated in the surgery and anesthesia wore PPE, and the surgery was performed in a negative-pressure operating room. The anesthesiologist and nurse inside the main operating room wore liquid-resistant protective suits, double gloves, boots, shoe covers, and aprons with a powered air-purifying respirator (PAPR) hood (Fig. 2), whereas the staff outside the main operating room wore N95 masks, anteroposterior (vinyl) gowns, and gloves. During the preparations for surgery and anesthesia, the assistant staff, who wore protective suits, double gloves, boots, shoe covers, aprons, N95 masks, and face shields, planned and controlled the patient’s path to the operating room.

After the preparations had been completed, the sedated patient was transferred to the operating room and connected to a portable ventilator equipped with a high-efficiency particulate absorbing (HEPA) filter in the expiratory circuit by medical staff wearing the same PPE who controlled patient’s path. An anesthesiologist and a nurse stood by in the operating room, and the patient was taken over from the accompanying medical staff by the surgeon in the waiting room and subsequently transferred to the operating room through the anteroom (Fig. 3). An assistant surgeon followed the patient and sterilized the site where the cart had moved on the floor by spraying a diluted 1:100 solution of bleach (NaClO 4%). After the patient moved onto the operating table, the stretcher used for patient transfer was similarly disinfected with a diluted 1:100 solution of bleach in the operating room and was again disinfected when it was moved into the anteroom.

Invasive arterial blood pressure (ABP), ECG, heart rate, SpO₂, and bispectral index monitoring were commenced in the operating room; the patient’s vital signs were stable. After clamping the endotracheal tube, the tube was detached from the portable ventilator and connected to the anesthesia machine, which had a HEPA filter in the expiratory circuit, and end-tidal carbon dioxide monitoring was started. General anesthesia was induced by 0.5 mg/kg.
the anteroom where the item was collected by the medical staff in the main operating room once the outside nurse had left the anteroom. An arterial blood sample obtained during surgery was sent out of the operating room in the same way for analysis. The operation lasted 120 min, without any notable events, and the perforated ulcer was found at the expected site. The operative procedure included pyloric exclusion with primary closure of the perforation and formation of a gastrojejunostomy.

The patient was intravenously injected with 0.07 mg/kg midazolam and 0.3 mg/kg rocuronium for sedation during transfer to the ward, while maintaining the intubation. Prior to the detachment of the anesthesia machine from the patient’s tube, closed in-line tracheal suction was performed. Subsequently, the anesthesiologist switched the ventilator to manual mode, opened the adjustable pressure-limiting valve, and clamped the tracheal tube. The patient was transferred to a stretcher cart that was placed in the anteroom. Monitoring of ECG, SpO$_2$, and ABP continued, and 10 L/min of oxygen was supplied through an Ambu bag with a HEPA filter. The patient was transferred to the waiting room after passing through the anteroom and was finally moved to the intensive care unit (ICU) by the surgeon who had, in the meantime, changed the external gloves and footwear (Table 1).

The patient was continuously monitored in the ICU. Antibiotics were administered intravenously, and hydroxychloroquine was administered via L-tube to treat pneumonia. No surgical complications, such as re-bleeding or perforation of the surgical site, were observed. However, despite continued pneumonia treatment up to the fifth postoperative day, elevated C-reactive protein and fever between 37.3 and 38.8°C persisted, and the patient consistently tested positive for SARS-CoV-2 by RT-PCR. From chest radiography, increased pneumonic infiltration and pleural effusion were observed (Fig. 1C). Other vital signs were stable, except for body temperature. On the sixth postoperative day, the patient developed a fever of 39.5°C, and hypotension was observed. The administration of fluid and norepinephrine was initiated after the pulmonary medicine staff diagnosed septic shock that developed due to fail-

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**Fig. 3.** Overall design of the negative-pressure operating room. Negative pressure is maintained only in (1) and (2), and when the doors of these rooms are opened, the negative pressure is temporarily lost. Square dotted arrow: pathway for entry of medical staff and patients; round dotted arrow: pathway for the patient’s exit, solid arrow: pathway for the exit of medical staff who do not participate in the patient transfer, overlaid arrow: pathway for medical staff who participate in the patient transfer after changing PPE that was worn during surgery. (1) main operating room, (2) anteroom, (3) waiting room, (4) doffing area, (5) buffer area. PPE: personal protective equipment.
ure to control the infection despite the continuous treatment for pneumonia. Despite persistent resuscitation, the patient expired on the seventh postoperative day.

**DISCUSSION**

We described the case of an emergency exploratory laparotomy under general anesthesia for suspected duodenal perforation in a patient with a highly infectious respiratory viral disease. For COVID-19 patients, avoiding surgery whenever possible is the best option for the safety of the patient and the medical staff [4,5], particularly when such patients require ventilatory support, as they are more likely to shed more of the infectious agent [3]. However, peptic ulcer perforation is a potentially lethal surgical emergency, wherein the mortality rate increases with every hour of surgical delay [6]. Therefore, we decided to perform surgery despite the infection risk. This patient had stopped taking aspirin for 2 days, which he had been taking every day since undergoing PCI 2 years earlier, and his general condition was exacerbated by aggravated pneumonia secondary to COVID-19. Considering the general condition of the patient and risk of intraoperative bleeding and postoperative re-bleeding, and due to the concern about infecting medical staff with COVID-19, our multidisciplinary team opted to perform an exploratory laparotomy for pyloric exclusion with primary repair of the perforated site and gastrojejunostomy, instead of performing laparoscopic surgery, to minimize the need for further invasive treatment. Although regional anesthesia is preferred over general anesthesia given the infectivity of COVID-19 [4], this operation was performed under general anesthesia because it was difficult to obtain sufficient motor and sensory blockade for the surgical site through regional anesthesia, and the patient was already intubated and receiving ventilatory support.

In this patient, peptic ulcer perforation was diagnosed using portable chest radiography. When a chest X-ray is used to diagnose peptic ulcer perforation, it may not show the exact cause of pneumoperitoneum, as it has only 75% sensitivity [6]. Abdominal CT has a greater sensitivity (up to 98% sensitivity) and is more valuable for differential diagnosis [7]. Nevertheless, we suspected ulcer perforation based on the detection of a duodenal ulcer in the preoperative EGD and subphrenic free air on the chest X-ray. As the patient’s clinical findings supported the portable X-ray findings, and given the time and procedure required for infection control and transport, emergency surgery was immediately performed without additional CT. It is difficult to control the spread of infection when transferring COVID-19 patients; therefore, tests that require patient transfer demand time and resources, which may limit information gathering prior to anesthesia and may delay emergency surgery. As a result, anesthesiologists need to balance the need for preoperative examination and the urgency of the operation.

According to the recommendations of anesthesia management for COVID-19 patients, surgery on COVID-19 patients should be performed in a negative-pressure operating room, with the use of PPE, to prevent the infection of medical staff [3,4]. When this patient was treated, no previous COVID-19 patient had undergone surgery in Korea, and no surgical protocol had been established for COVID-19 patients. Our hospital had established a surgical protocol for

**Table 1. Timeline of Patient with Confirmed SARS-CoV-2**

<table>
<thead>
<tr>
<th>Time</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>February 28, 2020</td>
<td>The patient is admitted to the Pohang Medical Center after confirmation of COVID-19.</td>
</tr>
<tr>
<td>March 1, 2020</td>
<td>The patient is transferred to the Samsung Medical Center for intensive care as pneumonia progresses.</td>
</tr>
<tr>
<td>March 2, 2020, 18:35</td>
<td>The patient undergoes transfusion, endotracheal intubation, and central venous catheter insertion after showing large amounts of melena with hypotension and decreased peripheral oxygen saturation.</td>
</tr>
<tr>
<td>March 3, 2020, 01:00</td>
<td>The patient is evaluated using esophagogastroduodenoscopy at the Samsung Medical Center.</td>
</tr>
<tr>
<td>March 3, 2020, 13:25</td>
<td>The patient is transferred to our hospital.</td>
</tr>
<tr>
<td>March 3, 2020, 18:40</td>
<td>The patient undergoes endoscopic hemoclipping and embolization at our hospital.</td>
</tr>
<tr>
<td>March 4, 2020, 17:35</td>
<td>The patient complains of abdominal pain and subphrenic free air is observed from chest radiography.</td>
</tr>
<tr>
<td>March 4, 2020, 18:35</td>
<td>The multidisciplinary team discusses the patient’s surgical plan and transportation plan.</td>
</tr>
<tr>
<td>March 4, 2020, 20:30</td>
<td>Exploratory laparotomy is started.</td>
</tr>
<tr>
<td>March 4, 2020, 22:30</td>
<td>Exploratory laparotomy is completed.</td>
</tr>
<tr>
<td>March 4, 2020, 23:00</td>
<td>The patient is transferred from negative-pressure operating room to intensive care unit while maintaining tracheal intubation.</td>
</tr>
</tbody>
</table>

MERS-CoV patients during the MERS epidemic in 2015; thus, we planned this surgery based on our MERS protocol and surgical experience with MERS patients. According to this protocol, surgery on MERS-CoV patients should be performed in a negative-pressure isolation room, and all healthcare workers involved in aerosol-generating procedures should wear PPE.

In our hospital, every operating room has an individual ventilation system with a HEPA filtration [8]. The airflow inside the operating room forms a laminar flow from the ceiling and escapes through four prefilters located on the wall, protecting the surgical field from airflow. The operating room was maintained at 12–15 air changes per hour and at a negative-pressure between –2.5 Pa and –20 Pa. To prevent airborne infection, the operating room needs to be maintained at a continuous negative air pressure below –2.5 Pa [9]. Negative-pressure operating rooms in other hospitals often have an anteroom in front of the main operating room, through which medical staff must pass when entering and exiting the operating room [4,10]. If the anteroom is used when medical staff members need to be replaced, for instance, due to prolonged surgery, the room needs to be sterilized, and the space cannot be used while replacing the medical staff and disinfecting the anteroom. In contrast, our main operating room has an additional exit (separate from the anteroom) with a dusting area and shower booth leading to its entrance, so that medical staff can leave the operating room without passing through the anteroom (Fig. 3). With this additional passageway, the anteroom can be kept clean throughout the surgery, allowing external staff to deliver additional equipment via the anteroom.

The anesthesiologist and surgeons who were involved in the surgery all wore PPE, which included a PAPR. An N95 mask may seal leaks and increase resistance to breathing, while a PAPR is comfortable to wear for a relatively long period. However, the disadvantages of a PAPR include the impossibility of auscultation, interference of communication between medical staff due to fan noise, and limited battery power [5], which we experienced during this surgery. There is no evidence that wearing a PAPR during aerosol-generating procedures reduces viral transmission secondary to airborne spread, compared to wearing an N95 mask [3]. Therefore, anesthesiologists must take this into consideration when wearing a PAPR and should fully discuss the anesthesia and surgery plan with the medical team ahead of time to minimize the difficulties that could be caused by communication error.

There was a risk of aerosol propagation as this patient was transferred while maintaining tracheal intubation. In previous cases associated with COVID-19 and MERS, no patient was transferred while maintaining tracheal intubation [11–13]. Our patient’s transfer was conducted after passage control, with the accompanying staff wearing PPE. To prevent unexpected hospital-acquired infection, a HEPA filter was added to the expiratory circuit of the portable ventilator when the patient entered the operating room, and it was applied between the Ambu bag and the tracheal tube when the patient left the room. Recommendations for the transportation of COVID-19 patients state that HEPA filters need to be added to the Ambu bag or portable ventilator [14]. Prior to transfer, it is advisable to sedate the patient using sedatives and neuromuscular blockade agents to prevent aerosol propagation from coughing or spontaneous breathing. Additionally, a dental mask was applied to cover the patient’s mouth. Such preventive measures are considered to be effective for infection control during patient transfer.

Contaminants in the air of the operating room and surfaces of the anesthesia machine and monitoring device should be reliably disinfected after the anesthesia. In our case, after the surgery was completed, the negative-pressure operating room was closed and room ventilation was performed for an hour. When room ventilation is performed for 35 min under the condition that 12 air changes per hour are satisfied, 99.9% of aerosol type contaminants in the operating room are removed [8,9]. The surface of the operating room and surfaces of the devices used for anesthesia were disinfected with a diluted 1:100 solution of bleach, and decomposable parts of the anesthesia machine, such as bellows and adjustable pressure-limiting valves, were sterilized with ethylene oxide. Replaceable items, such as carbon dioxide absorbent and breathing bag, were discarded. In our case, the sampling line and water trap were discarded because the sampling gas from the patient was collected before passing through the HEPA filter. In addition, we considered that the aerosol generated from the COVID-19 patient could contaminate the inside of the anesthesia machine even after passing through the HEPA filter of the expiratory circuit and the filter inside the water trap; the anesthesia machine was covered with vinyl and unused for more than 72 h. SARS-CoV-2 showed no viability after 72 h on surfaces of plastic or steel [15]. Up to 2 months after surgery, medical staff who participated in this...
surgery showed no significant signs or symptoms of infection, and no nosocomial infections were reported. As COVID-19 spreads rapidly worldwide, it is likely that more cases of severe COVID-19 patients requiring surgery will be encountered. Therefore, clinical guidelines for anesthesia management and infection control during the transportation of severe COVID-19 patients should be established. We hope that this case report will contribute to the establishment of clinical guidelines for the surgical management of patients with COVID-19 and the design of negative-pressure operating rooms.

**CONFLICTS OF INTEREST**

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

**AUTHOR CONTRIBUTIONS**

Project administration: Mi Jung Yun. Writing - original draft: Seong Su Lee. Supervision: Ji Hyun Park, Gunn Hee Kim, Mi Young Kwon, Hee Yeong Kim, Yeon Jin Moon, Su Jin Kim.

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Morbidly obese patients tend to desaturate faster than non-obese patients due to decreased functional residual capacity, increased O$_2$ consumption, and increased shunt flow [1]. Airway management is more challenging in morbidly obese patients because of the likelihood of a difficult airway [2].

Transnasal Humidified Rapid Insufflation Ventilatory Exchange (THRIVE) has been widely used outside of the operating room, but its use in the operating room is now also increasing [3]. Optiflow® (Fisher & Paykel Healthcare, New Zealand), a new commercial THRIVE device, supplies warmed, humidified, high flow O$_2$ (~70 L/min) through a nasal cannula. It can be applied over the entire range of anesthesia, from preoxygenation [4,5] to post-extubation [6]. Optiflow® can also be safely applied in morbidly obese patients [7] to improve oxygenation and respiratory mechanics.

Despite the benefits of THRIVE, the use thereof through a nasal cannula is limited in situations such as nasal obstruction, epistaxis, and recent nasal trauma or surgery [8]. And in the case of steroid injection into the region of subglottic stenosis as adjunctive treatment after dilatation [9], the transoral approach with rigid laryngoscope is limited due to severe gag reflex.

Therefore, the transnasal approach is commonly performed with a laryngoscope with a flexible working channel. The transnasal approach may limit O$_2$ supply through a nasal cannula. In such cases, O$_2$ can be supplied through the oral route. We experienced a morbidly obese patient who received serial transnasal steroid injections due to...
subglottic stenosis using a standard facial mask and THRIVE through the oral route under general anesthesia with spontaneous breathing. We report our experience and introduce the use of THRIVE through the oral route as an alternative for supplying $O_2$.

**CASE REPORT**

This study was approved by the Institutional Review Board of Soonchunhyang University Bucheon Hospital (IRB No. 2020-02-026-001). And written informed consent, included the consent to publish images, was obtained from the patient in this study.

The patient was a 37-year-old man (148 kg, 183 cm, body mass index [BMI] 44.2 kg/m$^2$) with a history of tracheostomy due to hypertensive intracranial hemorrhage that occurred 4 years ago. He was diagnosed with grade I tracheal stenosis above the tracheostomy site 2 years ago. Despite conservative treatment, dyspnea developed and the patient underwent endoscopic tracheal dilatation under general anesthesia. Baseline peripheral capillary $O_2$ saturation ($SpO_2$) was 94% and Cormack-Lehane grade was 3 at the time of intubation. Surgery was performed using the intermittent apnea technique with extubation, and a total of six apnea events occurred, with a mean duration of apnea was 147 s. The lowest $SpO_2$ was 64%, and $SpO_2$ recovered to 96-98% after manual ventilation via endotracheal tube. The patient had been treated conservatively after balloon dilation with portable $O_2$ at home. Dyspnea worsened again 1 year ago, despite $O_2$ therapy, and serial fiberoptic steroid injections to the subglottic stenosis site were planned. In our hospital, fiberoptic steroid injections are usually performed according to the following steps. Topical anesthesia at nostrils is followed by sedation, applied by surgeon. The fiberscope is inserted through the nostril, and the glottis and lesions are sprayed with additional local anesthetics. Then, the lesion is injected with steroid. The otolaryngologist consulted us for safe sedation and monitoring due to the possibility of emergency caused by airway edema or airway obstruction. Considering the patient’s general condition, symptoms, and experience of previous surgery, we decided to perform the operation under general anesthesia with spontaneous breathing in preparation for airway manipulation, because general anesthesia using the intermittent apnea technique could limit the view of surgical field and damage the larynx and subglottic lesions.

On entering the operating room, the patient was placed in a 30° sitting position for the first steroid injection. Standard American Society of Anesthesiologists monitoring (non-invasive blood pressure [NIBP], electrocardiogram, and $SpO_2$) and bispectral index (BIS) monitoring were applied. The baseline vital signs were as follows: BP, 105/52 mmHg; heart rate (HR), 66 beats per minute (beats/min); $SpO_2$, 95%. Oxygenation was applied at 6 L/min $O_2$ through a standard facial mask. End-tidal $CO_2$ ($EtCO_2$) was monitored continuously by capnography to confirm self-respiration. Dexmedetomidine was used for sedation. After delivering a loading dose of 1 $μg$/kg over 10 min, continuous infusion of 0.6 $μg$/kg/h was maintained. During infusion of the loading dose, the $EtCO_2$ level decreased gradually until apnea was induced. An oral airway was inserted and the jaw-thrust maneuver was applied to maintain airway patency and support self-respiration. After confirming that the patient was unresponsive to verbal commands and tactile stimulus, the surgery was started while self-respiration was maintained. The surgeon requested lowering of the facial mask so that it would not interfere with the procedure and applied topical anesthesia by packing gauze soaked with Bosmin® (0.1% epinephrine) and Beracaine® (10% lidocaine) into both nostrils. The fiberscope was passed through the nostril to access the glottic and subglottic lesions, and additional 2% lidocaine was sprayed around glottis and lesions, and 3 ml of tamcetone® (Triamcinolone 40 mg/ml) was then injected. The procedure was interrupted by bag-valve-mask ventilation because $SpO_2$ fell to 86%. After ventilator assistance for 117 s, $SpO_2$ recovered to 96%. During surgery, HR remained within 20% of the baseline, but BP increased by more than 20% of the baseline. However, systolic BP remained below 160 mmHg, so no additional drug administration was necessary. The value of BIS was maintained between 55 and 80. The total surgery time was 20 min and the total anesthesia time was 40 min. The patient was discharged after 1 day of monitoring in the Intensive Care Unit (ICU), without dyspnea or complications.

Dyspnea improved noticeably, but on physical examination, grade II subglottic stenosis and stridor remained, thus necessitating a second steroid injection 1 month later. Based on our previous experience, we considered that there was a need to improve oxygenation during the procedure, so we decided to apply Optiflow®. In the same manner as in the first operation, the patient was placed in the 30° sitting position, and standard American Society of Anesthesiologists and BIS monitoring were applied. Baseline vital signs were as follows: BP, 102/58 mmHg; HR, 70 beats/
min; and SpO$_2$ 94%. O$_2$ (100% warmed, humidified) was supplied through a nasal cannula at a rate of 30 L/min for preoxygenation. The patient tolerated this well, without any complaints. Dexmedetomidine was used for sedation at the same dose as before. Once the patient was unconscious, the O$_2$ flow rate was raised to 70 L/min. EtCO$_2$ was monitored by placing the EtCO$_2$ sampling line at the nostril next to the Optiflow® nasal cannula; however, a low value was obtained, so we could only confirm self-respiration by monitoring the shape of the waveform (Fig. 1A). Topical anesthesia was applied by packing gauze into both nostrils. This disturbed the O$_2$ supply through the Optiflow® nasal cannula; therefore, we inserted an oral airway to maintain airway patency, and the Optiflow® nasal cannula was transferred to the opening of the oral airway. The EtCO$_2$ line was also transferred to the opening of the oral airway, but it still showed a low value; thus, only the shape of waveform was monitored (Fig. 1B). SpO$_2$ was maintained at 98–100%, and no intervention, such as mask ventilation or jet ventilation, was required during surgery. Despite self-respiration, there was a drop in SpO$_2$ to 86% (Fig. 1C) due to O$_2$ leakage; the Optiflow® nasal cannula dislocated from the airway opening. After fixing the nasal cannula to the airway with plaster (Fig. 2), SpO$_2$ immediately recovered to 99% and no additional desaturation events occurred. The vital signs were stable within 20% of baseline. Additional bolus of midazolam was injected to prevent the event of awareness because the value of BIS was maintained between 70 and 79 when the procedure was performed; 1mg for oral airway insertion, 2 mg for gauze packing into both nostrils. During the operation, the value of BIS was well maintained between 35 and 50, and spontaneous breathing was generally maintained well. The patient endured
the surgical stimuli without coughing and movement throughout entire operation. The total operation time was 15 min and total anesthesia time was 40 min. The surgeon had prepared jet ventilation because of the experience during the previous surgery, but ultimately did not use it; thus, the surgeon was highly satisfied with THRIVE. After the surgery, the patient was transferred to the ICU. Arterial Blood Gas Analysis (aBGA) was performed after arrival in the ICU; partial pressure of O$_2$, 94 mmHg; partial pressure of CO$_2$ (PaCO$_2$), 49 mmHg; pH, 7.30; bicarbonate, 21.3 mEq/L. The patient was discharged after 1 day of monitoring without complications.

**DISCUSSION**

We confirmed the effectiveness of THRIVE through the oral route in a morbidly obese patient receiving steroid injections due to subglottic stenosis. Some patients may be contraindicated for THRIVE through the nasal route, and a nasal cannula can prevent manipulation of the fiberscope during trananasal approach. In our case, it was impossible to supply O$_2$ through a nasal route due to nasal packing, so we used the oral approach using an oral airway. Heard et al. [10] reported that oxygenation through a Ring-Adair-Elwyn (RAE) tube placed in buccal region results in significantly less desaturation in patients with a BMI of 30–40 kg/m$^2$. Achar et al. [11] reported that oxygenation through a nasopharyngeal catheter is better than through nasal prongs. These results were based on the distance from the O$_2$ supply outlet to the laryngeal inlet being reduced, such that O$_2$ was effectively delivered to the inlet [11]. In our case, high O$_2$ flow might be delivered well by reducing the distance to the laryngeal inlet through the oral airway as mentioned above. Also there was a desaturation event occurred due to dislocation of the THRIVE nasal cannula from the airway opening. Toner et al. [12] reported desaturation due to obstruction of an RAE tube. Therefore, it is important to note that patency of airway and the O$_2$ supply device must be maintained.

EtCO$_2$ monitoring is necessary to confirm self-respiration and CO$_2$ accumulation. However, because EtCO$_2$ monitoring is limited when using THRIVE, alternative option for CO$_2$ monitoring is essential. The rate of increase in EtCO$_2$ is lower in the case of THRIVE with spontaneous breathing [13] than THRIVE with apneic oxygenation [14]. In our case, postoperative aBGA showed that PaCO$_2$ was 49 mmHg, which was not a significantly increase. Several studies have reported a difference between EtCO$_2$ and PaCO$_2$ over time when using THRIVE, but a good correlation between PaCO$_2$ and transcutaneous CO$_2$ (tcCO$_2$) has also been reported [14,15]. Therefore, it is reasonable to consider tcCO$_2$ monitoring when using THRIVE. The lack of CO$_2$ monitoring through tcCO$_2$ may be limitation in our case.

Our first attempt using a facial mask led to frequent desaturation events. However, our second attempt, using the THRIVE through the oral route, resulted in stable O$_2$ saturation. The effectiveness of our technique cannot be confirmed based on only one case. Thus, further investigations are needed to determine whether supplying O$_2$ through the oral route using THRIVE is comparable to supplying O$_2$ through a nasal cannula. However, our experience demonstrates the possibility of applying THRIVE through the oral route.

In conclusion, THRIVE may be beneficial in morbidly obese patients undergoing upper airway surgery under general anesthesia with spontaneous breathing. As in our case, in cases where applying THRIVE through a nasal cannula is difficult, effective oxygenation can be achieved by application through the oral route.

**CONFLICTS OF INTEREST**

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

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**REFERENCES**


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

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

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

4. Protection of human and animal rights

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

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

5. Registration of the clinical research

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

6. Reporting guidelines

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

7. Author and authorship

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

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

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

8. Plagiarism and duplicate publication

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

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

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

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

IV. Manuscript Preparation

APM recommends compliance with some or all of the following guidelines (www.equatornetwork.org/library).
- CONSORT for reporting of randomized controlled trials (http://www.consort-statement.org)
- STARD for reporting of diagnostic accuracy studies (http://www.stard-statement.org)
- STROBE for reporting of observational studies in epidemiology (http://www.strobe-statement.org)
- PRISMA for reporting of systematic reviews (http://www.prisma-statement.org)
- MOOSE for reporting of observational studies (http://www.emgo.nl/kc/reporting-your-study-results-in-a-scientific-article)
- GLOBAL ADVANCES in Health and Medicine for reporting of clinical cases (http://www.gahmj.com)

1. Word processors and format of manuscripts

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

2. Abbreviation of terminology

Abbreviations should be avoided as much as possible. When they are used, full expression of the abbreviated words should be provided at the first use, with the abbreviation following in parentheses.
   Ex) target controlled infusion (TCI)
After that, “TCI” can be used instead of “target controlled infusion.” Common abbreviations may be used, however, such as DNA. Abbreviations can be used if they are listed as a MeSH subject heading (https://www.ncbi.nlm.nih.gov/mesh).

3. Word spacing

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

4. Citations

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

5. Arrangement of manuscript

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

6. Organization of manuscript

1) Clinical or experimental research
   (1) Cover page (upload separately)
   ① Title
      Title should be concise and precise. The first word should be capitalized. Drug names in the title should be written with generic names, not brand names. For the title, only the first letter of the first word should be capitalized.
      Ex) Effect of smoking on bronchial mucus transport velocity under total intravenous anesthesia ·········· [○]
      Ex) Effect of Smoking on Bronchial Mucus Transport Velocity under Total Intravenous Anesthesia ·········· [×]
      Provide drug names as generic names, not product names.
      Ex) In CPR, Isosorbide Dinitrate is, ·········· [○]
      Ex) In CPR, Isosorbide Dinitrate (Isoket®) is, ·········· [×]
      Ex) In CPR, Isoket® is, ·········· [×]
   ② Running title
      A running title of no more than 40 characters, including letters and spaces in Korean, or 10 words in English, should be provided. If this title is inappropriate, the Editorial Board may revise it.
      Ex) Kim et al. [1]
   ③ Author information
      First name, middle initial, and last name of each author, with their highest academic degree(s) (M.D., Ph.D., etc.), and institutional affiliations; make sure the names of and the order of authors as they appear on the Title Page and entered in the system match exactly.
   ④ Previous presentation in conferences
      Title of the conference, date of presentation, and the location of the conference may be described.
   ⑤ Funding statement
      Disclosure of all financial support for the work, including departmental or institutional funding/support.
   ⑥ Conflicts of interest
      Any conflicts of interest for any or all authors within the 36 months of submission. If no competing interests, please add the following statement: “The authors declare no competing interests.” If any of these elements are not applicable to your submission, write “not applicable” after the number and topic; for example, “Prior Presentations: Not applicable.”
   (2) Manuscript
   ① Title and Running title (without author information)
      It should be the same as the Cover page.
   ② Abstract
      All manuscripts should contain a structured abstract that is written only in English. Authors should provide an abstract of no more than 250 words. It should contain 4 subsections: Background, Methods, Results, and Conclusions. Citation of references is not
permitted in the abstract. A list of key words at least 4, with a maximum of 10 items, should be included at the end of the abstract. Key words should be selected from MeSH (https://www.ncbi.nlm.nih.gov/mesh), and these should be written in small letters with the first letter capitalized. Separate each word with a semicolon (;), and include a period (.) at the end of the last word. Ex) Keywords: Carbon dioxide; Cerebral vessels; Oxygen; Spinal analgesia.

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

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

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

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

• Machines and equipment
Provide model name and manufacturer’s name, and country. Do not put “.” between words when writing the names of countries.
Ex) U.S.A. [×], USA [O]
For drug names, use generic names. If a brand name should be used, insert it in parentheses after the generic name. Provide® or ™ as a superscript and the manufacturer’s name and country.
• Ions
Ex) Na⁺[O], Mg²⁺[O], Mg²⁺[×], Mg²⁺[×]
Ex) Premedicated magnesium [O]
Ex) Premedicated Mg²⁺ [O]

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

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

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

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

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

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

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

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

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

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

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

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

7 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.

8 Acknowledgments
Persons or institutes that contributed to the manuscript but not sufficiently to be coauthors may be recognized. Financial support, including foundations, institutions, pharmaceutical and device manufacturers, private companies, or intramural departmental sources, or any other support, should be described.

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

• The format for references follows the descriptions below. Otherwise, it follows the NLM Style Guide for Authors, Editors, and Publishers (Patrias, K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling, DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007 [updated 2015 Oct 2; cited Year Month Day]. Available at: www.ncbi.nlm.nih.gov/books/NBK7256/).
• If necessary, the Editorial Board may request original documents for the references.
• Six authors can be listed. If there are more than 6 authors, only list 6 names with “et al.”
• Provide the start and final page numbers of the cited reference.
• Abstracts of conferences may not be included in the references. The American Society of Anesthesiologists (ASA) refresher course lecture is not acceptable as a reference.
• Description format
  A. Regular journal

B. Monographs
  - If reference page is only 1 page, mark ‘p’
  - Note if it is beyond the 2nd edition.
  - Translated documents cannot be used as references. The original documents should be provided as references.

C. Chapter
  Any separate author of a chapter should be provided.

D. Electronic documents

E. Online journal article

F. Advance access article

Tables
• Only one table is to be drawn per page in the order cited in the text.
• The title of the table is to be in English and written at the top of the table in the form of a phrase.
• Words in the table excluding the title should use capital letters for the first word, and the following words are to be written in small letters.
• For demographic data, gender is recorded as M/F, age as yr, (if necessary, use days or months in children) without decimal point. The “±” sign within
Figure 1: Illustration of anatomical structures. Figure 2: Comparison of treatment outcomes.

References:
spective video clip(s) should be, but are not always required to be, accompanied by legends. The video clip file name(s) should refer to the corresponding figure number(s).

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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