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), The Korean Spinal Pain Society (KSPS), Korean Society of Regional Anesthesia (KSRa), and Korean Society for Airway Management (KSAM). The abbreviated title is "Anesth Pain Med". It is published four times a year on the last day of January, April, July, and October in English.

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: anesthesia-related issues from affiliated neuroanesthesiology (KSNACC), experimental, laboratory works or clinical relevance of anesthetic pharmacology (KSAP), anesthesia for operative delivery, pain relief in labor, care of the critically ill parturient, preclinical 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), anesthesia for cardiothoracic and vascular surgery and management of patients undergoing various surgeries for patients with cardiac, pulmonary, and vascular diseases (KSCVA), peripartum anesthesia care of transplantation surgery, physiology or pharmacology related with transplantation anesthesia (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 (KSRa), all fields of airway management including difficult airway and complications (KSAM).

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Reappearance of 1–2 PTCs: 4

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The prevalence of obesity is increasing worldwide. This review describes safe analgesic techniques for labor and anesthetic management during cesarean sections in obese parturients. The epidural analgesic technique is the best way to provide good pain relief during the labor phase and can be easily converted to a surgical anesthetic condition. However, the insertion of the epidural catheter in obese parturients is technically more difficult compared to that in non-obese parturients. The distance from the skin to the epidural space increases in proportion to the body mass index (BMI): 4.4 cm in mothers of normal weight and 7.5 cm in mothers with BMI 50 and above. Neuraxial blocks are the ideal anesthetic methods and gold standard techniques for cesarean section in pregnant women with obesity. Single-shot spinal anesthesia is the most common type of anesthesia used for cesarean sections. The advantage of single-shot spinal anesthesia is a dense-sufficient block of rapid onset. A combined spinal-epidural (CSE) anesthetic technique is also recommended as an attractive alternative method. In obese parturients, the operation time can be longer than expected, and therefore, the CSE technique provides the advantage of rapid onset and intense block for prolonged operation with postoperative pain control. The risk of postoperative complications is very high in obese parturients. Therefore, detailed communication of the parturient’s medical condition and the details of surgery and anesthesia between the anesthesiologist and obstetrician is important prior to cesarean section in obese pregnant women.

**Keywords:** Analgesia; Anesthesia; Morbid obesity; Pregnancy.
associated with regional anesthesia, and airway problems related to general anesthesia. Obese parturients should try to control their weight during pregnancy so that they do not reach an obese level because obesity increases the risk to both the fetus and the mother. The weight-gain recommendation guidelines (Table 1) are presented according to the BMI level before pregnancy, and weight control through exercise and diet control leads to safe delivery by preventing obesity [4]. The weight gap between delivery and self-reported pre-pregnancy is defined as the gestational weight gain (GWG). Although GWG as an indicator is reportedly more effective, BMI is a more common and universal method for clinical application, and thus, BMI is more commonly used in practice. This review describes safe analgesic techniques for labor and anesthetic management of cesarean sections in obese parturients.

**GENERAL CHARACTERISTICS**

**Definition**

BMI is the most common statistical tool used to assess obesity. The height and weight are required for BMI calculations and are typically determined using the weight and height measured in the clinical setting or the self-reported weight and height of individuals. BMI is the weight divided by height (kg/m²). Obesity is defined based on the World Health Organization’s international classification of adult BMI; individuals with a BMI ≥ 30 are obese. This classification of BMI is used in individuals of the white, black, and Hispanic races. There is some debate about the World Health Organization classification because the cut-off values underestimate the risk of obesity in Asian and South Asian populations. In Asian and South Asian populations, some investigators insist that the cut-off value of BMI should be 25 or higher [5].

**Prevalence**

In Korean women, the frequency of obesity above BMI 25 is reported to be 28.1 percent for women aged 19 and older and 30.4 percent for women aged 30 and older [1]. Although lower than the percentage of obese women reported in Western countries, this increase in the number of obese women has been pointed out as a threat to the health of pregnant women and fetuses. The exact figure for the proportion of obese people among pregnant women in Korea is yet to be determined, however, it is estimated to be increasing.

**Physiologic changes**

1. **Respiratory system**

Pregnancy affects the oxygenation and ventilation of parturients, and the physical, mechanical, and hormonal changes associated with pregnancy bring lead to changes to the respiratory tract. In obese parturients, obstructive sleep apnea is not uncommon, but pregnancy itself has some protective effect on sleep apnea despite nasal passage edema and hyperemia. In the early stages of pregnancy, increased sensitivity of the respiratory center reduces apneic events, and in the second half of pregnancy, parturients tend to lie on their sides and sleep, reducing the possibility of airway obstruction. Long-lasting hypoxemia, hypercapnia, and pulmonary hypertension in obese parturients significantly increase maternal morbidity and mortality [6,7]. Despite being a lower abdominal surgery, cesarean sections can lead to reduced lung capacity and volume in obese parturients compared to non-obese parturients [8]. Weight increase in pregnancy further increases the breathing workload, and obese parturients need more energy to move their weight-bearing chest walls during ventilation. The increased abdominal weight limits the movement of the diaphragm, which intensifies in the supine and Trendelenburg positions, reducing the tidal volume. Fortunately, not all changes related to pregnancy in patients with obesity are harmful. The respiratory function can be slightly improved in parturients [9]. In particular, the functional residual capacity is improved. Hormonal changes reduce airway resistance through the relax-

### Table 1. Institute of Medicine Guidelines for Weight Gain during Pregnancy in Women with Singletons

<table>
<thead>
<tr>
<th>Pre-pregnancy BMI</th>
<th>Total weight gain (kg)</th>
<th>Rate of weight gain in the 2nd and 3rd trimesters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (&lt; 19.8 kg/m²)</td>
<td>12.5–18</td>
<td>0.5 kg/wk</td>
</tr>
<tr>
<td>Normal (19.8–26.0 kg/m²)</td>
<td>11.5–16</td>
<td>0.4 kg/wk</td>
</tr>
<tr>
<td>High (26.0–29.0 kg/m²)</td>
<td>7–11.5</td>
<td>0.3 kg/wk</td>
</tr>
<tr>
<td>Obese (≥ 29.0 kg/m²)</td>
<td>≥ 7</td>
<td>Not specified</td>
</tr>
</tbody>
</table>

BMI: body mass index (kg/m²). Modified from the book of Institute of Medicine Committee (Nutrition during pregnancy: part I, weight gain; part II, nutrient supplements 1990: 5-10) [4].
Obesity itself is a high-risk factor for both increased de- 
ferred time. Damaged myocardial diastolic relaxation fur- 
ther leads to myocardial relaxation. Fat deposition in myo-
cardial tissues can have a serious effect on conduction and
to pano et al. [15].

2. Cardiovascular system
A wide range of cardiovascular changes can occur as the 
patient. Therefore, systolic or diastolic dysfunction can 
occur frequently in the left ventricle. Patients with pulmo-
nary hypertension and obstructive sleep apnea may experi-
ence right ventricular impairment. Congestive heart failure 
is a result of additional stress [14]. The effect of the enlarged 
uterus compressing major blood vessels in the abdomen and 
causing supine hypotensive syndrome (SHS) can also be 
seen in obese parturients. This can worsen significantly in 
obe parturients, where a large panniculus with an en-
larged uterus exacerbates uterine compression. This prob-
lem can be extended after surgery if the panniculus is large 
le magnitudes of general anesthesia, and hiatal hernia may be 
more common in obese parturients. When pregnancy is as-
ociated with obesity, the chances of regurgitation and aspi-
ration increase significantly. Some researchers have report-
ed that the gastric volume of obese parturients is five times 
greater than that of non-obese parturients in labor [16].

4. Diseases associated with morbid obesity in pregnancy
Diabetes and hypertension are common problems during 
pregnancy. Continuous inflammation and pregnancy-relat-
ed hormonal changes in obese patients worsen blood glu-
cose levels. Major complications reported to be related to 
osity during pregnancy include hypertension, diabetes mellitus, respiratory disease, thromboembolic disorders, in-
fecions, and an increased risk of postpartum hemorrhage.
The association between obesity and hypertension, diabetes mellitus, and an increased incidence of cesarean section is well known [17,18]. In addition, labor-related complications such as an increased rate of instrumental delivery, failure to progress, intrapartum fetal distress, meconium aspiration, abnormal fetal presentation, and shoulder dystocia are com-
mon in obese parturients [19]. Furthermore, the success rate of vaginal delivery after cesarean surgery has been shown to decrease proportionally with increased maternal BMI [20,21]. The incidence of post-delivery endometriosis and wound infections is considerably higher in obese patients [19]. Obesity itself is a high-risk factor for both increased de-
ivery-related blood loss and postpartum hemorrhage [22]. 
A meta-analysis showed that the odds ratios of a cesarean 
section in obese parturients were 1.46 (overweight, 95% con-
fidence interval [CI]: 1.34–1.60), 2.05 (obese, 95% CI: 1.86–
2.27), and 2.89 (severely obese, 95% CI: 2.28–3.79), relatively 
higher than that in normal weight pregnant women [23]. 
According to the literature, obese parturients have a 14–25% 
prevalence of preeclampsia, a 6–14% prevalence of gesta-
tional diabetes, and a 30–47% incidence of cesarean sections 
[17]. Parturient obesity is highly associated with an increased 
risk of fetal macrosomia, fetal death, and birth defects [24– 
26]. Many studies have reported an increased risk of neural 
tube defects, omphalocele, fetal heart defects, and multiple 
malformations [25]. In addition, obesity itself makes it difficult to 
detect fetal anomalies in the early stages with diagnostic ul-
trasound. The high incidence of fetal anomalies in morbidly 

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obese parturients may be due to the inability to adequately evaluate the fetus because of maternal obesity and underlying maternal medical diseases such as preeclampsia and diabetes mellitus.

**ANESTHETIC MANAGEMENT**

Obese pregnant women have a high incidence of comorbid diseases, and therefore, they need to be thoroughly evaluated and prepared before anesthesia at an early stage. An appropriate-sized blood pressure cuff should be used for noninvasive blood pressure measurements because if the width of the cuff is relatively small compared to the arm circumference, the blood pressure measurement can show higher values. Therefore, the blood pressure cuff is sometimes applied on the mother’s forearm to avoid this problem. The blood pressure with forearm measurements correlate well with the upper arm measurements, but exceed an average of 10 mmHg. Conical noninvasive blood pressure cuffs for obese patients were introduced and used in clinical settings and are known to correlate well with measured arterial blood pressure values [27]. If blood pressure measurements using noninvasive blood pressure methods do not reflect the actual blood pressure, invasive blood pressure measurements using intra-arterial catheters may be more useful. Obesity can cause difficulties in securing intravenous lines; therefore, appropriate veins should be secured early in delivery. If a peripheral venous line cannot be secured, intravenous cannulation under ultrasonic guidance or the central vein should also be considered. Sufficient manpower is essential for the transport of obese patients. In addition, beds, mobile carts, and operating tables that can withstand proper size and weight are also checked in advance. Sufficient pads are required to place obese patients on labor beds or operating tables, and a long spinal or epidural Tuohy needle may be required.

**Analgesia for labor**

Analgesia for labor is effective and important for a good outcome of the fetus and good satisfaction of the parturient. Neuraxial analgesia is effective and useful for reducing labor pain in parturients. For obese mothers, the epidural analgesic technique is the best and safest way to provide labor analgesia [28]. It is the best way to provide a good pain relief effect during the labor phase, and can be easily converted to surgical anesthetic conditions in the case of cesarean section, if required. Since the incidence of fetal macrosomia is high, epidural analgesia can help in the successful management of shoulder dystocia. Therefore, frequent evaluation for well-functioning epidural catheters is extremely important to verify that the epidural method can be reliably extended to provide appropriate surgical anesthesia, if required. However, the insertion of the epidural catheter in obese parturients is technically more difficult compared to that in non-obese parturients. Anesthesiologists have more difficulties in the identification of the midline in the lumbar spine, detection of epidural space, and placement of epidural catheters in obese parturients. Knee- chest positioning in the lateral decubitus is comparatively more difficult to sustain in the obese parturient than in the non-obese group. Gravity in the lateral decubitus position can also force the panniculus down, which obscures the midline of the lumbar spine. For this reason, the sitting position is preferred to easily locate the midline for epidural catheterization. More objectively, the midline can be identified under ultrasound, and the epidural space can be found using images to measure the depth from the skin to the epidural space. In pregnant women, ultrasound imaging before epidural catheterization can significantly reduce the number of attempts and help identify the correct intervertebral space and epidural depth. However, viewing ultrasound images is more difficult in obese parturients, and the fact that all anesthesiologists are not familiar with using ultrasound is still considered a limitation. The distance from the skin to the epidural space increases in proportion to BMI: 4.4 cm in mothers of normal weight and 7.5 cm in BMI 50 and above [29] (Table 2). Therefore, even in obese parturients, a typical Tuohy needle can be used to identify the epidural space; therefore, it is preferable to use a standard-length epidural Tuohy needle at first, which can be

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI &lt; 25</td>
<td>4.40 ± 0.81</td>
<td>4.5</td>
<td>3.0–7.0</td>
</tr>
<tr>
<td>25–29</td>
<td>4.80 ± 0.85</td>
<td>5.0</td>
<td>3.0–11.0</td>
</tr>
<tr>
<td>30–34</td>
<td>5.30 ± 0.93</td>
<td>5.0</td>
<td>3.0–10.0</td>
</tr>
<tr>
<td>35–39</td>
<td>6.2 ± 1.2</td>
<td>6.0</td>
<td>3.0–10.5</td>
</tr>
<tr>
<td>40–44</td>
<td>6.6 ± 1.3</td>
<td>7.0</td>
<td>3.0–11.0</td>
</tr>
<tr>
<td>45–49</td>
<td>7.2 ± 1.2</td>
<td>7.5</td>
<td>4.0–11.0</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>7.5 ± 1.2</td>
<td>7.5</td>
<td>5.0–11.0</td>
</tr>
</tbody>
</table>

Mean depth for all BMI: 5.3 ± 1.2 | 5.0 | 3.0–11.0 |

BMI: body mass index (kg/m²). Modified from the article of Clinkscales et al. (Int J Obstet Anesth 2007; 16: 323-7) [29].
Anesthesia for cesarean section

Anesthesiologists need thorough preparation, especially in obese parturients, prior to cesarean section. In particular, anesthesiologists should evaluate parturient airways completely prior to general anesthesia. Even if neuraxial anesthesia is performed, a thorough evaluation of the airway is needed because the anesthetic technique can be converted to general anesthesia due to inadequate sensory blockade or prolonged operation time. In obese pregnant women, intubation and manipulation of blade handling can be difficult because of the large breasts, increased anterior-posterior chest diameter, airway swelling, and shortening of the jaw and chest spacing. When laboring mothers present to the operating room for cesarean section, many staff members are required to move the parturient from the ward bed to the operating table. In the presence of a neuraxial blockade, it is difficult to safely bring an obese mother to the operating table. This shift poses a potential risk of injury to both the parturient and the staff supporting this transition. It can be very difficult to properly and safely position obese pregnant women in a surgical bed for a cesarean section, which must be supplied with right wedges for left-uterus displacement. In addition, medical staff must securely fasten the obese parturient to the bed to prevent falls before tilting to the left. However, it is more important to position the left uterus as soon as possible because SHS appears relatively faster and can be more serious than that in normal-weight pregnant women. Pulling the panniculus toward the head of a morbidly obese pregnant woman can cause pressure on the upper abdomen and chest, reducing venous return and cardiac output, resulting in hypotension.

Regional anesthesia

Neuraxial blocks are the ideal anesthetic method and gold standard technique for cesarean section in obese pregnant women. There are three anesthetic techniques: spinal, epidural, and combined spinal-epidural (CSE). Single-shot spinal anesthesia is the most common type of anesthesia used for cesarean sections. The advantage of single-shot spinal anesthesia includes a dense, sufficient block of rapid onset. However, the associated problems include technical difficulties in obese women, potential risk for high spinal blockade, profound dense thoracic motor blockade leading to suppression of cardiorespiratory function, and inability to prolong the duration of anesthesia. Neuraxial anesthesia is very difficult in obese women because of the marked adipose tissue on the spine and the difficulty in palpating the spinous process [31]. A critical step for success in performing neuraxial anesthesia is the identification of the midline. The advantage of a midline approach in spinal or epidural anesthesia is that the success rate is high, and the provider can easily feel the needle tip through engagement in the supraspinous ligament. In cases where the midline approach is not used, a paramedian approach may be used. In a paramedian approach, there are no tactile advantages with respect to the location of the needle tip, as the needle is located in the paraspinal muscle and not the supraspinous ligament. It is widely accepted that local anesthetic requirements for neuraxial anesthesia are lower in pregnant women and in obese women. Obesity increases intra-abdominal pressure and causes compression of the inferior vena cava, which leads to the engorgement of the epidural venous plexus and increases the pressure of the epidural space. This mechanism reduces the cerebrospinal fluid volume in the subarachnoid space. Therefore, some anesthesiologists insist that the dose regimen should be adjusted in obese parturients, with the aim of achieving appropriate surgical anesthesia while minimizing hemodynamic complications. However, many researchers have reported that dose reduction in obese patients may not be recommended [32–34]. They reported that the ED50 of bupivacaine for successful spinal anesthesia in morbidly obese mothers was 9.8 mg, similar to the other reports in the non-obese group [32]. There were no significant differences in the incidence of nausea, vomiting, and phenylephrine dose requirement [32]. However, many anesthesiologists are concerned about high spinal anesthesia in a morbid obesity parturient, and single-shot spinal anesthesia with a pencil point needle may be technically difficult. Therefore, a CSE anesthetic technique is recommended as an attractive alternative method. Placing an epidural Tuohy needle may be easier than a spinal needle insertion and
can be used as a guide for the spinal needle as a needle through the needle CSE method. In an obese parturient, the operation time can be longer than expected, and therefore, the CSE technique provides the advantage of rapid onset and intense block for prolonged operation with postoperative pain control. In addition, a lower dose of intrathecal bupivacaine can be administered, and the level of block can be adjusted with an epidural catheter to achieve adequate surgical anesthesia. In parturients with severe cardiovascular disease, a lower dose of intrathecal bupivacaine and slowly titrated local anesthetics lead to minimal hemodynamic changes, and therefore, a sudden onset of hypotension may be prevented effectively. CSE has a beneficial effect on obese parturients with cardiovascular diseases.

**General anesthesia**

In Korea, approximately 28.8% of cesarean sections have been performed under general anesthesia over the past five years [35], but the rate of general anesthesia limited to the obese parturient group has not yet been reported. The rate of general anesthesia in Korea is significantly higher than that in Western countries [36]. Considering that the fatal complication rate is high under general anesthesia, if possible, it would be desirable to replace general anesthesia with regional anesthesia. Owing to the anatomic and physiologic changes in obese mothers, difficult intubation and urgent desaturation can occur in such patients. Therefore, proficient assistance may be needed to maintain airways. The jaw-thrust maneuver can also require the use of both hands of the anesthesiologists, and therefore, other staff may be needed for positive pressure ventilation and downward pressing on the cricoid cartilage. Various equipment (such as laryngoscope with short blades, supraglottic airway devices, video laryngoscope, fiberoptic intubation devices, Bullard laryngoscope, or cricothyrotomy devices) should be prepared for difficult intubation situations. If intubation fails, the intubation failure algorithm must be started, and help must be requested immediately [37]. If intubation is expected to be difficult, rapid sequence induction is recommended, and during apnea, pregnant women fall into hypoxia faster, with obese mothers reaching hypoxia even faster; therefore, sufficient preoxygenation should be performed before initiating general anesthesia. Proper parturient positioning for the best laryngoscopic view can assist in securing a difficult airway. The ramped position improves the laryngoscopic view compared to the traditional sniffing position and can be accomplished by elevating the head of an obese parturient above the shoulders by modifying the operating table or by applying blankets under the upper body [38,39] (Fig. 1). As soon as the parturient is transferred to the operating table, the facial mask is firmly fixed to the face, and oxygen administration begins subsequently. Preoxygenation is an essential process for delaying the desaturation of obese mothers and providing sufficient oxygen. The dosage of induction anesthetics in obese women should be calculated based on the ideal body weight rather than the actual weight [40]. Succinylcholine and rocuronium are widely used as neuromuscular blockers for rapid tracheal intubation during general anesthesia. One study attempted to determine the appro-

![Fig. 1. Comparison of positions suitable for tracheal intubation in morbidly obese parturients. (A) Sniffing position. (B) Ramped position (by applying blankets under the upper body). (C) Ramped position (by modifying the operating table). Modified from the book of The Korean Society of Obstetric Anesthesiologist (Obstetric anesthesia 2016: 351-4) [39].](image-url)
Anesthesia in morbidly obese parturients

The risk of postoperative complications (hypoxemia, pulmonary atelectasis, deep vein thrombosis, pulmonary edema, postpartum cardiomyopathy, and wound complications) is very high in the obese parturient group [46]. Moreover, a BMI-dependent decrease in respiratory function may occur even after regional anesthesia [47]. Postoperative pulmonary events may lead to severe complications. Therefore, postoperative early ambulation has also been reported to improve respiratory function during the postoperative period [47]. In morbidly obese parturients, postpartum complications occur after cesarean section and do not occur after vaginal delivery [44]. Postoperative pain should be properly controlled and reduced to facilitate postoperative mobilization and lung care because postoperative pulmonary complications are very important determinants of prognosis. PCEA with dilute local anesthetics mixed with opioids may improve the quality of postoperative pain relief. The risk factor of thrombosis is associated with pregnancy, cesarean section, and obesity, and postoperative pulmonary thromboembolism remains a major cause of maternal mortality. Both pharmacological and mechanical interventions can be used for prophylaxis; therefore, perioperative use of an adequate anticoagulant and intermittent pneumatic compression are recommended [48]. In obese parturients, postoperative wound complications occur more frequently than in the non-obese group, which often leads to prolonged recovery and long hospitalization, and the midline vertical abdominal incision is associated with a higher incidence of wound complications than a Pfannenstiel incision [49]. Morbidly obese parturients may be hospitalized for significantly longer duration because of the increased incidence of postoperative complications and antepartum medical disease. The length of hospital stay and costs in morbidly obese parturients have been shown to increase after both vaginal delivery and cesarean operations [50].

CONCLUSIONS

The high prevalence of obese parturients may lead to maternal and fetal morbidity and can also increase the incidence of side effects from labor, cesarean section, and anesthesia; therefore, careful evaluation and preparation before delivery and surgery is needed in such cases. Prior to the cesarean section for obese parturients, detailed communication between the anesthesiologist and obstetrician regarding the parturients’ medical condition and details of surgery and anesthesia for the parturient should be established. Neuraxial anesthetic techniques are the gold standard method in morbid parturients, but neuraxial anesthesia may be converted to general anesthesia because of the prolonged operation time or technical failure; therefore, airway evaluation and equipment for airway assistance must be in place at all times. For rapid recovery from surgery, adequate postoperative pain control and an adjusted anticoagulant dose for an appropriate duration are recommended. Careful observation of airway obstruction is required in morbid parturients because respiratory depression after delivery and obstructive sleep apnea can occur in such cases.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.
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Real-time ultrasound guided thoracic epidural catheterization: a technical review

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Thoracic epidural analgesia is known to have superior perioperative pain control over intravenous opioid analgesia in open abdominal surgery and is an essential enhanced recovery after surgery component in major abdominal surgeries. Recently, the ultrasound-guided thoracic epidural catheter placement (TECP) technique has drawn attention as an alternative for the traditional landmark palpation-based TECP or fluoroscopic-guided TECP technique due to the equipment’s improvement and increased popularity. However, only a small number of studies have introduced the advantages and usefulness of ultrasound-guided TECP. Moreover, a certain level of ultrasound-guided in-plane technique is required to perform this technique. Thus, to apply ultrasound-guided TECP correctly and reduce the likelihood of side effects and complications, the practitioner must have a thorough understanding of the anatomical region, optimal block positioning, device selection, and management. In this technical review, the authors have compared the advantages and disadvantages of ultrasound-guided TECP to traditional techniques and described its technical aspects from patient positioning, ultrasound probe selection and scanning, needle insertion under ultrasound guidance, and successful thoracic epidural catheter insertion confirmation through ultrasound imaging. Additionally, the recommended epidural catheter tip placement level with the extent of its injectate epidural spread is further described in this review in reference to a recent prospective study published by the authors.

Keywords: Catheterization; Epidural analgesia; Thoracic vertebrae; Ultrasonography.
niques have been widely accepted and used for a long time in clinical practice, they also have well-known drawbacks. Landmark palpation-based TECP, in particular, is associated with a relatively high failure rate (12–40%) [7,8]. On the other hand, fluoroscopic-guided TECP has a higher success rate than the former since it can accurately identify anatomical structures and epidural spaces using imaging devices [9]; however, due to the difficulty of using fluoroscopy in daily clinical practice and the burden of radiation exposure, its practical use is limited [10].

Recently, the ultrasound-guided TECP technique has drawn attention with the equipment’s improvement and increasing popularity [11,12]. Despite this, only a small number of studies have introduced the advantages and usefulness of the technique [8,13,14]. Thus, in this technical review, the authors investigated the advantages of the ultrasound-guided TECP technique as compared to the other two. Thereafter, the technique’s application for enhanced recovery after surgery in major surgeries was described based on the author’s clinical experience.

COMPARISON WITH OTHER TECHNICAL APPROACHES FOR THORACIC EPIDURAL CATHETER PLACEMENT

The ultrasound-guided thoracic epidural approach provides further information on the spinal anatomical structure as compared to the landmark palpation-based technique. Utilizing ultrasound imaging of the spine before the neuraxial procedure will allow the preprocedural determination of the spinal level and depth up to the ligamentum flavum and posterior dura, as well as identify the anatomical abnormality, thus increasing its success rate [15–17]. A previous study by Salman et al has assessed the accuracy of preprocedural ultrasound scanning of the thoracic spine to measure the depth to the epidural space and determine the optimal puncture site for epidural needle placement of the thoracic spine. The authors found a good correlation of the distance to the epidural space between the ultrasound guided estimation and actual needle distance in total 33 study patients, demonstrating a Pearson correlation coefficient of 0.75 [17]. Additional advantages of this technique is that, it can further be applied to patients with significant degenerative spinal changes or had previously undergone spinal surgeries, wherein procedure performance and success rate are improved, as long as there is sufficient space for the needle to pass [16]. Furthermore, by using the real-time ultrasound-guided technique, the practicing physician can also monitor the target point location (ligamentum flavum or posterior epidural space) and epidural needle tip position in real time.

However, compared to the landmark palpation-based technique and preprocedural ultrasound imaging technique, a certain level of ultrasound-guided in-plane technique is required for real-time ultrasound-guided approach. Thus, sufficient experience and operation ability for ultrasound procedures is needed. Additionally, it is not easy to determine loss of resistance (LOR) with only one hand, while holding the probe with the other. Therefore, when it is visually confirmed that the epidural needle has touched the ligamentum flavum or upper end of the lamina, further entry and confirmation of the needle tip in the epidural space with LOR may be accomplished using the traditional blind technique. If any air enters the field during the procedure, an adequate image cannot be obtained, and thus saline should be used rather than air for LOR confirmation. Further technical descriptions are provided in the next section.

The greatest advantage of ultrasound-guided TECP as compared to fluoroscopy-guided TECP is that it avoids the burden of radiation exposure, which is a significant benefit for both patients and practicing physicians. Owing to the compact features of many modern ultrasound equipment, this becomes more feasible compared to the relatively bulky fluoroscopic machine, which is a spatial advantage in operation and anesthetic theaters with limited spaces. Another advantage is that the procedure is possible in any position, except in the supine position.

However, the disadvantage of the real-time ultrasound-guided technique over fluoroscopic-guided TECP is the difficulty in observing the catheter tip and drug epidural spread. Although visual confirmation of epidural lumbar spine catheterization and the posterior epidural spread of local anesthetics can be done by downshifting of the dura even in the ultrasound-guided technique, this differs at the thoracic level since the interlaminar space width varies from individual to individual, wherein the posterior dura is often not visible. Thus, in some cases, the catheter tip may exit through the transverse foramen, which may not be noticed until the patient’s dermatome is checked postoperatively and is mainly due to different viewing directions performed intraoperatively (fluoroscopic-guided TECP, anteroposterior view; ultrasound-guided technique, sagittal view). Another disadvantage is the difficulty in performing the procedure again at the same spinal level should a small amount of air enter and distort the ultrasound view.

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TECHNICAL DESCRIPTION OF REAL-TIME ULTRASOUND-GUIDED THORACIC EPIDURAL CATHETER PLACEMENT

Real-time ultrasound-guided TECP can be performed in either prone, lateral, or sitting positions. However, without the aid of a positioning device or assistant, it can be difficult to maintain a fixed patient position while sitting. Therefore, the authors perform TECP in either the prone or lateral position, with more preference towards the prone position approach.

After entering the operation theater or preinduction room, basic monitors, including pulse oximetry, noninvasive blood pressure monitoring, and electrocardiogram, are applied to the patient. Following this IV access is performed, wherein a small amount of midazolam may be injected for patient comfort, but the procedure is generally performed without sedation. The patient is then placed in the prone position with a pillow under the upper abdomen to widen the interlaminar space. Traditionally, the interlaminar space between T6 and T8 has been recommended as a target space for epidural catheterization in patients undergoing upper abdominal surgery [18]. However, based on the clinical experience of two physicians (LJH and KDH) who have done this procedure at several different levels for more than two years, the T10–T11 interlaminar space is selected as the preferred target in our institute for real-time ultrasound guided TECP in order to place the catheter tip in the T9 vertebral level. The evidence for selecting the target level of the catheter tip is further described in the next section of the current article [12].

Before skin disinfection of the treatment area, an ultrasound prescan of the procedure area is done to check the target interlaminar space in the following order:

First, a high-frequency linear ultrasound probe is selected and placed in the longitudinal sagittal plane over the thoracic spinal column. In young children, the spinal column can be penetrated in part by ultrasound, and all or most parts of the relevant anatomical structures (spaces between the spinal processes, vertebral discs, ligamentum flavum, dura mater, intrathecal space, spinal cord, nerve roots, and nerve fibers) can be clearly distinguished using the linear probe [19]. In adults, a curved convex ultrasound probe is widely used in most of the previous reports when an epidural catheter is inserted under ultrasound guidance, especially in the lumbar regions [20–22]. However, when performing ultrasound-guided TECP, both linear and curved probes may be used. Since the thoracic spines are dorsally convex at shallow depths as compared the lumbar level spines, a linear probe is sufficient to identify the main object around the epidural space in majority of cases, unless the patient is very obese. This is supported by Pak and Gulati’s previous study [13], which performed thoracic epidural catheterization in a similar manner, determining the mean parasagittal distance from the skin to the epidural space was 5.2 ± 1.1 cm. Aside from this, it is also helpful to use a linear probe when accurately checking the needle tips in real time is essential.

After confirming the level of the spine desired by the operator, the probe is placed on the midline to observe the spinous process (Fig. 1A-5, 6). This authors use the method of rib counting upwards after finding the 12th rib to check the level. Then, by sliding the probe in the lateral direction, the corresponding laminae can be confirmed (Fig. 1B-5, 6). In this state, the probe laterally tilts to obtain the paramedian sagittal oblique view. However, if tilting is insufficient or the interlaminar space is too narrow, the superior articular processes of the inferior vertebrae between the laminae may be seen (Fig. 1C-5, 6). At the lumbar level, an epidural needle can be advanced in this state, but at the thoracic level which has narrower interlaminar spaces, the operator can slightly tilt the probe laterally, making it possible to secure a paramedian sagittal oblique view with a wider interlaminar space (Fig. 1D-5, 6).

Consequently, the posterior complex (the ligamentum flavum and posterior dura) is observed as a linear hyperechoic structure between the laminae (Fig. 1D-5, 6), and the intrathecal space and spinal cord (anechoic), as well as the alternative complex (hyperechoic), can be visualized in this view. Moreover, the cephalad end of the probe can be further pivoted medially to decrease the laminal height at the level below (Fig. 1E-5, 6).

After checking the target interlaminar space through the ultrasound prescan, the patient’s skin is marked and disinfected to sterilize the procedure area. After local infiltration with 2% lidocaine at the intended needle entry site, an 18-gauge Tuohy needle is inserted from the caudal end of the probe and advanced with in-plane view under real-time ultrasound guidance until the needle tip reaches the posterior complex in the target interlaminar space (Fig. 2). Needle-beam alignment can be maintained by advancing the needle in a similar lateral-to-medial trajectory. Furthermore, the probe and beam position should be held in constant to keep the target in view, in which the needle trajectory can be adjusted to keep the epidural needle visualized until the tip
is located just in front of the posterior complex. If the needle tip is not visible, tilting the probe to the medial and lateral sides while shaking it slightly helps to determine its position, which is a method described in Gnaho et al.’s study [14] for real-time ultrasound-guided epidural catheter insertion in obese parturients and can be usefully applied in other types
of real-time ultrasound-guided procedures. Simultaneously, the LOR also should be checked, but if it cannot be done using only one hand, this can be further checked with a blind technique using both hands with normal saline from the point after the needle tip reaches the posterior complex in the ultrasound view. At this point, the performing physician should secure the needle with the operating hand to avoid needle tip position changes and further advance in the desired direction. After needle entry confirmation into the thoracic epidural space using saline LOR, the epidural catheter is advanced through the needle such that 3–5 cm of the catheter remained in the epidural space. After epidural catheterization, a small amount of test drug or saline injection via the epidural catheter will further help to confirm its placement. If the catheter is outside the epidural space, bulging around the lamina can be observed, and if the catheter is within it, visualization of the posterior dura downward shifting in the ultrasound image can possibly be observed. In a previous study, air was used to check the LOR \[13\]. However, in our experience, if air is used for LOR, it may be difficult to observe the downward shifting of the posterior dura when catheterization is successful or the bulging around the lamina when it fails due to the ultrasound image artifact caused by air insertion. Moreover, it becomes difficult to retry the procedure at the same level when it is required due to this obstruction.

Fig. 2. Real-time ultrasound views for needle. PC indicate the posterior complexes. The arrow and open arrow indicate the epidural needle and the needle tip, respectively. PC: posterior complex, SP: spinous process, L: laminae.

**ACCURACY OF REAL-TIME ULTRASOUND GUIDED THORACIC EPIDURAL CATHETERIZATION**

Regardless of how well the catheterization is performed, if a segmental block cannot be confirmed, the practicing physician may not be confident about the epidural patient-controlled analgesia (PCA) effectiveness. Therefore, epidural spreading identification is of clinical importance. Under the ultrasound-guided technique, however, it is difficult to determine the exact degree of epidural spreading, although it is possible to determine whether an epidural spread was done. Thus, the author conducted a prospective study to determine epidural spreading by injecting a contrast agent under fluoroscopic guidance following ultrasound-guided catheterization \[12\].

This was recently conducted as a prospective study to identify fluoroscopic findings in patients who underwent a continuous thoracic epidural catheter using the real-time ultrasound-guided technique \[12\]. The average age of the 38 patients in this study was 62.5 ± 9.9 years, with 60.5% of them being male. The target interlaminar level for catheter entry in the epidural space was determined at either T9–10 or T10–11, and the average time it took to mark the skin for treatment was 49.5 ± 13.8 s, which took less time as compared to Auyong et al.’s \[8\] results that had an average time to mark spaces in 85 s and needling time of 188.5 s. The reason for this difference was that the authors omitted to perform the midline checking procedure by changing the ultrasound probe to the transverse view during the prescan, which was also done in their current study. The median time for epidural needle placement was noted to be 49 s (IQR: 39–65 s), and there were 9 (23.7%) cases of needle withdrawal with epidural needle direction changes, since the entry of the Tuohy needle into the epidural space was not successful at the first attempt, along with 2 (5.3%) cases in which the needle direction was changed more than once. Overall, the probability of successful catheter insertion at the first attempt was similar to that in a previous study by Auyong et al. \[8\], which was approximately 70%, and all patients in this study only underwent a single skin puncture for catheterization. The depth from the skin was mostly approximately 4 cm, but since the epidural needle entered obliquely from the skin, the mean distance between the skin and epidural space was 5.6 ± 0.5 cm, which is comparable to Pak and Gulati’s \[13\] previous results (5.2 ± 1.1 cm).

After injecting contrast medium through the indwelling
epidural catheter, the epidural spread was identified using a fluoroscope. All catheter tips were successfully placed in the epidural space, mostly at the level between T9 and T10 (n = 32, 84.3%) and at the median epidural space (n = 26, 68.4%). After injecting the 4 ml mixture of contrast medium, the mean cranial dispersion was noted to be in 5.4 ± 1.6 vertebral body levels mostly up to T4, with a mean caudal spread of 2.6 ± 1.0 vertebral body levels. In the cephalad direction, 94.7% of patients had an injectate spread of more than the T6 level, and 58% presented with more than the T4 level. Meanwhile, in the caudal direction, 97.4% presented with a spread of more than the T11 level, and 28.9% of the patients went over the L1 level. These data provide further information on the epidural spread extent for adjustment of the hourly volume limit when an epidural PCA pump will be planned for postoperative analgesia.

**CONCLUSION**

In this review, we described the technical methods and tips of real-time ultrasound-guided thoracic epidural catheterization. It was found that ultrasound guidance during thoracic epidural catheterization reduced epidural needle placement time and the number of needle passes as compared to the landmark palpation technique [8]. Moreover, it gives more confidence to the practitioner as the needle tip position is visible throughout the procedure, making it possible to determine whether or not there was epidural spread [12]. Ultrasound guidance for epidural surgery has gained popularity and interest, especially for lumbar epidural needle placement and catheterization [23–25], and its application in thoracic epidural surgeries has also been receiving attention. However, studies describing its technical aspect, efficacy, and safety as compared to traditional techniques are still limited. Therefore, further studies to elucidate the advantages of ultrasound-guided thoracic epidural needles and catheter placement are essential in the future.

**CONFLICTS OF INTEREST**

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

**DATA AVAILABILITY STATEMENT**

Not applicable.

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INTRODUCTION

Although first reported in 1981 [1,2], the term “ex-utero intrapartum treatment (EXIT)” was introduced in 1997 by a team that had successfully performed fetal surgery [3]. Also described as “operation on placental support” or “airway management on placental support, EXIT allows surgical procedures or airway management in the fetus by maintaining uteroplacental circulation outside the uterus. Cesarean section is completed only after ensuring the neonate’s safety. However, managing the airway of a neonate while maintaining umbilical circulation is a major challenge for anesthesiologists. Anesthesiologists must understand the physiology of both the mother and fetus, and extensive discussions with obstetricians, pediatricians, otolaryngologists, and nursing staff prior to the procedure are essential. This review provides an overview of the EXIT and details of airway management for neonates.

Keywords: Airway management; Anesthesia; Ex-utero intrapartum treatment; Fetus; Neonate.

INDICATIONS FOR EXIT

While EXIT can be used in patients with significantly compromised fetal airways, previous studies have suggested sev-
eral indications, including airway displacement due to fetal neck mass [6], tracheal occlusion at delivery, tracheostomy for congenital high upper airway obstruction syndrome (CHASOS), surgical resection for thoracic abnormality, extra-corporeal membrane oxygenation (ECMO) [7], and conjoined twins [8].

**Airway displacement due to fetal neck mass (tracheoesophageal displacement index > 12 mm)**

In fetuses with large neck masses, Lazar et al. [6] identified several characteristics predictive of airway difficulty, including polyhydramnios, diagnosis of teratoma, or a tracheoesophageal displacement index (TEDI) > 12 mm. Their data suggested that fetuses without these findings may be delivered safely without EXIT. TEDI is defined as the sum of the lateral (L) and ventral (V) displacements of the tracheoesophageal complex (T) from the ventral aspect of the cervical spine (S) on fetal MRI (Fig. 1). The fetus in Fig. 1 was planned for EXIT with a 17-mm TEDI, and endotracheal intubation was successful after three attempts using direct laryngoscopy for 9 min; tracheostomy was not required. In Fig. 1C, the fetal air-

![Fig. 1. Preoperative evaluation of the fetal airway.](image-url)
way is filled with amniotic fluid, and the white shaded line (green arrow) connects to the lungs. Although the structure of the oral cavity cannot be predicted in detail, the airway is continuously maintained in the presence of fluid.

**Tracheal occlusion state at delivery (PLUG state)**

In the most severe cases of CDH, the liver occupies a large portion of the chest [9]. Right-sided hernia (10% of CDH) is challenging to diagnose owing to the difficulty of differentiating between CDH and other malformations such as congenital cystic adenomatoid malformation (CCAM). Metkus et al. [10] reported that fetuses with a lung-to-head ratio (LHR; lung area/ head circumference) < 0.6 did not survive despite postnatal treatment, but the survival rate of fetuses with an LHR > 1.35 was 100%. LHR values < 1.0 are used to select fetuses for PLUG, which may help to grow their lungs and improve their outcomes. The tracheal occlusion procedure is commonly performed after a gestational age of 27–29 weeks to prevent the normal outflow of surfactant-rich fetal lung fluid. If this occurs over a period of 4–5 weeks, the lung expands, and its function appears to improve. Recently, as fetoscopy technology has improved, UNPLUG is performed 4–5 weeks after PLUG to avoid the risk of EXIT. If the fetus is in the proper position, the balloon is punctured under ultrasound guidance at approximately 34 weeks of gestation. The deflated balloon is subsequently expelled from the trachea by lung fluids. If needle puncturing is not possible, a grasper can be used to hold the balloon while it is punctured. The deflated balloon is then removed from the fetus’ airway using a grasper. The mother and fetus are subsequently monitored carefully until delivery. In this case, unlike with EXIT, vaginal delivery is possible at full term. If the fetus is in “PLUG” before delivery, “UNPLUG” is using EXIT.

**Tracheostomy for congenital high upper airway obstruction syndrome**

CHAOS, which manifests as a laryngeal web, cyst, or as tracheal or subglottic atresia, has a poorer prognosis than extrinsic lesions, such as a neck mass because the obstruction occurs earlier in gestation [11]. Without fetal intervention to relieve back pressure, the lungs do not develop properly, and ventilation and oxygenation cannot be achieved even after successful EXIT. Most fetuses with CHAOS require EXIT for tracheostomy [12].

**Surgical resection for thoracic abnormality**

CCAM, which accounts for more than 50% of congenital lung malformations, may also be an indication for EXIT. CCAM occurs during early embryonic development due to disorganization of peripheral bronchioles and adenomatous tissue proliferation. Renal dysplasia, congenital heart disease, foregut malformation, bronchogenic cysts, and skeletal malformations may also be present. Chromosomal abnormalities such as trisomy 13, 18, or 21 syndrome have also been reported [13]. Prognosis is mainly determined by the size of the mass. If the CCAM volume ratio (width × height × length × 0.523) is > 1.6, fetal hydrops is more likely to be present, and ECMO, as well as fetal intervention and ventilatory support, may be required [7]. Furthermore, a thoracoamniotic shunt for the largest cyst or premature delivery with EXIT may be required [14].

**MATERNAL ANESTHESIA**

It is now recognized that the key to successful EXIT is maintaining maximal relaxation of the uterus. Thus, neuraxial anesthesia, if used, should be combined with general anesthesia using volatile anesthetics. However, in rare cases where volatile anesthetics cannot be used (e.g., malignant hyperthermia), intravenous nitroglycerin should be continuously administered to relax the uterus [15]. Nitroglycerin can be maintained at a rate of 1–20 μg/kg/min after loading with 25–100 μg. Nitroglycerin is essential when anesthesia is maintained with only neuraxial anesthesia or total intravenous anesthesia [16]. Nitroglycerin is often used in general anesthesia with halogenated gas. In this case, dopamine (5–10 μg/kg/min) or phenylephrine is continuously administered to maintain blood pressure. It is safe to secure a central venous line for vasoactive drugs and blood transfusions while accurately monitoring arterial and venous pressures by securing arterial and central venous routes.

Most cesarean sections with EXIT are performed under general anesthesia with a volatile anesthetic agent. Relatively high doses of volatile agents should be used solely for uterine relaxation (2–3 MAC). However, due to the risk of a decrease in uterine blood flow, it is essential to maintain normal maternal blood pressure. Although both ephedrine and phenylephrine can be used, recent studies suggest the use of phenylephrine since ephedrine crosses the placenta more readily than phenylephrine [17]. The authors use sevoflurane, which can be administered at high concentrations,
for inhalation gas and intermittently use ephedrine as needed, along with a continuous infusion of phenylephrine (10–50 µg/min). The maternal mean arterial pressure is maintained above 70 mmHg. After hysterotomy, the uterine cavity is filled continuously with warm (37°C) lactated Ringer solution using a fast-flow fluid warmer or pump to maintain adequate uterine volume and prevent compression of the umbilical cord. The fetal head, upper torso, and arms are exteriorized, while the rest of the body remains within the uterine cavity to maintain uterine volume and fetal temperature.

A previous study showed that postpartum wound complications were more common in patients who underwent EXIT than in those who underwent cesarean sections only (15% vs. 2%; P = 0.03) [18]. Estimated blood loss was higher in the patients who underwent EXIT (1,104 ml vs. 883 ml; P < 0.001), but there was no difference between groups with respect to hematocrit level change or postpartum hospital stay [18].

INTRAOPERATIVE FETAL MANAGEMENT

As the exact period when the fetus begins to feel pain remains uncertain, adequate analgesia should always be provided during EXIT procedures. Studies have also suggested that anesthesia is required to blunt the stress response in the fetus [19]. This is especially important when maternal anesthesia is accomplished using neuroaxial anesthesia without the use of volatile agents. In such cases, nitroglycerin and remifentanil are often infused to induce uterine relaxation and provide fetal analgesia and immobilization [20,21]. However, most EXIT procedures are performed under maternal general anesthesia while providing adequate uterine relaxation. Although adequate fetal anesthesia may be accomplished by placental passage of inhalant anesthetics, previous studies have also used intramuscular injections of anesthetics, opioids, muscle relaxants, and atropine (as premedication) to obtain optimal conditions [22]. George et al. [21] used intramuscular ketamine for fetal anesthesia. Rocuronium 1–3 mg/kg can be directly injected into the fetus if immobilization is required. The combination of medications (fentanyl 5–15 µg/kg, atropine 20 µg/kg, and vecuronium 0.1–0.4 mg/kg) can be drawn up in unit doses in a 1 ml syringe and can be administered to the fetus intramuscularly, intravascularly, or via the umbilical cord [12]. If EXIT is prolonged, this combination may be repeated every 45 min to ensure an adequate level of fetal anesthesia.

During EXIT, the fetus depends on uteroplacental support and is often in a critical condition. Full uterine relaxation is essential because changes in placental vascular tone significantly affect fetal cardiac output. Although fetal myocardial contractions are significantly weaker than in children, contractions can be increased by contractile agents or by increased preload. Blood transfusions and fluid therapy may be necessary because of the small blood volume, low levels of coagulation factors, and less active baroreceptors that limit vasoconstriction in response to hypovolemia. It is also important to recognize the high risk of hyperthermia from heat loss due to the relatively thin skin, which must be avoided. The additional pathophysiology of certain fetal malformations can also lead to serious damage. Therefore, continuous fetal monitoring should be performed during EXIT to evaluate the effects of anesthesia, surgical procedures, and possible circulatory insufficiency due to illness [23].

Fetal pulse oximetry monitoring is essential during EXIT. Although often difficult to measure, the pulse oximeter can be wrapped in foil on either fetal hand to minimize interference from bright lights in the operating room and to continuously monitor the oxygen saturation status and heart rate. Normal fetal oxygen saturation ranges from 40% to 70%, and prompt treatment is required when arterial saturation drops below 40%. Immediate action is also necessary when the fetal heart rate falls more than 20% below baseline or below 140 beats/min [23]. The anesthesiologist must first notify the surgeon of possible fetal distress and increase maternal inspired oxygen, optimize uteroplacental circulation by maintaining maternal blood pressure and heart rate, rule out aorticaval compression, and achieve uterine relaxation in the presence of uterine contractions. Surgeons should also reposition the fetus to resolve possible umbilical cord compression, increase the amniotic fluid volume, and rule out placental abruption. If fetal distress is not resolved, fetal resuscitation must be initiated.

Additional fetal monitoring during EXIT has also been shown to provide valuable information. Fetal echocardiography can characterize the fetal heart rate, chamber volume with heart contractions, capacity of the atroventricular valves, and vascular stenosis. Fetal hemoglobin and blood gases can be routinely sampled from the umbilical artery and vein by the surgeon. The normal values of cord blood gas vary depending on several factors, including gestational age and delivery type. Although normal values for fetuses undergoing EXIT procedures have not been established, lower limits of pH 7.10 and −12 mmol/L base excess have been used [24]. Peripheral venous access can be difficult due to the small size of the patients, limited exposure, and im-
paired ability to properly position the baby at the surgical site. A properly inserted catheter may still fall out due to vernix caseosa on the skin and must be sutured in place. If veins are not accessible, drugs can be administered intramuscularly or through the cord blood path.

**AIRWAY MANAGEMENT OF THE FETUS**

According to a previous review [12], CHAOS is the only malformation that requires tracheostomy for laryngeal obstruction. No clear trend was observed for other malformations. In addition, there were no clear features of airway obstruction that could recommend one airway intervention over others. In cases of cervical teratoma, neither the magnitude nor the extent of anatomical distortion was predictive of the type of airway intervention used. Although endotracheal intubation under direct laryngoscopy is typically performed in cases without specific conditions (CHAOS), diverse airway equipment should be prepared after preoperative consultation with pediatricians and otolaryngologists. Doctors’ familiarity with airway equipment should also be considered, and it is important to discuss the scenario in advance and perform aseptic preparation by sterilizing all necessary equipment. Previous reports have shown that advanced airway interventions, including tracheostomy, rigid bronchoscopy, retrograde wire intubation, partial mass resection, and tracheostomy can be performed [19,25]. A possible scenario for fetal airway management is shown in Fig. 2.

**Intubation under direct or video laryngoscopy**

During the initial intubation attempt, it is helpful to check the overall structure and condition of the airway using a direct laryngoscope. Although starting with the smallest sized laryngoscopy blade and performing stepwise increases until the size of the tongue base is visible is recommended, using a size 2 or 3 Macintosh blade from the beginning may help quickly examine the structure of the airway in cases with a

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**Fig. 2.** Flow chart for airway management of a fetus requiring ex-utero intrapartum treatment (EXIT). FOI: fiberoptic intubation, LMA: Laryngeal mask airways, ECMO: extracorporeal membrane oxygenation.
relatively large mass or mouth. If the mass is a vascular neoplasm in the oral cavity, more careful selection of the blade size is required, and it is better to determine it based on preoperative imaging analysis. When the size is appropriate, but the angle makes it difficult to visualize the vocal cords, a video laryngoscope of the same size can be used. Video laryngoscopes should also be aseptically prepared in advance so that various sizes can be used without delay. Video laryngoscopes can be used to help lift the fetus a little farther from the uterus, extend the angle of the fetus’s neck, or push the mass to one side for better visibility of the vocal cords to enable image sharing with other medical staff. One study reported using a video laryngoscope in the first attempt at endotracheal intubation [26]. To confirm the proper position of the endotracheal tube, auscultation should be performed because single-lung ventilation cannot be ruled out using capnography. Ultrasound can also be used to determine the exact location of the tip of the endotracheal tube [27] or tracheostomy tube. Tube positioning must be confirmed before any deviation from umbilical circulation occurs, and the position of the tube should be confirmed using at least two methods.

**Intubation with rigid bronchoscopy**

Intubation can also be performed under rigid bronchoscopy in fetuses who undergo treatment for endoscopic tracheal occlusion due to severe diaphragmatic hernia [3,28]. After the bronchoscopic procedure is completed, only the bronchoscope is removed while holding the external endotracheal tube. By setting the telescope and tube size at 0° and 4 mm, respectively, the telescope can be inserted into a 3.0 endotracheal tube [29].

**Use of laryngeal mask airways**

Another possible strategy is the use of a supraglottic airway. Laryngeal mask airways (LMAs) have been suggested as an alternative method for establishing an airway during neonatal resuscitation [30]. Previous studies have also reported successful airway management in cases of failed endotracheal intubation under direct laryngoscopy during EXIT. Baker et al. reported achieving fiberoptic intubation through an LMA during EXIT in a fetus diagnosed with a dysgnathia complex [31]. Other studies have reported performing tracheostomy under ventilation with LMA insertion [32]. Although several studies have compared the efficiency of diverse LMAs in children [33], there are limited data in neonates [34].

**Retrograde wire intubation**

Since placental circulation is maintained during EXIT, it is possible to attempt retrograde intubation, which is less invasive than tracheostomy. However, there are several important limitations when performing retrograde intubation in neonates. For instance, due to the lack of a Murphy’s eye in small endotracheal tubes, there is no way to increase the distance between the insertion site of the retrograde guide and the vocal cord [35]. In addition, because of the narrow inner diameter of the tube, only a suction catheter or guide-wire sheath can be used as an anterograde guide. Although ultrathin fiberoptic bronchoscopes (outer diameter [OD] of 1.8 or 2.2 mm) can be placed inside a 3-mm tube, they cannot be used as anterograde guides because they lack working chambers and suction channels [36]. A 2.8-mm-OD bronchoscope that can be used to insert a 4-mm-inner diameter (ID) tube has a 1.2-mm channel, but there is often significant resistance when passing the retrograde guide. Fortunately, a 4 French central venous catheter guidewire can be used as a retrograde guide. It is important to confirm that the retrograde guide catheter can be properly inserted into the channel of the bronchoscope, acting as an anterograde guide.

**Surgical airway management**

Tracheostomy must be performed immediately if the intervention cannot be delayed. An otolaryngologist must be on standby in case of emergency situations. Although tracheostomy is more invasive than retrograde intubation, it does not independently affect infants’ language and cognitive development [37]. Performing a tracheostomy in newborns requires careful preparation and skill, as the trachea is narrow and difficult to position relative to that in adults. The anatomy of the fetus is often more difficult to navigate during EXIT, and it is crucial to find an access location using ultrasound in advance. Since there is a possibility that the airway is deviated to one side, it is important to identify the location and direction of the airway using MRI before EXIT and confirm the airway using ultrasound before the skin incision. Although both vertical and horizontal skin incisions can be used, a vertical tracheal incision over the third and fourth rings is recommended during tracheostomy [38]. Incisions should not be made over the cricoid cartilage or the first tracheal ring. Maintaining “stay sutures” for a week with 4/0 Prolene nonabsorbable suture provides stability and
helps with “maturation.” After a week, the tube can be changed and the stay sutures removed. The smallest Shiley Tube has an ID of 3.0 and an OD of 4.5 mm, and Portex® and Bivona® (Smiths Medical, UK) products have also been developed with an ID of 2.5 mm [39]. If the depth from the skin to the tracheotomy site is increased due to large neck masses, the airway must be secured with an endotracheal tube. The tagging should be firm to prevent the tube from falling out after separation from the placenta or during transfer. If the airway is secured with a tracheostomy tube, a dedicated tape can be used, but it should be fixed firmly so that only one finger can pass under the tape. This prevents hypoxic damage or death due to accidental decannulation. Even after successful tracheostomy, continuous management after the procedure is very important. Warming and humidification should be continued, and tube suction should be performed every 30 min during the first day to prevent tube obstruction caused by secretion.

If direct access to the trachea is difficult due to a huge neck mass, partial resection of the mass may be necessary [8]. Decompression with aspiration may be useful for cystic lesions. If tracheostomy is successful with partial resection of the solid mass, an anesthesia machine capable of neonatal anesthesia and an extra operating room should be prepared and kept warm because additional surgery may be required. If the preoperative imaging evaluation suggests that this is highly probable, O-negative red blood cells should be prepared and an intravenous route should be secured to enable the delivery of medication and fluid therapy, as well as blood, to the newborn.

**ECMO**

ECMO can be considered during EXIT in airways assessed to be extremely difficult. ECMO circulates blood through the carotid artery and internal jugular vein, and after the umbilical cord is clamped, an umbilical arterial and venous catheter is added to enable the ECMO circulation. The first study to provide a standard for neonatal ECMO treatment reported that 25 of 45 newborns with respiratory failure were saved using ECMO, and 20 of the 25 survivors subsequently exhibited normal lung function without brain damage [40]. For 14 fetuses diagnosed with severe CDH but who experienced PLUG failure, veno–arterial ECMO was applied using an 8 French arterial cannula and a 10 French venous cannula, and veno–venous ECMO was performed using a 12 French double-lumen cannula [41]. The authors reported a 1-year neonatal survival rate of 64%. However, the situation is sig-

![Fig. 3. Example of an operating room layout for EXIT. EXIT: ex-utero intrapartum treatment, ECMO: extracorporeal membrane oxygenation.](www.anesth-pain-med.org)
significantly different in the presence of large neck masses. If the neck mass is large enough to make tracheostomy unfeasible or cause severe anatomical variation, it is highly possible that carotid artery and internal jugular vein access is also difficult, even after mass resection. In such cases, central ECMO through sternotomy may be necessary. As central ECMO requires multiple experts, including radiologists, obstetric anesthesiologists, obstetricians, pediatric surgeons, pediatric anesthesiologists, neonatologists, and pediatric thoracic surgeons, special attention is needed to prevent perioperative infection (Fig. 3).

**CONCLUSION**

The purpose of EXIT is to separate the fetus from the mother after resolving airway obstruction of the fetus while maintaining placental circulation. This can only be accomplished by a multidisciplinary team composed of experts who continuously discuss the optimal treatment method for the fetus. Anesthesiologists must be aware of the difficulties associated with airway management during EXIT and thoroughly prepare for multiple scenarios.

**CONFLICTS OF INTEREST**

Chaeseong Lim has been an editor of the *Anesthesia and Pain Medicine* since 2020; however, he was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

**DATA AVAILABILITY STATEMENT**

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

**AUTHOR CONTRIBUTIONS**

Conceptualization: Woosuk Chung, Chaeseong Lim. Writing - original draft: Woosuk Chung. Writing - review & editing: Chaeseong Lim.

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Awake craniotomy has become a feasible treatment option for patients with brain tumors residing within or close to regions presumed to have language or sensorimotor functions [1]. Different anesthetic techniques, including conscious sedation with monitored anesthesia care (MAC) and the asleep-awake-asleep technique, have been applied for awake craniotomy [2]. However, in all these techniques, respiratory depression, including desaturation and hypercapnia during surgery, has been reported as an important complication [3].

Various techniques have been introduced to reduce the risk of respiratory insufficiency. The use of a high-flow nasal cannula (HFNC) can improve oxygenation compared to conventional oxygen devices by reducing the anatomical dead space, producing positive airway pressure, and facilitating the clearance of carbon dioxide in patients with spontaneous respiration [4]. Moreover, HFNC with a humidifier and heated circuit can deliver a conditioned gas mixture through a nasal cannula at up to 60 L/min with a fraction of inspired oxygen (FiO₂) ranging from 0.21 to 1 for better pa-

Case Report

Awake craniotomy using a high-flow nasal cannula with oxygen reserve index monitoring - A report of two cases -

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Background: Awake craniotomy is a well-tolerated procedure for the resection of brain tumors residing within or close to the eloquent cortical areas. Monitored anesthesia care (MAC) is a dominant anesthetic approach for awake craniotomy; however, it is associated with inherent challenges such as desaturation and hypercapnia, which may lead to various complications. The prevention of respiratory insufficiency is important for successful awake craniotomy. As measures to avoid respiratory depression, the use of high-flow nasal cannula (HFNC) can improve patient oxygenation and monitor the monitoring the oxygen reserve index (ORi) can detect hypoxia earlier.

Case: We report two cases of awake craniotomy with MAC using HFNC and ORi. We adjusted the fraction of inspired oxygen of the HFNC according to the ORi level. The patient underwent successful awake craniotomy without a desaturation event or additional airway intervention.

Conclusions: Combined HFNC and ORi monitoring may provide adequate oxygen reserves in patients undergoing awake craniotomy.

Keywords: Airway obstruction; Craniotomy; Hypoxia; Respiratory insufficiency; Sleep apnea, obstructive.
tient comfort [3]. On the other hand, the oxygen reserve index (ORi), a tool for measuring the oxygen reserve, is reportedly useful for the early detection of hypoxia [5,6]. The measurement of partial pressure of oxygen (PaO₂) by atrial blood gas analysis is intermittent and requires invasive techniques. Pulse oximetry saturation (SpO₂) can detect hypoxia, but responds slowly and may not significantly decrease until the PaO₂ is below 80 mmHg [7]. ORi is a unitless index from zero to 1, which correlates with PaO₂. A sharp decrease in ORi or a drop to zero means that the oxygen reserve is low, and hypoxia is expected soon. This continuous and noninvasive technique enables early warning to prevent desaturation.

We report two cases of patients who underwent moderate to conscious sedation for awake craniotomy. In two cases, a combination of HFNC and ORi was used to prevent respiratory insufficiency. Our Institutional Review Board (no. SMC 2020-11-109) approved this study and waived the requirement for written informed consent.

CASE REPORT

Case 1

The patient was a 58-year-old male with glioblastoma located near Broca’s area. Brain functional magnetic resonance imaging showed that the motor and sensory cortices were located anterior to the mass. To preserve language and motor function, an awake craniotomy was scheduled [1]. Preoperative physical examination with an anesthetic evaluation, including the airway, was performed. The patient was taking medication for dyslipidemia, and his cardiopulmonary function was normal. His mallampati score was 2, and there were no abnormalities in the anatomy of the airway. The body mass index (BMI) was 26.5 kg/m², and the patient reported that he snores heavily when sleeping. To assess obstructive sleep apnea (OSA), the STOP-BANG (acronym for Snoring, Tiredness, Observed apnea, high blood Pressure, Body mass index, Age, Neck circumference, and Gender) questionnaire was used, based on which he was classified as having a high risk of OSA. We applied the HFNC (AIRVO 2 system, Fisher & Paykel, New Zealand) to improve oxygenation during surgery [4]. EtCO₂ was monitored using a commercial sample line provided with the AIRVO 2 system. In addition, we monitored ORi to measure the oxygen reserve and the effectiveness of HFNC.

We used standard monitors (electrocardiogram, noninvasive blood pressure, end-tidal carbon dioxide, and pulse oximeter) with a bispectral index (BIS VISTA, Aspect Medical Systems, USA) sensor and administered 4 mg of ondansetron, 0.2 mg of glycopyrrolate, and 1 mg of midazolam as premedication. The scalp nerve block (a perineural injection of 0.75% ropivacaine [26 ml] mixed with 1:200,000 epinephrine) was performed by an experienced anesthesiologist to block the supraorbital, supratrochlear, auriculotemporal, zygomaticotemporal, lesser occipital, and greater occipital nerves [8]. After initiating MAC with propofol and remifentanil, radial arterial cannulation was performed for invasive arterial monitoring, followed by insertion of a peripheral intravenous cannula and Foley catheter. For effect-site target-controlled infusion (TCI) for MAC, a commercial TCI pump (Orchestra Base Primea, Fresinus Vial, France) was used, and the pharmacokinetic set used to calculate the target effect site concentration (Ce) was the Minto model for remifentanil and Schneider model for propofol [2]. Usually, the target BIS is 60–70 during sedation for craniotomy [4], but in this case, we targeted the BIS above 70 to reduce the potential risk of airway obstruction following deep sedation. We applied both HFNC and ORi at the beginning of sedation and adjusted the flow and FiO₂ of HFNC when ORi dropped to nearly zero, which is an early indicator of hypoxia.

Fig. 1 shows the values of ORi, FiO₂ of HFNC, and SpO₂ during surgery. At the beginning of sedation, HFNC was applied at 15 L/min and FiO₂ at 0.4. At this time, the PaO₂ and SpO₂ were 118.3 mmHg and 100%, respectively. When we increased the target Ce of remifentanil before the expected stimulation, such as head fixation and incision, a sudden decrease in ORi to zero occurred, but ORi was recovered by increasing FiO₂. During the speech test, ORi dropped to zero. Although oxygen saturation was maintained at 100%, ORi remained at zero even when the flow of HFNC increased from 15 L/min to 30 L/min. As he was almost awake, the possibility of airway obstruction was low; therefore, we checked the HFNC machine and found that the nasal cannula was pulled out while the patient was speaking. When the nasal cannula was applied to the patient again, the ORi recovered above 0.2. When ORi was zero, SpO₂ was 100%, but dropped to 95% transiently after ORi recovered. During the speech test, the ORi repeatedly dropped to zero, confirming that the nasal cannula was removed from the patient. After the neurologic examination, ORi was maintained above 0.2 with FiO₂ at 0.6 and a flow rate of 30 L/min with HFNC until the end of the surgery (Table 1). The estimated blood loss was 300 ml, heart rate was approximately 70 beats per minute, and mean arterial blood pressure was main-
tained above 70 mmHg during the surgery. The patient underwent successful awake craniotomy and tumor resection without any loss of neurological function or perioperative adverse events.

Case 2

The patient was a 33-year-old male with a low-grade glioma located in the left basal ganglia near the inferomedial aspect of Broca’s area. He had smoked for 14 years, and his cardiopulmonary function was within normal limits. His BMI was 25.3 kg/m², and physical examination revealed a mallampati score of 2 and no evidence of airway abnormality or signs of OSA with normal PaO₂ before surgery. Anesthesia was performed in the same order as described in the previous case. The scalp nerve was blocked using 30 ml of 0.75% ropivacaine with 1:200,000 epinephrine. We applied HFNC at 30 L/min and FiO₂ at 0.5, with ORi monitoring. After sedation, the PaO₂ was 387.3 mmHg under HFNC. The patient was sedated with a target BIS of 60–70. The ORi value was recorded throughout the surgery.

After the initiation of sedation, the ORi suddenly decreased to zero; therefore, we increased the FiO₂ to 0.77. Five minutes later, the ORi was restored to 0.29; accordingly, the FiO₂ was changed to 0.5. During the surgery, the ORi suddenly decreased again from 0.45 to 0.2, for which the FiO₂ was increased briefly to 0.77 before reducing it back to 0.5 after recovery of ORi. Oxygen saturation remained at 100%, while ORi changed from 0 to 0.85 throughout the surgery. During surgery, sedation and awake procedures were performed. While the ORi tended to increase temporarily when the patient woke up, there was no significant relationship between changes in ORi and patient consciousness.

The patient underwent extensive sensory and motor testing as well as neurocognitive testing, including naming, reading, counting, and verbal fluency. The total estimated blood loss was 300 ml, heart rate was 90 to 100 beats per minute, and mean arterial blood pressure was above 80 mmHg, which was similar to that before surgery. TCI sedative agents and HFNC regimen were recorded (Table 2). The patient underwent successful awake craniotomy and tumor resection without any loss of neurological function or perioperative adverse events.

**DISCUSSION**

In these two cases, the patients underwent MAC during awake craniotomy. They were awake during the neurolog-
Awake craniotomy with HFNC and ORi

Table 1. TCI Sedative Agents and HFNC Regimen in Relation to Intraoperative Events in Case 1

<table>
<thead>
<tr>
<th>Event (time)</th>
<th>HFNC</th>
<th>TCI, remifentanil (Ce, μg/kg/min)</th>
<th>TCI, 2% propofol (Ce, μg/kg/min)</th>
<th>SpO$_2$ (%)</th>
<th>PaO$_2$ (mmHg)</th>
<th>PaCO$_2$ (mmHg)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start of sedation (0:50)</td>
<td>0.4</td>
<td>0.8</td>
<td>1</td>
<td>100</td>
<td>118.3</td>
<td>51</td>
<td>Increased the anesthetics in advance due to expected stimulation</td>
</tr>
<tr>
<td>Head pin fixation (1:10)</td>
<td>0.4</td>
<td>1.1</td>
<td>1.2</td>
<td>98</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORi decreased to 0 (1:10 to 1:30)</td>
<td>0.56</td>
<td>0.8</td>
<td>0.9</td>
<td>98-97</td>
<td></td>
<td></td>
<td>ORi recovered by raising FiO$_2$ of HFNC</td>
</tr>
<tr>
<td>ORi fell close to 0 (1:50)</td>
<td>0.68</td>
<td>0.5</td>
<td>0.8</td>
<td>98-99</td>
<td>143</td>
<td>58</td>
<td>Start of surgery, ORi recovered by raising FiO$_2$ of HFNC</td>
</tr>
<tr>
<td>ORi dropped to 0 (3:00 to 3:50)</td>
<td>0.68</td>
<td>0.4</td>
<td>0.3</td>
<td>100-95</td>
<td>223</td>
<td>40</td>
<td>Speech test Raised flow rate of HFNC, detect dislodged nasal cannula &amp; re-apply, desaturation developed</td>
</tr>
<tr>
<td>End of testing (4:10)</td>
<td>0.6</td>
<td>0.4</td>
<td>0.3</td>
<td>98</td>
<td>223</td>
<td>40</td>
<td>Decreased FiO$_2$ of HFNC, because PaO$_2$ was 223 mmHg</td>
</tr>
</tbody>
</table>

BIS: bispectral index, Ce: effect site concentration, FiO$_2$: fraction of inspired oxygen, HFNC: high flow nasal cannula, TCI: target-controlled infusion, ORi: oxygen reserve index, PaO$_2$: partial pressure of oxygen, SpO$_2$: oximetry saturation, PaCO$_2$: partial pressure of alveolar carbon dioxide. When we recorded BIS, it was the lowest value for that time period. The time and arrow in parentheses is the same as the time and arrow in Fig. 1. ORi decreased rapidly, raised FiO$_2$. The time and arrow in parentheses is the same as the time and arrow in Fig. 1. ORi recovered above 0.2. SpO$_2$ reacted later than ORi (marked by ④ in the Fig. 1). After the neurologic exam, PaO$_2$ in arterial blood gas analysis was 223 mmHg, we adjusted FiO$_2$ as 0.6 and flow rate as 30 L/min with HFNC until the end of the surgery.

Table 2. TCI Sedative Agents and HFNC Regimen in Relation to Intraoperative Events in Case 2

<table>
<thead>
<tr>
<th>Event</th>
<th>HFNC</th>
<th>TCI, remifentanil (Ce, μg/kg/min)</th>
<th>TCI, 2% propofol (Ce, μg/kg/min)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>During induction</td>
<td>0.5</td>
<td>1</td>
<td>1</td>
<td>Increased the anesthetics in advance due to expected stimulation at the beginning of the surgery</td>
</tr>
<tr>
<td>Head pin fixation, dura opening</td>
<td>0.5</td>
<td>1.3</td>
<td>1.3</td>
<td>Raised FiO$_2$ of HFNC</td>
</tr>
<tr>
<td>ORi decreased to 0</td>
<td>0.77</td>
<td>1.3</td>
<td>1.3</td>
<td>ORi has recovered, FiO$_2$ is lowered again</td>
</tr>
<tr>
<td>Neurologic exam</td>
<td>0.5</td>
<td>0</td>
<td>0</td>
<td>ORi has recovered, FiO$_2$ is lowered again</td>
</tr>
<tr>
<td>End of testing</td>
<td>0.77</td>
<td>0.5</td>
<td>0.7</td>
<td>ORi has recovered, FiO$_2$ is lowered again</td>
</tr>
<tr>
<td>Wound closure</td>
<td>0.5</td>
<td>1.1</td>
<td>1.2</td>
<td></td>
</tr>
</tbody>
</table>

BIS: bispectral index, Ce: effect site concentration, FiO$_2$: fraction of inspired oxygen, HFNC: high flow nasal cannula, TCI: target-controlled infusion, ORi: oxygen reserve index. When we recorded BIS, it was the lowest value for that time period. The TCI model used the Schneider model.

Case 1: awake craniotomy with HFNC and ORi in Case 1. We used propofol and remifentanil as sedatives in a pendent manner. In particular, in patients with OSA, even a small increase in the sedative dose may cause unexpected respiratory insufficiency; therefore, the dose of the sedative was adjusted under close monitoring of BIS. Airway obstruction due to respiratory insufficiency can cause intracranial hypertension; therefore prompt management is required. However, securing the airway with laryngeal mask airway in patients undergoing awake craniotomy because of unusual positions
and head fixation, which may delay prompt airway intervention and lead to serious consequences during surgery.

To prevent respiratory insufficiency, we attempted to improve oxygenation by applying HFNC. MAC with HFNC is a reasonable option for patients undergoing awake craniotomy, especially for those with OSA [4]. A high flow of oxygen is supplied to generate resistance to expiratory flow, resulting in a continuous positive airway pressure effect. According to the other study, when HFNC was applied at 35 L/min, positive pressures produced 2.7 cmH₂O with the mouth open and 1.2 cmH₂O with the mouth closed, and the difference was more pronounced when the BMI was higher [9]. In addition, carbon dioxide is easily released and the dead space is decreased, which is effective in resolving dyspnea [10]. In addition, humidified gas improves mucociliary function, helps secretion clearance, and reduces atelectasis [4]. These advantages of HFNC are particularly useful in patients with OSA undergoing awake craniotomy.

ORi is a noninvasive and continuous supplemental tool that can provide early warning to clinicians regarding changes in a patient’s oxygen reserve. It is a unitless index between 0 and 1, where 0 indicates a decrease in PaO₂ and impending hypoxia [5,11]. In the study of ORi and PaO₂, they were significantly correlated; moreover, a decrease in ORi to approximately 0.24 may provide an advanced indication of decreasing PaO₂ [11]. The ORi was reported to detect an impending desaturation at a median duration of 31.5 s before any noticeable changes in SpO₂ occurs during surgery in children [12]. In the first case, ORi decreased several times but was recovered by slightly increasing the FiO₂ of the HFNC. During neurological examination, ORi detected hypoxia faster than SpO₂. The ORi dropped to zero while the HFNC was pulled out, but SpO₂ remained at 100%. After reapplying HFNC, ORi was maintained above 0.2, but SpO₂ dropped to 95% only and recovered soon, indicating that the change in ORi was faster than that of SpO₂. At that time, we could not measure the exact value of PaO₂ by arterial blood gas analysis, but if we did not measure the ORi, it would have been late to find out that HFNC was pulled out and respiratory insufficiency would have occurred. Although the patient was awake, remifentanil was continuously infused during the neurological examination; therefore, he could easily experience hypoxia. ORi allows real-time surveillance of the oxygenation status and may enable proactive interventions to avoid hypoxia. In the second case, we adjusted the FiO₂ of the HFNC when ORi decreased; thus, SpO₂ remained at 100%. The flow rate of HFNC was maintained at 30 L/min from the beginning, but as in the first case, the oxygen reserve could be properly maintained by adjusting the flow rate of the HFNC. HFNC helps to prevent hypoxia while preventing airway obstruction by controlling FiO₂ to values from 0.2 to 1 and providing a positive end-expiratory pressure effect. Although it is still controversial, since hyperoxia might have a negative effect on craniotomy [13], it is recommended to maintain normoxia during and after craniotomy [14]. Hyperoxia could occur due to HFNC; thus, decreasing the FiO₂ when the ORi approaches 1 might help to maintain normoxia.

In conclusion, the combination of HFNC and ORi monitoring could provide adequate oxygen reserve in patients while effectively preventing a decrease in oxygen saturation during awake craniotomy.

CONFlicts OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

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REFERENCES


Preoperative 2D-echocardiographic assessment of pulmonary arterial pressure in subgroups of liver transplantation recipients

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Background: The clinical efficacy of preoperative 2D-echocardiographic assessment of pulmonary arterial pressure (PAP) has not been evaluated fully in liver transplantation (LT) recipients.

Methods: From October 2010 to February 2017, a total of 344 LT recipients who underwent preoperative 2D-echocardiography and intraoperative right heart catheterization (RHC) was enrolled and stratified according to etiology, disease progression, and clinical setting. The correlation of right ventricular systolic pressure (RVSP) on preoperative 2D-echocardiography with mean and systolic PAP on intraoperative RHC was evaluated, and the predictive value of RVSP > 50 mmHg to identify mean PAP > 35 mmHg was estimated.

Results: In the overall population, significant but weak correlations were observed (R = 0.27; P < 0.001 for systolic PAP, R = 0.24; P < 0.001 for mean PAP). The positive and negative predictive values of RVSP > 50 mmHg to identify mean PAP > 35 mmHg were 37.5% and 49.9%, respectively. In the subgroup analyses, correlations were not significant in recipients of deceased donor type LT (R = 0.129; P = 0.224 for systolic PAP, R = 0.163; P = 0.126 for mean PAP) or in recipients with poorly controlled ascites (R = 0.215; P = 0.072 for systolic PAP, R = 0.21; P = 0.079 for mean PAP).

Conclusions: In LT recipients, the correlation between RVSP on preoperative 2D-echocardiography and PAP on intraoperative RHC was weak; thus, preoperative 2D-echocardiography might not be the optimal tool for predicting intraoperative PAP. In LT candidates at risk of pulmonary hypertension, RHC should be considered.

Keywords: Catheterization; Echocardiography; Hypertension; Liver transplantation; Pulmonary; Swan-ganz.
INTRODUCTION

Pulmonary hypertension (PH) is not uncommon in end-stage liver disease, and the presence of PH is of particular concern in liver transplantation (LT) [1,2]. The current diagnostic criteria for porto-pulmonary hypertension require hemodynamic measurements obtained via right heart catheterization (RHC): mean PAP (mPAP) > 25 mmHg, pulmonary vascular resistance > 3 Woods units, and pulmonary capillary wedge pressure < 15 mmHg [3]. Reportedly, the mortality of LT exponentially increased at the threshold of mean pulmonary artery pressure (PAP) over 35 mmHg [4]. Thus, RHC, the gold standard for evaluating pulmonary hemodynamics in high-risk candidates, has been justified despite the invasiveness of the procedure associated with fatal complications such as bleeding and arrhythmia [5].

To select patients at risk, the current guidelines recommend echocardiographic assessment for screening for all LT candidates [6]. 2D-Echocardiography is a non-invasive, widely available, and relatively inexpensive diagnostic method [7], and previous studies have demonstrated its clinical efficacy in LT candidates [8,9]. Because PH that responds well to preoperative treatment is indicated for LT [1], continuous monitoring of PAP is crucial in liver allocation as well as screening of PH [10,11]. 2D-Echocardiographic assessment has shown benefits in monitoring progression or improvement of PH [7], but reliability of preoperative 2D-echocardiography in predicting actual intraoperative PAP remains uncertain.

Our institution is a large-volume center with experience of more than 2,000 LT cases over 20 years. Preoperative 2D-echocardiography is included in the routine preoperative evaluation and is performed and interpreted by echocardiographers and cardiologists. All intraoperative parameters measured by direct cannulation are recorded in the institutional LT database by attending anesthesiologists. This study evaluated the correlation between right ventricular systolic pressure (RVSP) on preoperative 2D-echocardiography and PAP measured by intraoperative RHC and whether preoperatively high RVSP could predict intraoperative mPAP > 35 mmHg.

MATERIALS AND METHODS

Study population and data collection

The Institutional Review Board at our institution approved this study and waived the need for individual consent (no. 2018-12-095-001). The study was conducted according to the principles of the Declaration of Helsinki. Study data were derived from the institutional LT database and retrospectively analyzed. From October 2010 to February 2017, 415 adult LT recipients with intraoperative RHC were enrolled in the registry. Exclusion criteria were recipients undergoing multiple organ transplantations (n = 6) or without RVSP measurement on preoperative 2D-echocardiography (n = 65). Clinical, laboratory, and outcome data were collected by a trained coordinator using standardized case report protocols from institutional electric medical records. All recipients were analyzed anonymously.

Study endpoints

The primary endpoint was the correlation between RVSP on preoperative 2D-echocardiography and systolic PAP (sPAP) on intraoperative RHC according to demographic characteristics (sex and body mass index), disease severity (model for end-stage liver disease [MELD] score and presence of ascites), type of LT (living donor or deceased donor), and etiology of disease (cirrhotic or non-cirrhotic). The secondary endpoints were the correlations between RVSP on preoperative 2D-echocardiography and mean pulmonary arterial pressure (mPAP) on intraoperative RHC in the above subgroups.

The positive and negative predictive values of RVSP > 50 mmHg for identifying mPAP > 35 mmHg and sPAP > 50 mmHg were calculated [4,7]. Based on intraoperative RHC, recipients with porto-pulmonary hypertension, defined as mPAP > 25 mmHg, pulmonary vascular resistance > 3 Woods units, and pulmonary capillary wedge pressure < 15 mmHg according to the current guideline [3], were identified, and the baseline characteristics and preoperative treatments in these recipients were reported.

Pulmonary pressure on 2D-echocardiography and RHC

Following institutional protocol, preoperative 2D-echocardiography was performed in every patient scheduled for LT using various models of commercially available equipment. The following formula was used to calculate RVSP with the assumption of no significant right ventricular outflow tract obstruction:

$$RVSP = 4 \times (V)^2 + \text{assumed right atrial pressure}$$

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$V =$ peak velocity of the tricuspid valve regurgitant jet (meters per second);

Right atrial pressure was estimated to be 5, 10, or 15 mmHg according to diameter and collapsibility of the inferior vena cava [12].

According to institutional protocol, a pulmonary arterial catheter (Edward Lifesciences LLC, USA) was inserted by the attending anesthesiologist and connected to an electronic transducer to measure hemodynamic parameters. To minimize stress, PAP was measured after stabilization from induction of anesthesia but before surgical incision.

**Anesthetic care**

Anesthetic care was standardized according to institutional protocol. After applying monitoring devices (peripheral capillary oxygen saturation, five-lead electrocardiography, noninvasive arterial blood pressure), anesthetic induction was achieved with thiopental sodium and maintained with isoflurane. Remifentanil was infused to respond to hemodynamic changes. The respiratory rate was set to achieve normocapnea. Fluids and pressor drugs were infused to maintain mean arterial pressure 70 mmHg.

**Statistical analysis**

The mean pressures between 2D-echocardiography and RHC were compared using t-test and are presented as mean ± standard deviation (SD). The correlation was analyzed using Spearman’s correlation coefficient and presented as R and P values. Scatter plots and Bland-Altman plots for subgroups were generated. Statistical analyses were performed with IBM SPSS Statistics software Version 20.0 (IBM, USA). P values < 0.05 were considered statistically significant.

**RESULTS**

A total of 344 recipients was enrolled for analysis. The median age of recipients was 54 years (interquartile range, 49.2–60.0 years). The median duration between 2D-echocardiography and RHC was 20 days (interquartile range, 13.0–40.8 days). The mean value of RVSP on preoperative 2D-echocardiography was significantly higher than that of sPAP on intraoperative RHC (27.2 ± 7.1 vs. 22.0 ± 7.3; P value < 0.001). Similar results were observed in most subgroups (Table 1). Correlations of the entire population between RVSP on preoperative 2D-echocardiography and PAP on intraoperative RHC were significant but weak for both sPAP and mPAP (R = 0.27; P < 0.001 for sPAP, R = 0.24; P < 0.001 for mPAP) (Table 2). However, different results were found in some subgroup analyses. In recipients without ascites or with controlled ascites, RVSP on 2D-echocardiography correlated well with both sPAP and mPAP, whereas recipients with uncontrolled ascites showed nonsignificant results (R = 0.215; P = 0.072 for sPAP, R = 0.21; P = 0.079 for mPAP). The correlation also showed inconsistent significance according to type of LT, being significant in recipients of living donor LT but not in those of deceased donor LT (R = 0.226; P < 0.001 vs. R = 0.129; P = 0.224 for sPAP, R = 0.193; P = 0.002 vs. R = 0.163; P = 0.126 for mPAP). Analyses according to disease progression showed that the correlations were significant irrespective of MELD score (Table 2).

A scatter plot of the entire population is shown in Fig. 1. Scatter plots for separate analyses according to type of LT (Fig. 2) and degree of ascites (Fig. 3) are presented. In addition, Bland-Altman plots were generated. According to t-test and regression analysis, the bias between RVSP and sPAP (mean value of RVSP-sPAP) was 5.24 mmHg (SD ± 8.45), and the 95% limits of agreement were 21.80 and −11.32 mmHg (Fig. 4). For mPAP, the bias between RVSP and mPAP was not found in some subgroup analyses.

### Table 1. Mean RVSP on 2D-Echocardiography and sPAP on RHC

<table>
<thead>
<tr>
<th>Variable</th>
<th>RVSP</th>
<th>sPAP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall recipients (n = 344)</td>
<td>27.2 ± 7.1</td>
<td>22.0 ± 7.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male (n = 258)</td>
<td>26.9 ± 7.2</td>
<td>21.7 ± 7.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Female (n = 86)</td>
<td>28.2 ± 6.7</td>
<td>22.9 ± 6.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI &lt; 25 (n = 247)</td>
<td>27.2 ± 7.5</td>
<td>21.7 ± 7.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI ≥ 25 (n = 97)</td>
<td>27.1 ± 6.1</td>
<td>22.7 ± 6.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MELD &lt; 25 (n = 247)</td>
<td>27.0 ± 6.3</td>
<td>21.8 ± 7.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MELD ≥ 25 (n = 97)</td>
<td>27.7 ± 9.3</td>
<td>22.6 ± 7.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No ascites (n = 162)</td>
<td>26.1 ± 5.9</td>
<td>20.7 ± 6.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Ascites (n = 182)</td>
<td>28.1 ± 8.0</td>
<td>22.9 ± 7.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Controlled ascites (n = 111)</td>
<td>28.8 ± 8.2</td>
<td>22.8 ± 8.6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Uncontrolled ascites (n = 71)</td>
<td>27.0 ± 7.5</td>
<td>23.5 ± 7.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Living donor LT (n = 254)</td>
<td>26.2 ± 6.5</td>
<td>20.8 ± 6.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Deceased donor LT (n = 90)</td>
<td>30.1 ± 7.9</td>
<td>25.3 ± 8.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cirrhotic disease (n = 281)</td>
<td>26.3 ± 6.4</td>
<td>20.6 ± 5.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HBV related disease (n = 227)</td>
<td>26.6 ± 6.6</td>
<td>20.7 ± 6.5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HCV related disease (n = 32)</td>
<td>27.4 ± 7.8</td>
<td>21.4 ± 6.0</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Alcoholic disease (n = 50)</td>
<td>27.7 ± 7.7</td>
<td>24.9 ± 9.6</td>
<td>0.110</td>
</tr>
<tr>
<td>Non-cirrhotic disease (n = 63)</td>
<td>31.2 ± 8.7</td>
<td>28.0 ± 9.4</td>
<td>0.046</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. RVSP: right ventricular systolic pressure, sPAP: systolic pulmonary arterial pressure, RHC: right heart catheterization, BMI: body mass index, MELD: model for end-stage liver disease, LT: Liver transplantation, HBV: hepatitis B virus, HCV: hepatitis C virus.
Preoperative pulmonary pressure in LT

Table 2. Correlation between RVSP on Echocardiography and PAP on RHC

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number (%)</th>
<th>sPAP R value</th>
<th>sPAP P value</th>
<th>mPAP R value</th>
<th>mPAP P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall recipients</td>
<td>344</td>
<td>0.27</td>
<td>&lt; 0.001</td>
<td>0.24</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Male</td>
<td>258 (75)</td>
<td>0.244</td>
<td>&lt; 0.001</td>
<td>0.184</td>
<td>0.003</td>
</tr>
<tr>
<td>Female</td>
<td>86 (25)</td>
<td>0.312</td>
<td>0.003</td>
<td>0.325</td>
<td>0.002</td>
</tr>
<tr>
<td>BMI ≤ 25</td>
<td>247 (71.8)</td>
<td>0.26</td>
<td>&lt; 0.001</td>
<td>0.252</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>BMI &gt; 25</td>
<td>97 (28.2)</td>
<td>0.305</td>
<td>0.002</td>
<td>0.192</td>
<td>0.060</td>
</tr>
<tr>
<td>MELD &lt; 25</td>
<td>265 (76.8)</td>
<td>0.213</td>
<td>&lt; 0.001</td>
<td>0.18</td>
<td>0.003</td>
</tr>
<tr>
<td>MELD ≥ 25</td>
<td>79 (22.8)</td>
<td>0.446</td>
<td>&lt; 0.001</td>
<td>0.424</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>No ascites</td>
<td>162 (46.7)</td>
<td>0.213</td>
<td>0.006</td>
<td>0.155</td>
<td>0.049</td>
</tr>
<tr>
<td>Ascites</td>
<td>182 (5.3)</td>
<td>0.281</td>
<td>&lt; 0.001</td>
<td>0.257</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Controlled ascites</td>
<td>111 (32.3)</td>
<td>0.316</td>
<td>0.001</td>
<td>0.307</td>
<td>0.001</td>
</tr>
<tr>
<td>Uncontrolled ascites</td>
<td>71 (20.6)</td>
<td>0.215</td>
<td>0.072</td>
<td>0.21</td>
<td>0.009</td>
</tr>
<tr>
<td>Living donor LT</td>
<td>254 (73.8)</td>
<td>0.226</td>
<td>&lt; 0.001</td>
<td>0.193</td>
<td>0.002</td>
</tr>
<tr>
<td>Deceased donor LT</td>
<td>90 (26.2)</td>
<td>0.129</td>
<td>0.224</td>
<td>0.163</td>
<td>0.126</td>
</tr>
<tr>
<td>Cirrhotic disease</td>
<td>281 (81.7)</td>
<td>0.19</td>
<td>0.001</td>
<td>0.133</td>
<td>0.026</td>
</tr>
<tr>
<td>HBV related disease</td>
<td>227 (66)</td>
<td>0.25</td>
<td>&lt; 0.001</td>
<td>0.17</td>
<td>0.010</td>
</tr>
<tr>
<td>HCV related disease</td>
<td>32 (9.3)</td>
<td>0.046</td>
<td>0.803</td>
<td>0.691</td>
<td>0.690</td>
</tr>
<tr>
<td>Alcoholic disease</td>
<td>50 (14.5)</td>
<td>0.317</td>
<td>0.025</td>
<td>0.313</td>
<td>0.027</td>
</tr>
<tr>
<td>Non-cirrhotic disease</td>
<td>63 (18.3)</td>
<td>0.203</td>
<td>0.110</td>
<td>0.254</td>
<td>0.045</td>
</tr>
</tbody>
</table>

RVSP: right ventricular systolic pressure, PAP: pulmonary arterial pressure, RHC: right heart catheterization, sPAP: systolic PAP, mPAP: mean PAP, BMI: body mass index, MELD: model for end-stage liver disease, LT: Liver transplantation, HBV: hepatitis B virus, HCV: hepatitis C virus.

(mean value of RVSP-mPAP) was 12.79 mmHg (SD ± 7.34), and the 95% limits of agreement were 27.17 and –1.59 mmHg (Fig. 5).

The positive and negative predictive values of RVSP > 50 mmHg on echocardiography for identifying mPAP > 35 mmHg were 37.5% and 49.9%, respectively, and 28.6% and 49.8% for sPAP > 50 mmHg (Table 3). According to intraoperative measurements from RHC, five recipients were diagnosed as porto-pulmonary hypertension. In contrast to the results from the other subgroups, preoperative RVSP was lower than sPAP in intraoperative RHC in these recipients (38.2 ± 16.5 vs. 40.6 ± 8.0).

**DISCUSSION**

In this study, we evaluated the correlation between RVSP on preoperative 2D-echocardiography and PAP on intraoperative RHC and found a significant but weak correlation in the overall population. In the Bland-Altman plots, the difference between RVSP and PAP tended to be more significant when RVSP or PAP was higher. The subgroup analyses demonstrated that the correlation was not significant in recipients with uncontrolled ascites or in recipients of deceased donor LT. The results of this study suggest that pulmonary pressure on preoperative 2D-echocardiography...
does not predict intraoperative state adequately, especially when PAP or RVSP is high or in LT recipients of deceased donor type or with uncontrolled ascites. Moreover, predictive values for identifying PH with high risk for LT were poor in the entire population and subgroup analysis. Although 2D-echocardiography is an effective modality in screening for porto-pulmonary hypertension in LT candidates, our results question whether preoperative 2D-echocardiography monitoring can reflect intraoperative pulmonary hemodynamics of LT recipients.

Survival after LT is highly dependent on cardiac function, and PAP is directly associated with clinical outcomes of LT [4,7,13]. A graded association was shown between mPAP and mortality in the subgroup of patients with high pulmonary vascular resistance, and sPAP was associated with increased risk of hospitalization for cardiac disease [14-16].
The use of RHC cannot always be justified as a screening tool due to invasiveness, but it is the only gold standard modality to confirm porto-pulmonary hypertension. Early studies demonstrated that echocardiography can be an effective tool for detecting PH in LT candidates [8,9], and these results have led to wide use of 2D-echocardiography as an initial screening method to determine the need for RHC by screening for cardiac abnormalities or PH. However, predicting intraoperative PAP based on preoperative echocardiographic results can be influenced by other perioperative factors. Therefore, we evaluated the correlation between RVSP on preoperative 2D-echocardiography and PAP on intraopera-

---

**Table 3.** Predictive Values of RVSP > 50 mmHg to Detect Pulmonary Arterial Hypertension on RHC

<table>
<thead>
<tr>
<th>Variable</th>
<th>RVSP &gt; 50 mmHg</th>
<th>mPAP &gt; 35 mmHg detection</th>
<th>sPAP &gt; 50 mmHg detection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>PPV</td>
<td>NPV</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>--------</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Overall recipients (n = 344)</td>
<td>5</td>
<td>3</td>
<td>37.5</td>
</tr>
<tr>
<td>Male (n = 258)</td>
<td>4</td>
<td>3</td>
<td>42.9</td>
</tr>
<tr>
<td>Female (n = 86)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>BMI &lt; 25 (n = 247)</td>
<td>0</td>
<td>1</td>
<td>100</td>
</tr>
<tr>
<td>BMI ≥ 25 (n = 97)</td>
<td>5</td>
<td>2</td>
<td>28.6</td>
</tr>
<tr>
<td>MELD &lt; 25 (n = 247)</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MELD ≥ 25 (n = 97)</td>
<td>1</td>
<td>3</td>
<td>75</td>
</tr>
<tr>
<td>No ascites (n = 162)</td>
<td>1</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>Ascites (n = 182)</td>
<td>4</td>
<td>2</td>
<td>33.3</td>
</tr>
<tr>
<td>Controlled ascites (n = 111)</td>
<td>3</td>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td>Uncontrolled ascites (n = 71)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Living donor LT (n = 254)</td>
<td>2</td>
<td>1</td>
<td>33.3</td>
</tr>
<tr>
<td>Deceased donor LT (n = 90)</td>
<td>3</td>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td>Cirrhotic disease (n = 281)</td>
<td>3</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>HBV related disease (n = 227)</td>
<td>2</td>
<td>1</td>
<td>33.3</td>
</tr>
<tr>
<td>HCV related disease (n = 32)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Alcoholic disease (n = 50)</td>
<td>1</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td>Non-cirrhotic disease (n = 63)</td>
<td>2</td>
<td>2</td>
<td>50</td>
</tr>
</tbody>
</table>

RVSP: right ventricular systolic pressure, RHC: right heart catheterization, sPAP: systolic pulmonary arterial pressure, mPAP: mean pulmonary arterial pressure, PPV: Positive predictive value, NPV: Negative predictive value, BMI: body mass index, MELD: model for end-stage liver disease, LT: Liver transplantation, HBV: hepatitis B virus, HCV: hepatitis C virus.
tive RHC in a large cohort of total LT recipients and its subgroups.

Although several indexes and methods have been adopted to increase accuracy and reproducibility [17], correlations between RVSP on 2D-echocardiography and PAP on RHC have been reported to be weak in the general population [7]. Methods to improve accuracy include measuring tricuspid annular plane systolic excursion, two-dimensional strain, tissue Doppler echocardiography, the speckle tracking method, acceleration time across the pulmonic valve, the pulmonary artery regurgitant jet method, and the tricuspid regurgitant jet method [18]. The most commonly used method is to measure the maximum velocity of the tricuspid regurgitant jet, which was used in this study.

In this study, the correlation between preoperative RVSP on 2D-echocardiography and intraoperative PAP on RHC was significant but weak, and the following inherent limitations might be related to this result. First, 2D-echocardiography was performed in the preoperative period, while PAP was measured intraoperatively by RHC. There is a difference in physiologic status between pre- and intraoperative periods. Second, the echocardiography beam cannot always be parallel to the tricuspid regurgitant jet when obtaining maximum velocity [19]. Third, distal obstruction such as right ventricular outlet obstruction, pulmonic valve stenosis, or supravalvular stenosis might be present [18]. Lastly, the continuous wave Doppler spectrum can be suboptimal or absent. In patients with limited echocardiographic view, contrast agent can be considered to enhance the velocity signal [20,21]. Another possibility is related to the time gap from 2D-echocardiography to LT. Due to the retrospective nature of this study, preoperative echocardiographic assessment was not repeated in candidates with normal findings, and this gap was inconsistent among study participants.

Unlike the overall population in which preoperative RVSP far exceeded intraoperative sPAP on RHC, preoperative RVSP slightly underestimated intraoperative sPAP in recipients diagnosed with porto-pulmonary hypertension by RHC. This result corresponds well with previous studies in that, while diagnostic value of 2D-echocardiography is pronounced in patients with moderate to severe PH, a weak correlation with pulmonary pressure was reported among LT candidates overall [7–9]. Our predictive values for identifying clinically significant PH are lower than those of one previous study [9], owing to the following differences in clinical setting. First, we evaluated the predictive value of preoperative RVSP for identifying intraoperative PH. Unlike a comparison between simultaneous measurements, induction of general anesthesia before catheter insertion as well as the time gap might have affected the results because anesthetics affect pulmonary hemodynamics [22]. Second, the study used a larger cohort and enrolled results of 2D-echocardiography performed in various clinical settings other than echocardiographic laboratories. Echocardiographic imaging is more difficult when related to position of the patient, lack of cooperation, tachypnea or artificial ventilation, and other factors [23]. Inter- and intra-observer variability of echocardiographic assessment can be pronounced in less experienced hands [24]. The strength of this study is that the results reflect the correlations of real-world practice in various clinical settings of LT recipients and are presented according to these subgroups.

In recipients with ascites, only the group with uncontrolled ascites showed a non-significant correlation. This result could be related to increased intra-abdominal pressure that might have affected right atrial pressure by altering venous return [25]. Previous studies on the effect of increased intra-abdominal pressure on the circulatory system have reported inconsistent results. While initial studies assumed that venous return would increase following intra-abdominal pressure, subsequent studies showed a decreased venous return [26]. To explain these contradictory results, a hypothesis that vascular waterfall occurs in the inferior vena cava at diaphragm level was proposed. The waterfall phenomenon was demonstrated in an animal study and is presumed to interact with intra-abdominal pressure, inferior vena cava pressure, and transmural closing pressure of the inferior vena cava [27].

Although 2D-echocardiography can be clinically valuable in screening PH in LT candidates, our findings suggest that preoperative 2D-echocardiography might not be sufficient for predicting intraoperative state. That is because some of the clinical settings in this study are inevitable; moreover, diagnostic criteria of porto-pulmonary hypertension require direct measurements from RHC such as mPAP, pulmonary vascular resistance, and pulmonary capillary wedge pressure. Thus, it is reasonable to consider intraoperative RHC actively for recipients at risk. Also, selection of LT candidates for preoperative RHC and measures to improve quality of preoperative 2D-echocardiography is an important issue that was not resolved by this study. The efficacy of intraoperative echocardiography and the correlation with RHC during LT procedures are beyond the scope of this study and require further randomized investigations.
Our study was limited by its retrospective design and potential selection bias. Different time intervals from preoperative 2D-echocardiography to surgery also might have caused variability. Sensitivity and specificity for detecting PH could not be analyzed because patients with marked elevation of PAP were allocated for transplantation only after successful treatment. Lastly, the association with clinical outcome was not analyzed in this study. Despite these limitations, this is the first study validating preoperative 2D-echocardiography for predicting intraoperative PAP in LT recipient subgroups.

In LT recipients, the correlations between RVSP on preoperative 2D-echocardiography and PAP on intraoperative RHC are significant but weak. Preoperative 2D-echocardiography might not be reliable in predicting intraoperative pulmonary hemodynamics, and it is reasonable to consider intraoperative RHC for recipients at risk of PH.

**CONFLICTS OF INTEREST**

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

**DATA AVAILABILITY STATEMENT**

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

**AUTHOR CONTRIBUTIONS**


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Preoperative hyperlactatemia and early mortality after liver transplantation: selection of important variables using random forest survival analysis

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Background: Generally, lactate levels > 2 mmol/L represent hyperlactatemia, whereas lactic acidosis is often defined as lactate > 4 mmol/L. Although hyperlactatemia is common finding in liver transplant (LT) candidates, association between lactate and organ failures with Acute-on-chronic Liver Failure (ACLF) is poorly studied. We searched the important variables for pre-LT hyperlactatemia and examined the impact of preoperative hyperlactatemia on early mortality after LT.

Methods: A total of 2,002 patients from LT registry between January 2008 and February 2019 were analyzed. Six organ failures (liver, kidney, brain, coagulation, circulation, and lung) were defined by criteria of EASL-CLIF ACLF Consortium. Variable importance of preoperative hyperlactatemia was examined by machine learning using random survival forest (RSF). Kaplan-Meier Survival curve analysis was performed to assess 90-day mortality.

Results: Median lactate level was 1.9 mmol/L (interquartile range: 1.4, 2.4 mmol/L) and 107 (5.3%) patients showed > 4.0 mmol/L. RSF analysis revealed that the four most important variables for hyperlactatemia were MELD score, circulatory failure, hemoglobin, and respiratory failure. The 30-day and 90-day mortality rates were 2.7% and 5.1%, whereas patients with lactate > 4.0 mmol/L showed increased rate of 15.0% and 19.6%, respectively.

Conclusions: About 50% and 5% of LT candidates showed pre-LT hyperlactatemia of > 2.0 mmol/L and > 4.0 mmol/L, respectively. Pre-LT lactate > 4.0 mmol/L was associated with increased early post-LT mortality. Our results suggest that future study of correcting modifiable risk factors may play a role in preventing hyperlactatemia and lowering early mortality after LT.

Keywords: Early mortality; Lactate; Liver transplantation; Random survival.

INTRODUCTION

Serum lactate level has been a useful tool for assessing severity of various diseases and is associated with poor outcomes in critically ill patients, such as septic, cardiogenic, hypovolemic shock, and liver failure [1–3]. Patients with end-
stage liver disease are prone to develop acute decompensation with progressive organ failures, which may lead to developing the acute-on-chronic liver failure (ACLF) [4]. However, relationships between pre-liver transplant (LT) lactate and liver disease severity with organ failures are poorly studied in LT candidates.

In the current study, we sought to comprehend the distribution of lactate in LT candidates and searched the risk factors for hyperlactatemia. Specifically, to identify the most susceptible organ failures for the development of hyperlactatemia, we employed random survival forest (RSF) analysis and definitions from the Chronic Liver Failure Consortium ACLF score (CLIF-C ACLFs) [5]. Random forest is the machine learning technique using ensemble learning method for classification, regression, survival and identifying important risk factors [6–8]. Additionally, we evaluated association between pre-LT hyperlactatemia and early mortality after LT.

**MATERIALS AND METHODS**

**Study population**

The study design and a waiver of informed consent for participants were approved by the Institutional Review Board (no. 2021-0711). Data was extracted from the institution's LT Registry, which prospectively registered patients who underwent LT. From January 2008 to February 2019, there were 4,406 potentially eligible LT recipients. Patients with toxic hepatitis (n = 141), fulminant hepatic failure (n = 134), were excluded. The patients who did not measure lactate within 7 days before LT (n = 1,822) and those with incomplete data (n = 307) were also excluded. After exclusion, 2,002 LT recipients were finally included. We included the majority of heterogenous LT recipients except acute toxic or fulminant hepatitis because we aimed to identify which co-morbidities, or organ failures were most susceptible to pre-LT hyperlactatemia.

**Data collection and definition of organ failures**

Patient demographics, medical history Model for End-stage Liver Disease score (MELDs), and laboratory variables were obtained automatically using a fully computerized data extraction software. Mortality data were obtained from patients’ electronic medical records and the updated record of the institution’s LT registry. To identify risk factors associated with hyperlactatemia, we thoroughly investigated the association of hyperlactatemia with comorbidities and six organ failures (liver, kidney, brain, coagulation, circulation, and lungs) incorporated in definitions from the CLIF-C ACLFs. Briefly, they were defined as follows; Liver failure: bilirubin level of > 12 mg/dl, Kidney failure: creatinine > 2.0 mg/dl or renal replacement, Brain failure: hepatic encephalopathy grade by West-Haven, 3–4, Coagulation failure: INR ≥ 2.5, Circulatory failure: use of vasopressor, Respiratory failure: PaO2/FiO2 ≤ 200; SpO2/FiO2 ≤ 214; or on ventilator treatment [5].

**Classification of patients with Lactate > 4.0 mmol/L and ≤ 4.0 mmol/L**

Among patients with > 1 pre-transplant lactate measurements, the most proximate to the date of transplant within seven pre-transplant days was used. Lactate levels greater than 2 mmol/L represent hyperlactatemia, whereas lactic acidosis is generally defined as a serum lactate concentration above 4 mmol/L.

We chose threshold of lactate as 4.0 mmol/L according to the Surviving Sepsis Campaign guidelines, in which A lactate > 4 mmol/L qualifies for administration of early quantitative resuscitation therapy [9].

**Statistical analysis**

Data were expressed as mean with standard deviation (SD) or median with interquartile range (IQR) for continuous variables, and numbers and percentages for categorical variables. Analyses between groups were performed using Student’s t-test, the Mann–Whiney U test, analysis of variance, or the Kruskal–Wallis test for continuous variables and the χ² test or Fisher’s exact test for categorical variables, as appropriate. Kaplan–Meier survival curve analysis with log-rank test was used to evaluate the risk of 90-day mortality.

**Identifying important variables for preoperative hyperlactatemia**

Variable importance (VIMP) was defined in classification and regression trees of RSF using a measure involving surrogate variables. Since VIMP is the difference between Out-of-Bag prediction error before and after permutation, a large VIMP value indicates that misspecification detracts from the variable predictive accuracy in the forest.
A random forest for pre-LT serum lactate levels was generated by creating 1,000 trees using gRandomForest R-software package. The following variables were included for predicting preoperative hyperlactatemia: MELDs, left ventricular ejection fraction, hemoglobin, sepsis, and six organ failures defined by CLIF-C ACLFs.

All statistical analyses were performed using R version 3.6.1 (R Foundation for Statistical Computing, Austria). P value of less than 0.05 was considered statistically significant.

RESULTS

Of 2,002 LT recipients included, their mean age was 53.0 (48.0, 58.0) years and 1,489 (74.4%) were men. The mean MELDs was 16.0 (10.0, 26.0). The primary causes of liver disease were B or C virus-related liver cirrhosis (69.2%), alcoholic liver disease (19.8%) and others (11.0%) (Table 1). Prevalence of organ failures defined by CLIF-C ACLFs [5] were liver failure (24.0%), respiratory failure (10.8%), kidney failure (8.3%), coagulation failure (9.3%), circulatory failure (5.6%), and brain failure (2.6%), respectively (Table 2).

Distribution of Lactate in LT candidates

Median lactate level was 1.9 mmol/L (range: 0.4–24.6, IQR: 1.4, 2.4 mmol/L) and 107 (5.3%) patients showed lactate > 4.0 mmol/L. When patients were grouped with MELDs of < 15, 15–35, > 35, their median lactate level were 1.7 (1.4, 2.2), 1.9 (1.5, 2.5), and 2.4 (1.9, 3.6) mmol/L, respectively (P < 0.001) (Fig. 1).

Important variables for pre-LT hyperlactatemia

When we ignored the negative value of VIMP, the four most important variables for hyperlactatemia were MELDs, circulatory failure, hemoglobin, and respiratory failure, respectively (Fig. 2).

Table 1. Descriptive Statistics by Lactate 4.0 mmol/L

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lactate ≤ 4 mmol/L (n = 1,895)</th>
<th>Lactate &gt; 4 mmol/L (n = 107)</th>
<th>Total (n = 2,002)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male</td>
<td>1,408 (74.3)</td>
<td>81 (7.5)</td>
<td>1,489 (74.4)</td>
<td>0.834</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>53.0 (48.0, 58.0)</td>
<td>53.0 (46.5, 57.0)</td>
<td>53.0 (48.0, 58.0)</td>
<td>0.563</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.0 (21.9, 26.5)</td>
<td>23.7 (21.0, 26.3)</td>
<td>24.0 (21.8, 26.4)</td>
<td>0.058</td>
</tr>
<tr>
<td>Re-transplantation</td>
<td>77 (4.1)</td>
<td>14 (1.3)</td>
<td>91 (4.5)</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>OLTLT</td>
<td>326 (17.2)</td>
<td>58 (5.4)</td>
<td>384 (19.2)</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>CAD</td>
<td>79 (6.3)</td>
<td>8 (0.7)</td>
<td>87 (6.6)</td>
<td>0.112</td>
</tr>
<tr>
<td>CVA</td>
<td>15 (0.9)</td>
<td>1 (0.1)</td>
<td>16 (0.8)</td>
<td>1.000</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>459 (24.2)</td>
<td>29 (2.7)</td>
<td>488 (24.4)</td>
<td>0.576</td>
</tr>
<tr>
<td>Hypertension</td>
<td>273 (14.4)</td>
<td>17 (1.5)</td>
<td>290 (14.5)</td>
<td>0.778</td>
</tr>
<tr>
<td>MELD</td>
<td>15.0 (10.0, 24.0)</td>
<td>34.0 (21.0, 41.0)</td>
<td>16.0 (10.0, 26.0)</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>Causes of liver disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis B virus</td>
<td>1192 (62.9)</td>
<td>54 (5.1)</td>
<td>1246 (62.2)</td>
<td>0.013*</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>135 (7.1)</td>
<td>6 (0.5)</td>
<td>141 (7.0)</td>
<td>0.687</td>
</tr>
<tr>
<td>Alcohol</td>
<td>366 (19.3)</td>
<td>31 (2.9)</td>
<td>397 (19.8)</td>
<td>0.021*</td>
</tr>
<tr>
<td>Others</td>
<td>202 (10.7)</td>
<td>16 (1.4)</td>
<td>218 (11.0)</td>
<td>0.853</td>
</tr>
<tr>
<td>Laboratory values</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>10.3 (8.8, 12.2)</td>
<td>9.0 (8.0, 10.2)</td>
<td>10.3 (8.7, 12.2)</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>WBC (x10³/μl)</td>
<td>3.6 (2.4, 5.2)</td>
<td>7.1 (4.2, 11.8)</td>
<td>3.7 (2.5, 5.5)</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>Natrium (mmol/L)</td>
<td>138.0 (135.0, 141.0)</td>
<td>137.0 (134.0, 141.5)</td>
<td>138.0 (135.0, 141.0)</td>
<td>0.954</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>0.4 (0.1, 1.3)</td>
<td>1.7 (0.7, 3.6)</td>
<td>0.4 (0.1, 1.4)</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>INR</td>
<td>1.4 (1.2, 1.8)</td>
<td>2.1 (1.5, 2.6)</td>
<td>1.5 (1.2, 1.9)</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>2.4 (1.2, 9.2)</td>
<td>15.4 (4.8, 30.2)</td>
<td>2.6 (1.3, 11.1)</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.8 (0.6, 1.0)</td>
<td>1.2 (0.7, 2.1)</td>
<td>0.8 (0.7, 1.0)</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>Lactate (mmol/L)</td>
<td>1.6 (1.4, 2.3)</td>
<td>5.5 (4.6, 7.0)</td>
<td>1.9 (1.4, 2.4)</td>
<td>&lt; 0.001†</td>
</tr>
</tbody>
</table>

Values are presented as median (1Q, 3Q) or number (%). BMI: body mass index, LT: orthotopic liver transplantation, CAD: coronary artery disease, CVA: cerebrovascular accident, MELD: model for end-stage liver disease, WBC: white blood cell, CRP: C-reactive protein, INR: international normalized ratio. P value < 0.05, †P value < 0.01.
Table 2. CLIF-C ACLF Organ Failures by Lactate 4.0 mmol/L

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lactate ≤ 4 mmol/L (n = 1,895)</th>
<th>Lactate &gt; 4 mmol/L (n = 107)</th>
<th>Total (n = 2,002)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLIF_liver</td>
<td>413 (21.8)</td>
<td>67 (62.6)</td>
<td>480 (24.0)</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>CLIF_respiratory</td>
<td>162 (8.6)</td>
<td>55 (51.4)</td>
<td>217 (10.8)</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>CLIF_kidney</td>
<td>138 (7.3)</td>
<td>28 (26.2)</td>
<td>166 (8.3)</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>CLIF_coagulation</td>
<td>157 (8.3)</td>
<td>29 (27.1)</td>
<td>186 (9.3)</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>CLIF_circulatory</td>
<td>77 (4.1)</td>
<td>36 (33.6)</td>
<td>113 (5.6)</td>
<td>&lt; 0.001†</td>
</tr>
<tr>
<td>CLIF_brain</td>
<td>41 (2.2)</td>
<td>11 (10.3)</td>
<td>52 (2.6)</td>
<td>&lt; 0.001†</td>
</tr>
</tbody>
</table>

Values are presented as number (%). CLIF-C ACLF: chronic liver failure consortium acute-on-chronic liver failure score, CLIF: chronic liver failure.

† P value < 0.01.

Fig. 1. Density histogram of pre-liver transplant lactate is showing rightward shift, according to MELDs classification of < 15, 15–35, > 35. MELDs: model for end-liver disease score.

Fig. 2. Random forest variable importance (VIMP). Blue bars indicate positive VIMP, red indicates negative VIMP. Importance is relative to positive length of bars. VIMP: variable importance, MELD: model for end-liver disease, CLIF_cir_F: circulatory failure by CLIF score, CLIF_resp_F: respiratory failure by CLIF score, CLIF_kidney_F: kidney failure by CLIF score, LVEF: left ventricular ejection fraction, CLIF_brain_F: brain failure by CLIF score.

Fig. 3. The 90-day Kaplan-Meier survival curve stratified by lactate 4.0 mmol/L with shaded 95% confidence bands.

Survival analysis on 30-day and 90-day mortality

The 30-day and 90-day mortality rates were 2.7% and 5.1%, however, patients with lactate > 4.0 mmol/L showed increased mortality rate of 15.0% and 19.6%, respectively. Kaplan-Meier analysis showed clear separation of survival curve of 90-day mortality (P < 0.001, Fig. 3).

DISCUSSION

Lactate levels is known to be a useful and rapid tool for assessing severity of disease in critically ill patients [10]. It has been shown that increased lactate levels and reduced lactate clearance are associated with mortality in critically ill patients with liver cirrhosis [1]. Therefore, lactate is believed to be a simple and accurate prognostic marker, and its incorporation improved performance of CLIF-C ACLFs significantly [10]. The Asian Pacific Association for the Study of the Liver (APASL) also incorporated lactate levels in its APASL...
ACLF research consortium-ACLF score [11].

Conventionally, lactate has been considered as a marker for tissue hypoxia, as lactate is overproduced and underutilized under anaerobic glycolysis due to impaired mitochondrial oxidation [12]. Therefore, increased serum lactate is usually the result from an imbalance of increased lactate production or reduced consumption [12]. Given that the liver is responsible for about 70% of whole-body lactate clearance, especially acute and fulminant hepatic impairment is associated with increased lactate levels and poor outcomes [13]. In contrast, under stable conditions, even severe liver cirrhosis has rarely been known to be associated with relevantly elevated lactate levels [12].

In the current study, after exclusion of toxic and fulminant hepatic failure, we investigated the important variables for preoperative hyperlactatemia in LT candidates and the relation between preoperative hyperlactatemia and early outcome after LT by using random forest survival analysis. We found that lactate monitoring is important in LT candidates because patients with lactate > 4.0 mmol/L showed increased 30-day mortality rate of 15.0% and 90-day mortality rate of 19.6%, respectively.

Although the lower limit of the normal range for the blood lactate level, 0.5 mmol/L, is generally accepted among clinical laboratories, the upper limit can vary considerably, from 1.0 mmol/L to 2.2 mmol/L [12]. However, a plasma lactate concentration that exceeds 4 mmol/L generally defines lactic acidosis, even among patients without systemic acedia. In the current study 5.3% of LT candidates fell into this category of lactate > 4 mmol/L.

The important variables related to hyperlactatemia were MELDs, circulatory failure, hemoglobin level, and respiratory failure in the order of importance. MELD score is useful for estimating overall disease severity and predicting survival in the patient with liver disease [14]. Therefore, the highest VIMP of MELD score in the current study may be related to hepatic dysfunction and reduced metabolism of lactate. Another important thing to be considered in the VIMP analysis is that circulatory failure and hemoglobin were chosen as VIMP in the current study. These results suggest that not only liver disease severity but also circulatory disturbance with anemia is an important contributor of pre-LT hyperlactatemia.

Circulatory failure has been defined typically as a condition in which the circulation is insufficient to deliver adequate oxygen to match the needs of the oxidizing tissues. However, the correlation between cardiac index and hyperlactatemia is not noticeably clear. A study reported that lactate levels were normal in about 75% of the patients with advanced heart failure [15], however, in LT candidates, circulatory failure defined by CLIF-C ACLFs remained one of important risk factors for pre-LT hyperlactatemia in the current study.

Both anemia and hypotension may induce tissue hypoxia due to reduced tissue oxygen delivery. In our study, patients who received transfusions or vasopressors would have higher plasma lactate concentrations due to anemia or hypotension. However, the retrospective nature of the current study cannot discriminate that high lactate was associated with either transfusions or vasopressors, or both.

Variables of importance for pre-LT hyperlactatemia was identified by machine learning using RSF in the current study. One of advantages of this analysis is that missing data are also less of a concern when using RSF. RSF performs excellently even with heavy missingness and when missing data are not missing completely at random [16,17]. Of 2,002 cases of lactic acid analysis, missing values were organ failures of 4, sepsis of 1, and left ventricular ejection fraction of 53 cases in the current study, respectively.

In this analysis, VIMP close to zero indicates the variable contributes nothing to predictive accuracy, and negative values indicate the predictive accuracy improves when the variable is misspecified. Therefore, we ignored variables with negative and near zero values of VIMP.

This study has several limitations. The enrolled patients are from the observational cohort study in a single center and retrospective observational design. Therefore, further prospective randomized control studies are warranted to validate our results.

In conclusion, about 50% and 5% of LT candidates showed pre-LT hyperlactatemia of > 2.0 mmol/L and > 4.0 mmol/L, respectively and those with lactate > 4.0 mmol/L was associated with increased early post-LT mortality. Four the most important variables for hyperlactatemia were MELD score, circulatory failure, hemoglobin, and respiratory failure. Our results suggest that future study of correcting modifiable risk factors, such as anemia and hypotension correction, may play a role in preventing hyperlactatemia and lowering early mortality after LT.

**ACKNOWLEDGEMENTS**

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Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HI18C2383).

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

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REFERENCES


Ability of dynamic preload indices to predict fluid responsiveness in a high femoral-to-radial arterial pressure gradient: a retrospective study

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Background: Dynamic preload indices may predict fluid responsiveness in end-stage liver disease. However, their usefulness in patients with altered vascular compliance is uncertain. This study is the first to evaluate whether dynamic indices can reliably predict fluid responsiveness in patients undergoing liver transplantation with a high femoral-to-radial arterial pressure gradient (PG).

Methods: Eighty liver transplant recipients were retrospectively categorized as having a normal (n = 56) or high (n = 24, difference in systolic pressure ≥ 10 mmHg and/or mean pressure ≥ 5 mmHg) femoral-to-radial arterial PG, measured immediately after radial and femoral arterial cannulation. The ability of dynamic preload indices (stroke volume variation, pulse pressure variation [PPV], pleth variability index) to predict fluid responsiveness was assessed before the surgery. Fluid replacement of 500 ml of crystalloid solution was performed over 15 min. Fluid responsiveness was defined as ≥ 15% increase in the stroke volume index. The area under the receiver-operating characteristic curve (AUC) indicated the prediction of fluid responsiveness.

Results: Fourteen patients in the normal, and eight in the high PG group were fluid responders. The AUCs for PPV in the normal, high PG groups and total patients were 0.702 (95% confidence interval [CI] 0.553–0.851, P = 0.008), 0.633 (95% CI 0.384–0.881, P = 0.295) and 0.667 (95% CI 0.537–0.798, P = 0.012), respectively. No other index predicted fluid responsiveness.

Conclusions: PPV can be used as a dynamic index of fluid responsiveness in patients with end-stage liver disease but not in patients with altered vascular compliance.

Keywords: End stage liver disease; Fluid therapy; Hemodynamic monitoring; Liver transplantation.

INTRODUCTION

Patients with end-stage liver disease who undergo liver transplantation have hyperdynamic circulation with increased cardiac output (CO) and low systemic vascular resistance (SVR) [1]. Liver transplantation increases the risk of
massive bleeding and sudden hemodynamic changes during surgery [2]. Although fluid management plays an important role in maintaining blood pressure during liver transplantation, excessive fluid loading may worsen postoperative outcomes. In general, the goal of fluid therapy in hemodynamically unstable patients is to increase CO and optimize tissue perfusion [3,4].

Various indices have been used to predict individual responses to fluid therapy. It has been found that dynamic indices such as stroke volume variation (SVV) and pulse pressure variation (PPV) are more reliable than static indices such as central venous pressure (CVP) or pulmonary arterial occlusion pressure (PAOP) [5–7]. Several studies have shown that use of SVV or PPV is beneficial, especially in hemodynamically unstable patients in intensive care units and in patients undergoing cardiac surgery [8,9]. The pleth variability index (PVI) is also as accurate as SVV in predicting fluid responsiveness, and intraoperative fluid management based on the PVI has been shown to reduce intraoperative and postoperative lactate levels [10].

However, there is a lot of debate about the usefulness of dynamic indices as an indicator of need for intraoperative fluid therapy in patients with end-stage liver disease undergoing liver transplantation [11–14]. The predictability of dynamic indices may be affected by vascular compliance; SVV did not predict fluid responsiveness in patients with coronary artery disease who had a wide pulse pressure (> 60 mmHg) [15]. Differences in the femoral-to-radial arterial pressure are often observed during liver transplantation [16]. However, no study has determined the ability of dynamic indices to predict fluid responsiveness in this condition. The aim of this study was to evaluate whether or not dynamic indices can reliably predict fluid responsiveness in patients undergoing liver transplantation with a high femoral-to-radial arterial pressure gradient (PG).

MATERIALS AND METHODS

Study population

The study protocol was approved by the Institutional Review Board (IRB) of Severance Hospital, Yonsei University Health System (no. 4-2019-0034). Patient records and information were anonymized before analysis; hence, the requirement for written informed consent to access medical records was waived. We retrospectively identified 91 patients over 20 years of age who underwent elective living donor liver transplantation at our hospital between August 1, 2017, and January 31, 2019. Patients with preoperative arrhythmia, reduced left ventricular function (ejection fraction < 40%), valvular heart disease, pulmonary hypertension, pulmonary disease (asthma, chronic obstructive pulmonary disease, history of lung resection), or chronic renal disease were excluded along with those who had incomplete medical records.

Anesthesia and hemodynamic monitoring

All patients underwent our institution’s standard anesthesia protocol for living donor liver transplantation. Routine non-invasive monitoring (5-lead electrocardiography, pulse oximetry, non-invasive blood pressure, and the bispectral index) was applied. The Masimo Radical 7 co-oximeter probe (MasimoSET® Rainbow, Masimo Corp., USA) was placed on the patient’s index finger and covered with a shield to eliminate light interference, as recommended by the manufacturer. Anesthesia was induced with intravenous propofol, sufentanil, and rocuronium and maintained with desflurane and a continuous infusion of sufentanil and rocuronium. After tracheal intubation, mechanical ventilation was started in volume-controlled mode with a tidal volume of 8 ml/kg, a respiratory rate of 10–15 breaths/min, and 5 cm H2O of positive end-expiratory pressure. Arterial catheters were inserted into the right radial artery and left femoral artery, and a Flotrac/Vigileo system (Edwards Lifesciences, USA) was connected to the radial arterial cannula. A pulmonary artery catheter (Swan-Ganz CCOMbo, Edwards Lifesciences) was inserted through the right internal jugular vein and connected to a Vigilance monitor (Edwards Lifesciences) for continuous measurement of CO. A central venous catheter was inserted in the left internal jugular vein or subclavian vein. All transducers were zeroed at the mid-axillary level. After induction of anesthesia and before the start of surgery, fluid loading was performed with 500 ml of balanced crystalloid solution (Plasma Solution-A®, CJ HealthCare, Korea) through a central line for 15 min following our institution’s routine liver transplantation anesthesia protocol. This fluid loading was performed to prevent hypotension during anesthesia and to confirm the patient’s fluid responsiveness. However, such crystalloid administration was excluded in patients with pre-existing lung disease, pulmonary hypertension, or chronic kidney disease, which was consistent with the exclusion criteria of the present study. A continuous infusion of norepinephrine was used to main-
tain a mean arterial pressure (MAP) > 60 mmHg.

Acquisition of demographic and hemodynamic data

Preoperative characteristics, including age, sex, body mass index, left ventricular ejection fraction, and the model for end-stage liver disease score was collected from the electronic medical records. The following hemodynamic parameters were obtained from the anesthesia records: heart rate, radial arterial pressure, femoral arterial pressure, CVP, PAOP, PPV, PVI, CO, cardiac index, end-diastolic volume index (EDVI), right ventricular ejection fraction (RVEF), SVR, SVR index (SVRI), and stroke volume index (SVI). Each parameter was noted at the value 1 min before (baseline) and the value 5 min after the fluid loading was completed. CO, cardiac index, EDVI, RVEF, SVR, SVRI, and SVI were collected from the Swan-Ganz CCOombo/Vigilance monitor, and SVV was obtained by the FloTrac/Vigileo system. The PPV and PVI were automatically measured using a patient monitor (Philips Intellivue, MX700, Philips, The Netherlands) and Masimo monitor with PVI software, respectively.

Patients were considered fluid responders if their SVI increased by at least 15% (from Swan-GanzCCombo/Vigilance) after fluid loading [17,18]. Furthermore, the femoral-to-radial arterial PG was calculated to compare the effect of vascular tone on the ability of dynamic indices to predict fluid responsiveness. The difference between the femoral and the radial arterial blood pressures was measured immediately after radial and femoral cannulation. A significant femoral-to-radial arterial PG was defined as a difference of 10 mmHg in systolic arterial pressure (SAP) and/or 5 mmHg in MAP [19]. According to the femoral-to-radial arterial PG, patients were divided into the normal PG group (a difference in SAP < 10 mmHg and MAP < 5 mmHg) and the high PG group (a difference in SAP ≥ 10 mmHg and/or MAP ≥ 5 mmHg).

Statistical analysis

To compare the demographic and hemodynamic data between the two groups (normal PG and high PG), continuous variables were analyzed using a Student’s t-test and categorical variable was analyzed using a chi-square test. Continuous variables were examined for normality by the Kolmogorov–Smirnov test. Variables that did not deviated from normal distribution were presented as mean and standard deviation, and were compared using the independent sample t-test. Variables that were not normally distributed were presented as median and interquartile range, and were compared using the Mann–Whitney U test. A paired t-test was used to compare hemodynamic variables of baseline and after fluid loading. The ability of the preload parameters (CVP, PAOP, SVV, PPV, and PVI) to predict fluid responsiveness was evaluated using receiver-operating characteristic (ROC) curves. Static preload parameters (CVP and PAOP) and dynamic preload parameters (SVV, PPV, and PVI) obtained 1 min before fluid loading were used to analyze ROC curves. The area under the ROC curve (AUC) of each value was calculated, and the respective values were compared with a value of 0.5. The comparison of AUC between the two groups of normal PG and high PG was analyzed using a z-test. The optimal cut-off values for preload variables were determined by considering the values that yielded the Youden index (Sensitivity + Specificity – 1) for predicting fluid responsiveness. Statistical analyses were performed using SPSS (version 23, IBM Corp., USA) and SAS (version 9.4, SAS Inc., USA). A P value < 0.05 was considered statistically significant.

RESULTS

Data for 80 of the 91 patients were available for the final analysis. Fifty-six of these 80 patients were in the normal PG group and 24 were in the high PG group. There was no significant between-group difference in the patient characteristics (Table 1).

Hemodynamic data of baseline and after fluid replacement are listed in Table 2. After fluid replacement, radial MAP, femoral MAP, CVP, PAOP, CO, cardiac index, and EDVI were significantly increased whereas SVV and PPV were significantly decreased in the normal PG group. In the high PG group, the CVP, PAOP, CO, and cardiac index were significantly increased and the SVV was significantly decreased after fluid replacement.

The baseline hemodynamic data for the fluid responders and non-responders in each group are listed in Table 3. Fourteen patients in the normal PG group and eight in the high PG group responded to fluid replacement. In the normal PG group, baseline SVR, SVRI, and PPV were higher in the responders, whereas CO, CI, and SVI were lower in the responders than those in the non-responders. However, there was no significant difference in the baseline hemodynamic data between responders and non-responders in the high PG group.
Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal PG (n = 56)</th>
<th>High PG (n = 24)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>54.8 ± 9.2</td>
<td>55.8 ± 10.5</td>
<td>0.671</td>
</tr>
<tr>
<td>Sex, male</td>
<td>40 (71.4)</td>
<td>17 (70.8)</td>
<td>0.957</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168 (161, 171.5)</td>
<td>167 (157.5, 172)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.2 ± 11.6</td>
<td>65.1 ± 14.3</td>
<td>0.185</td>
</tr>
<tr>
<td>BMI</td>
<td>24.9 ± 3</td>
<td>23.7 ± 3.7</td>
<td>0.129</td>
</tr>
<tr>
<td>MELD</td>
<td>10.79 (7.92, 14.58)</td>
<td>12.52 (8.98, 19.48)</td>
<td>0.156</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>68.7 ± 5.6</td>
<td>69.3 ± 5.8</td>
<td>0.686</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.74 ± 0.27</td>
<td>0.76 ± 0.29</td>
<td>0.696</td>
</tr>
</tbody>
</table>

Values are expressed as the mean ± SD, number of patients (%), or median (1Q, 3Q). BMI: body mass index, LVEF: left ventricular ejection fraction, MELD: model for end-stage liver disease, PG: pressure gradient.

Table 2. Hemodynamic Data of Before and After Fluid Replacement

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before</th>
<th>After</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal PG (n = 56)</td>
<td>High PG (n = 24)</td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>69 ± 11</td>
<td>77 ± 16</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Radial MAP (mmHg)</td>
<td>80 ± 14</td>
<td>91 ± 18</td>
<td>0.001</td>
</tr>
<tr>
<td>Femoral MAP (mmHg)</td>
<td>82 ± 14</td>
<td>92 ± 19</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>10 ± 4</td>
<td>12 ± 5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PAOP (mmHg)</td>
<td>13 ± 5</td>
<td>16 ± 6</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>6.5 ± 2.4</td>
<td>7.2 ± 2</td>
<td>0.08</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>3.7 ± 1</td>
<td>4.1 ± 1</td>
<td>0.013</td>
</tr>
<tr>
<td>EDVI (ml/m²)</td>
<td>153 ± 40</td>
<td>160 ± 37</td>
<td>0.027</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>36 ± 10</td>
<td>34 ± 9</td>
<td>0.059</td>
</tr>
<tr>
<td>SVR (dyne/sec/cm²)</td>
<td>966 ± 364</td>
<td>1,005 ± 388</td>
<td>0.379</td>
</tr>
<tr>
<td>SVRI (dyne/sec/cm²/m²)</td>
<td>1,713 ± 705</td>
<td>1,629 ± 631</td>
<td>0.346</td>
</tr>
<tr>
<td>SVI (ml/m²/beat)</td>
<td>52 ± 15</td>
<td>52 ± 13</td>
<td>0.719</td>
</tr>
<tr>
<td>SVV (%)</td>
<td>7 ± 3</td>
<td>5 ± 3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>7 ± 3</td>
<td>5 ± 2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>PVI (%)</td>
<td>11 ± 5</td>
<td>12 ± 6</td>
<td>0.276</td>
</tr>
</tbody>
</table>


The AUCs for the ability of several preload indices to predict an increase in SVI of ≥ 15% are shown in Fig. 1. The AUCs for PPV as a predictor of fluid responsiveness were 0.702 (95% confidence interval [CI] 0.553–0.851, P = 0.008), 0.633 (95% CI 0.384–0.881, P = 0.295) and 0.667 (95% CI 0.537–0.798, P = 0.012) in the normal PG group, high PG group and whole cohort of patients, respectively. The threshold PPV value of 6% discriminated between responders and non-responders to fluid replacement with a sensitivity of 86% and a specificity of 45% in the normal PG group. There were no statistically significant between-group differences in the AUCs for CVP, PAOP, SVV, or PVI (Table 4).

DISCUSSION

In this study, we analyzed the ability of dynamic preload indices to predict fluid responsiveness in patients undergoing elective liver transplantation. We divided patients into two groups according to their femoral-to-radial arterial PG and investigated whether or not the predictive ability of these dynamic indices is affected by vascular compliance. Thirty percent of patients showed a significant femoral-to-radial arterial PG (difference in SAP ≥ 10 mmHg and/or MAP ≥ 5 mmHg). Only PPV was found to be a reliable predictor of fluid responsiveness in the patients with normal PGs, whereas no dynamic preload index appeared to be sensitive enough to predict fluid responsiveness in patients with high PGs.
Table 3. Hemodynamic Data before Fluid Replacement in Fluid Responders and Non-responders

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal PG (n = 56)</th>
<th>High PG (n = 24)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Responders (n = 14)</td>
<td>Non-responders (n = 42)</td>
<td></td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>70 ± 9</td>
<td>69 ± 12</td>
<td>0.699</td>
</tr>
<tr>
<td>Radial MAP (mmHg)</td>
<td>78 ± 12</td>
<td>81 ± 15</td>
<td>0.484</td>
</tr>
<tr>
<td>Femoral MAP (mmHg)</td>
<td>80 ± 12</td>
<td>82 ± 14</td>
<td>0.609</td>
</tr>
<tr>
<td>CVP (mmHg)</td>
<td>9 ± 4</td>
<td>10 ± 4</td>
<td>0.192</td>
</tr>
<tr>
<td>PAOP (mmHg)</td>
<td>11 ± 4</td>
<td>14 ± 5</td>
<td>0.050</td>
</tr>
<tr>
<td>CO (L/min)</td>
<td>5.5 ± 1.4</td>
<td>6.9 ± 2.5</td>
<td>0.011</td>
</tr>
<tr>
<td>CI (L/min/m²)</td>
<td>3.2 ± 0.7</td>
<td>3.9 ± 1.2</td>
<td>0.035</td>
</tr>
<tr>
<td>EDVI (ml/m²)</td>
<td>146 ± 37</td>
<td>156 ± 41</td>
<td>0.449</td>
</tr>
<tr>
<td>RVEF (%)</td>
<td>32 ± 10</td>
<td>37 ± 9</td>
<td>0.124</td>
</tr>
<tr>
<td>SVRI (dynes/sec/cm⁵)</td>
<td>1,158 ± 414</td>
<td>902 ± 326</td>
<td>0.021</td>
</tr>
<tr>
<td>SVRI (dynes/sec/cm²/m²)</td>
<td>2,212 ± 856</td>
<td>1,547 ± 567</td>
<td>0.015</td>
</tr>
<tr>
<td>SVI (ml/m²/beat)</td>
<td>45 ± 11</td>
<td>55 ± 15</td>
<td>0.026</td>
</tr>
<tr>
<td>SVV (%)</td>
<td>8 ± 3</td>
<td>7 ± 3</td>
<td>0.242</td>
</tr>
<tr>
<td>PPV (%)</td>
<td>9 ± 3</td>
<td>7 ± 3</td>
<td>0.023</td>
</tr>
<tr>
<td>PVI (%)</td>
<td>11 ± 6</td>
<td>11 ± 5</td>
<td>0.752</td>
</tr>
</tbody>
</table>


Fig. 1. Receiver-operating characteristic curves showing the ability of static and dynamic preload indices to predict an increase in stroke volume index ≥ 15% after fluid challenge. (A) Normal femoral-to-radial arterial pressure gradient group (n = 56). (B) High femoral-to-radial arterial pressure gradient group (n = 24, difference of ≥ 10 mmHg in systolic blood pressure and/or mean blood pressure ≥ 5 mmHg). (C) Whole cohort of patients (n = 80). CVP: central venous pressure, PAOP: pulmonary arterial occlusion pressure, PPV: pulse pressure variation, PVI: pleth variability index, SWV: stroke volume variation. *P < 0.05.

Dynamic variables have been reported to be useful for predicting fluid responsiveness in patients with septic shock and those undergoing cardiac surgery with cardiopulmonary bypass who may have a similar physiology to that of patients with end-stage liver disease [9,20,21]. However, previous studies of fluid responsiveness in liver transplant patients have not yielded consistent results [11–14]. In a study of 31 patients who received liver transplantation with fluid challenges, dynamic indices of SVV, PPV, and PVI were useful for predicting fluid responsiveness with AUCs of 0.754, 0.794, and 0.800, respectively [11]. Moreover, the femoral SVV obtained using the Vigileo monitor could reflect fluid responsiveness with an AUC of 0.894 in recipients during the anhepatic phase of liver transplantation [12]. However, the PPV
failed to predict fluid responsiveness during liver transplantation in another study [13]. Likewise, Konur et al. [14] reported that the PVI derived from a Masimo monitor was not a reliable predictor of fluid responsiveness during the dissection phase or anhepatic phase in liver transplantation. In the present study, PPV was a reliable predictor of fluid responsiveness with an AUC of 0.702 in patients with a normal PG, but failed to predict fluid responsiveness in those with a high PG. In contrast, SVV and PVI could not predict fluid responsiveness in patients with a normal PG or those with a high PG.

It is not known exactly why the predictive ability of dynamic indices varies in patients undergoing liver transplantation, but it may be due to the characteristic physiology of patients with end-stage liver disease. Patients with liver cirrhosis often present with hyperdynamic circulation characterized by an increased heart rate and CO with reduced SVR [1,22]. Splanchnic arterial vasodilation in cirrhosis leads to a functional hypervolemia (decreased preload) despite a volume overload in absolute terms [23]. Even with an increased basal CO, patients with cirrhosis show blunted responsiveness to volume, exercise, or pharmacological stimuli, known as cirrhotic cardiomyopathy [23]. This blunted cardiac response of cirrhotic cardiomyopathy fails to overcome the decrease in the effective circulating volume [23]. Owing to these characteristics of end-stage liver disease, the dynamic indices, which predict fluid responsiveness well under other conditions, may fail to predict fluid responsiveness in patients undergoing liver transplantation.

There are several confounders in clinical practice that can significantly reduce the predictive value of dynamic indices of fluid responsiveness, including low tidal volume, cardiac arrhythmias, intra-abdominal hypertension, elevated positive end-expiratory pressure, and use of vasopressor drugs [24,25]. In particular, the SVV failed to predict fluid responsiveness in patients with increased arterial stiffness [15]. Moreover, changes in vascular tone with a vasoconstrictor or vasodilator can affect the predictability of the dynamic index [26,27]. An animal study reported that the predictability of PPV or systolic pressure variation in fluid responsiveness is poor when vasomotor tone is increased by infusion of the α1 agonist phenylephrine [26]. In addition, vasodilator treatment in patients ventilated postoperatively created a relative hypovolemic state, resulting in an increased PPV and SVV [27], which may affect the reliability of these indices.

In the current study, we divided patients into two groups according to their femoral-to-radial arterial PG and investigated whether or not the predictability of dynamic variables is affected by vascular compliance. An arterial pressure difference between the femoral artery and the radial artery is often observed during liver transplantation [28]. This is similar to that observed after cardiopulmonary bypass in cardiac surgery or deep hypothermic circulatory arrest and is often caused by peripheral arterial vasodilation [29,30]. Therefore, the high PG in our patients may reflect severe peripheral arterial vasodilation. [16] Our study is the first to demonstrate that dynamic indices such as PPV, SVV, and PVI cannot be used to predict fluid responsiveness in the condition of a high femoral-to-radial arterial PG.

There are several limitations to our study. First, the data were collected retrospectively, which introduces potential confounding factors. However, the anesthesia of all the enrolled patients was performed by one anesthesiologist, and the data were entered into the electronic medical records according to our protocol. Moreover, the number of patients analyzed in our study was larger (n = 80) than that in previous studies investigating fluid responsiveness in liver transplant patients (n = 15–37) [11–14]; this may help overcome the limitation of the retrospective design. Second, our patients received 500 ml of crystalloid solution based on our institution’s routine anesthesia protocol, which is less than that in previous studies (10 ml/kg of colloids or crystalloid solution) on liver transplantation [11,12,14]. Therefore, the 500 ml of crystalloid administered in our study could have been insufficient to assess fluid responsiveness and may
have affected the predictability of dynamic indices in the patients with normal PG. Third, use of a vasoconstrictor such as norepinephrine can increase vascular tone [26], which could affect the predictive ability of dynamic indices. Given the retrospective design of our study, the contribution of norepinephrine could not be ascertained. Fourth, in our study, the radial arterial catheter was connected to the Flotrac/Vigileo monitor, and the femoral arterial catheter was connected to a disposable pressure transducer (Edwards Lifesciences). According to the manufacturer, the proprietary algorithm of the Flotrac/Vigileo system allows CO monitoring independent of the signal detection site, considering the differences in the vascular structure. Additionally, the two transducers were simultaneously calibrated at the mid axillary level for atmospheric pressure (zeroed) in the present study. Therefore, although arterial pressure was not obtained via the radial and femoral arterial catheters using the same transducer, the difference in the arterial pressure is considered to be insignificant. Finally, our data were collected after induction of anesthesia and before the start of surgery. Therefore, the results of the study did not reflect the overall state of liver transplantation. Liver transplantation has different hemodynamic changes in each phase; therefore, further studies are required to identify reliable predictors in each phase.

In conclusion, patients with end-stage liver disease undergoing liver transplantation have extreme systemic arterial vasodilation, and this phenomenon could affect the reliability of the dynamic preload indices that have been widely used to predict fluid responsiveness. Our study demonstrated that PPV can be used as a dynamic index of fluid responsiveness in patients with altered vascular compliance, such as a high femoral-to-radial arterial PG. Further studies are needed to identify reliable predictors of fluid responsiveness in patients with altered vascular compliance.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

AUTHOR CONTRIBUTIONS


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REFERENCES

INTRODUCTION

Epidural analgesia (EA) is a commonly used modality for perioperative pain relief in thoracic and abdominal surgeries [1]. It provides an effective and predictable perioperative analgesia, obviates the need for systemic analgesic agents, prevents the risks of opioid-associated respiratory depression, and ensures better hemodynamic stability and recovery [2]. In children, EA through the lumbar or thoracic approach requires considerable experience and a high level of
expertise due to their small body size, narrow epidural space, and difficulty in predicting skin-to-epidural space distance. Soft connective tissue limits tactile sensation feedback for loss of resistance (LOR) in the identification of the epidural space. Moreover, these procedures are usually performed in children under deep sedation or general anesthesia (GA), and subjective warning signs (e.g., paresthesia, pain, or muscle twitch) of neural injury are missed [3]. Reports of unintentional dural puncture and spinal cord injury aggravate this fear for the safety of lumbar and thoracic epidurals in children [4,5]. This may also result in increased procedural time, multiple needle re-entry, and numerous bone contacts, leading to needle redirections [6].

The advent of ultrasonography has led to increased safety and success of regional anesthesia in children [6,7]. Due to the incomplete ossification of posterior elements of the spine in the pediatric population, an excellent acoustic window is available for visualization of structures, the needle trajectory, and its tip. The tip of the catheter, downward displacement of the dura while injection of saline or local anesthetic injection, and the spread of injected fluid can be visualized. Ultrasound (US) has been shown to improve the success rate and shorten block performance time [3,6,7]. US scanning can be performed before the procedure, which can help in finding the needle entry point and depth of the epidural space, but the needle is still advanced blindly.

The curiosity on using real-time US visualization for the advancement of the needle to facilitate rates of catheter placement at the lumbar spine is gradually developing [8,9]. Although US-guided epidural catheter insertion can be difficult in the thoracic spine, due to the narrow interlaminar space [10]. Pak and Gulati [11] performed a retrospective review of real-time thoracic epidural placement in adult patients and found it to be a successful and effective technique. They also emphasized the feasibility and the need for a prospective study comparing US-assisted epidural placement with traditional landmark-based techniques.

Due to the paucity of studies, we performed a randomized controlled trial that compared anatomical landmark-guided and the real-time US-assisted epidural catheter placement using an in-plane approach in children.

We hypothesized that a real-time in-plane ultrasound-guided technique for thoracic and lumbar epidural needle placement would be an effective technique in pediatric patients.

**MATERIALS AND METHODS**

This prospective, randomized, controlled trial was conducted in a tertiary care hospital after obtaining approval from the Institutional Ethical Committee and Clinical Trial Registry India (CTRI/2019/01/017022, dated 09/01/2019), between December 25, 2018, and March 20, 2020.

This clinical study was performed in accordance with the ethical principles for medical research involving human subjects outlined in the Helsinki Declaration of 1975 (revised 2013).

The study was conducted after written informed parental consent was obtained from all participants. Fifty-eight patients were enrolled in the study, of which 13 patients were excluded (not meeting the criteria [n = 7] and declined to participate [n = 6]). The remaining forty-five pediatric patients with the American Society of Anesthesiologists physical status I–III, aged 1–6 years, undergoing thoracic and abdominal surgeries under GA were randomized in this study (Fig. 1). Children with neurological disorders, seizures, history of spine surgeries or deformities, history of local anesthetic allergy, local site infection, or coagulopathies were excluded.

A thorough preoperative check-up of all patients was performed one day before surgery. Fasting instructions were given as per the institutional protocol. Anesthesia induction was performed using 2 µg/kg fentanyl and 1–2 mg/kg propofol, titrated to effect. Endotracheal intubation was facilitated by 0.5 mg/kg Atracurium. Anesthesia was maintained with sevoflurane (up to 1.5–2 vol%), along with boluses of fentanyl and Atracurium. Intraoperative monitoring included electrocardiogram, pulse oximetry, non-invasive arterial blood pressure, esophageal temperature, capnography, and end-tidal concentrations of volatile anesthetics.

Patients were randomized into group LT (landmark technique) (n = 22) and group UT (real-time US group) (n = 23) by using a computer-generated random number table by an anesthesiologist who was not involved in the study. The allocated group was sealed in an opaque envelope, which was opened immediately before the procedure. In both groups, epidural placement was performed at the lower thoracic or lumbar levels in the left lateral decubitus position under all aseptic precautions.

An anesthesiologist with sufficient experience in epidural placement (at least 30 real-time US guidance or landmark guidance) in the pediatric age group conducted all of these
An epidural set containing a 20 G Tuohy epidural needle of 50 mm length and a 24 G catheter (B Braun Melsungen, Germany) was used. The level of epidural puncture was determined by the surgical incision.

In the LT group, the epidural catheter was placed under surface anatomy guidance and the standard LOR technique with air through the midline approach. The skin-to-epidural space distance was measured after the block performance using the US. The probe was applied at the congruent thoracic/lumbar level to obtain a paramedian longitudinal view of the spine (Fig. 2). The distance from the skin to the epidural space was measured in freeze mode. The spinous process was visualized as a hyperechoic structure with an US machine (GE LOGIQe 9 L, GE Healthcare, USA). An epidural set containing a 20 G Tuohy epidural needle of 50 mm length and a 24 G catheter (B Braun Melsungen, Germany) was used. The level of epidural puncture was determined by the surgical incision.

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**Fig. 1.** Consort flow diagram. AIIMS: All India Institute of Medical Sciences, Jodhpur, India, ASA: American Society of Anesthesiologists.

**Fig. 2.** Orientation of the ultrasound probe in paramedian longitudinal plane.
Real time US guided epidural in pediatrics

The paramedian sagittal articular process view was then obtained by laterally moving the probe. As the articular processes were seen as a hump, the cephalad end of the probe was moved medially while maintaining a medial tilt to optimize the space between the laminae. In the paramedian sagittal oblique view, the epidural needle was inserted from the caudal end of the probe using an in-plane approach and advanced under real-time US guidance through interlaminar spaces until the tip of the needle was engaged in the ligamentum flavum. The posterior epidural space was seen as a hypoechoic area between the hyperechoic ligamentum flavum above and the shiny dura below (Fig. 3). Needle entry into the epidural space was confirmed by direct visualization of the needle tip and with the LOR to air method. We then injected saline to observe the downward displacement of the posterior dura mater (Fig. 4).

The epidural catheter was advanced 2–3 cm inside the epidural space and secured at the back with transparent dressings. A test dose of 0.1 ml/kg of 2% lignocaine with adrenaline (1:200,000) was administered, and the patient was placed in the supine position. The loading doses of ropivacaine 0.2%, 0.5 ml/kg for lumbar, and 0.3 ml/kg for thoracic epidural, respectively (total dose not exceeding 2.0 mg/kg), followed by 0.4% ropivacaine (0.2%) continued for 48 h postoperatively.

The primary objective was to compare the procedure time by an anesthesiologist who was unaware of the technique used. The timer was started by the observer as the 20 G Tuohy needle was inserted from the caudal end of the probe and advanced under real-time US assistance with the interspace always maintained in the center of the probe. The LOR to air was used to confirm the epidural space, which marked the endpoint of the timer. The secondary objectives were the number of bone contacts, needle redirections, number of attempts (re-insertion of the needle), skin-to-epidural distance using the US in both groups, and complications such as dural puncture, failure, and a bloody tap were recorded. In the case of a dural puncture, another attempt was made at an interspace higher than the previous one. We also evaluated the ease of catheter insertion using a 3-point scale described as easy: when the catheter could be passed without any resistance, moderate: when there was some resistance to the passage, but the catheter could still be threaded, and difficult, where the catheter could not be inserted.
threaded or some manipulation of the needle was required to thread in the catheter.

The surgical incision was allowed at least 20 min after the epidural loading dose. When an increase in heart rate or blood pressure of more than 20% from baseline in the intraoperative or postoperative period is observed, a top-up dose of ropivacaine 0.2% and 0.25 ml/kg in cases of lumbar and 0.15 ml/kg in thoracic epidural, respectively, were administered. If hemodynamics did not return to baseline even after the top-up dose of local anesthetic (LA), the epidural was considered as failure and fentanyl 1.0 µg/kg was administered. If hemodynamics did not return to baseline even after the top-up dose of local anesthetic (LA), the epidural was considered as failure and fentanyl 1.0 µg/kg was administered. The children requiring IV analgesia during the intraoperative period were not followed for pain evaluation in the postoperative period. On completion of the surgical procedure, all children were extubated after achieving extubation criteria. Complications associated with EA such as respiratory insufficiency, bradycardia, hypotension, and hypotonia were recorded and managed accordingly.

Postoperative pain was assessed using the FLACC score at 0, 6, 12, 24, and 48 h (FLACC score 0 = relaxed and comfortable 1–3 = mild discomfort 4–6 = moderate pain 7–10 = severe discomfort/pain). If a FLACC ≥ 4 is noticed, a bolus dose of ropivacaine (0.2%), 0.25 ml/kg of in case of lumbar (0.15 ml/kg), and the thoracic epidural was administered through the epidural catheter. Even after 20 min of a bolus injection of LA in the epidural catheter, if the FLACC is ≥ 4, fentanyl 1.0 µg/kg was administered, and block failure was considered.

The sample size calculation was based on a previous study by Willschke et al. [2]. The mean time to perform epidural surgery was 142 ± 49 s in the US group and 286 ± 145 s in the landmark-guided technique, at a 95% confidence interval, an alpha error of 0.05% and 95% power, and a minimum of 30 patients were required. A total of forty-five children were enrolled in our study to cover possible dropouts.

Data were analyzed using the Statistical Package for Social Sciences (SPSS) for Windows version 23.0. (SPSS, IBM Corp, USA). The normality of the distribution was determined using the Shapiro–Wilk test. Categorical data were analyzed using the chi-square test or Fisher’s exact test, as appropriate. The Mann–Whitney U test was used to compare non-normally distributed continuous data. The relationship between age, body weight, and skin–epidural depth in children was determined using the linear regression model and Pearson’s correlation coefficient. Results were considered statistically significant when the P < 0.05.

**RESULTS**

The number of patients included in groups LT and UT was 22 and 23, respectively. Demographic data, including age, weight, and sex, were comparable between the groups. The levels of epidural placement and types of surgeries were also comparable between the two groups (Table 1). The procedural time was shorter in the group LT (105.5 [297.0] seconds; median [interquartile range]) in comparison to group UT (143.0 [150]). In 82.6% (n = 19) of children, the epidural was placed in the first attempt in group UT, while it could be done only in 40.9% (n = 9) of children in group LT (P = 0.004). No bone contacts were encountered in 69.6% (n = 16) of the participants in group UT vs. 36.4% (n = 8) children in the LT group (P = 0.026). No needle redirections were required in 87.0% (n = 20) of the UT group vs. 40.9% (n = 9) in the LT group (P = 0.001). The catheter could be easily inserted in

| Table 1. Distribution of Demographic Parameters and Types of Surgery in the Two Groups |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Demographic parameters          | Group UT (n = 23) | Group LT (n = 22) | P value        |
| Age (mo)                        | 28.2 ± 15.9      | 36.2 ± 20.2      | 0.256          |
| Sex                             |                 |                 | 0.302          |
| Male                            | 15 (65.2)        | 11 (50.0)        | 0.013          |
| Female                          | 8 (34.8)         | 11 (50.0)        | 0.301          |
| Weight (kg)                     | 10.7 ± 2.8       | 11.8 ± 3.5       | 0.300          |
| Type of surgery                 |                 |                 | 0.476          |
| Thoracic                        | 2 (8.0)          | 0                | 0.000          |
| Upper abdominal                 | 5 (21.7)         | 7 (31.8)         | 0.019          |
| Lower abdominal and pelvic      | 16 (69.5)        | 15 (68.1)        | 0.550          |
| Level of epidural               |                 |                 | 0.237          |
| Thoracic                        | 7 (30.4)         | 7 (31.8)         | 0.937          |
| Lumbar                          | 16 (69.5)        | 15 (68.1)        | 0.550          |

Values are presented as mean ± SD or number (%). Group LT: landmark technique group, Group UT: real-time US group.
### Table 2. Data Showing the Procedural Time, Skin-to-epidural Distance, Number of Attempts, Bone Contacts, Needle Redirections, Ease of Catheter Insertion, Complications and Postoperative IV Analgesia Requirement in the Two Groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group UT (n = 23)</th>
<th>Group LT (n = 22)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time taken (in seconds)</td>
<td>143.0 (150 [25–960])</td>
<td>105.5 (297.0 [40–650])</td>
<td>0.407</td>
</tr>
<tr>
<td>Skin-epidural distance (mm)</td>
<td>12.9 (3.3 [10–17.8])</td>
<td>15.0 (5.0 [10–25])</td>
<td>0.027</td>
</tr>
<tr>
<td>Number of attempts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First attempt</td>
<td>19 (82.6)</td>
<td>9 (40.9)</td>
<td>0.004</td>
</tr>
<tr>
<td>Two or more attempts</td>
<td>4 (17.4)</td>
<td>13 (59.1)</td>
<td></td>
</tr>
<tr>
<td>Bone contacts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No bone contact</td>
<td>16 (69.6)</td>
<td>8 (36.4)</td>
<td>0.026</td>
</tr>
<tr>
<td>One or more bone contacts</td>
<td>7 (30.4)</td>
<td>14 (63.6)</td>
<td></td>
</tr>
<tr>
<td>Needle redirections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No needle redirections</td>
<td>20 (87.0)</td>
<td>9 (40.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>One or more needle redirections</td>
<td>3 (13.0)</td>
<td>13 (59.1)</td>
<td></td>
</tr>
<tr>
<td>Ease of catheter insertion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Easy</td>
<td>20 (86.9)</td>
<td>16 (72.7)</td>
<td>0.426</td>
</tr>
<tr>
<td>Moderate</td>
<td>2 (8.6)</td>
<td>5 (22.7)</td>
<td></td>
</tr>
<tr>
<td>Difficult</td>
<td>1 (4.3)</td>
<td>1 (4.5)</td>
<td></td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dura puncture</td>
<td>0</td>
<td>4 (18.2)</td>
<td>0.032</td>
</tr>
<tr>
<td>Bloody tap</td>
<td>1 (4.3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Failure</td>
<td>0</td>
<td>8 (36.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Postoperative IV analgesia</td>
<td>0</td>
<td>3 (13.6)</td>
<td>0.060</td>
</tr>
</tbody>
</table>

Data are represented as median (1Q, 3Q [range]) or number (%). Group LT: landmark technique group, Group UT: real-time US group.

86.9% (n = 20) of children in group UT and 72.7% (n = 16) of children in the LT group (P = 0.426) (Table 2). The dura puncture occurred in 18.2% (n = 4) of patients in the LT group, while none occurred in the UT group (P = 0.032). Bloody aspiration occurred in one patient in group UT. Intraoperative fentanyl was required in 8 (36.4%) patients in the LT group, and epidural catheter placement was considered to have failed (P = 0.001). However, none of the participants in the US group required intraoperative fentanyl supplementation (Table 2).

FLACC score > 4 was observed in 7 children in the LT group, which was successfully treated with a bolus administration of ropivacaine. Six children in the US group also required an epidural bolus of ropivacaine in the recovery room. Three children in the LT group received postoperative fentanyl (0.5 µg/kg IV), while none of the children in group UT required it (P = 0.060) (Table 2).

Multiple linear regression was calculated to predict the skin-epidural distance (in mm) based on age in months and body weight in kg of children. A significant regression equation was found (F (2, 42) = 6.48, P < 0.003, with an R2 of 0.23. Participants predicted that the skin-epidural distance is equal to 10.34 ± 0.17 (weight) + 0.05 (age), where weight is measured in kilograms and age is measured in months. The skin-epidural distance increased by 0.05 mm for each month of age and 0.17 mm for each kilogram of weight. The P value for age and weight as predictors of skin-epidural distance were 0.11 and 0.37, respectively (Fig. 5).

![Weight line fit plot](Fig. 5)
DISCUSSION

The results of our study showed that procedure time was shorter in group LT than in group UT, but the difference was not statistically significant. The number of bone contacts and needle redirections were fewer, and the success rate in the first attempt was higher in group UT.

Inadequate postoperative pain management in children may progress to the development of chronic pain in 20% of patients undergoing major surgery [12]. Traditionally, postoperative pain after major abdominal and pelvic pain is managed by caudal epidural block. The epidural block at the lumbar or thoracic level is technically challenging in pediatric patients because of the narrow space. The US proved a useful aid for the faster placement of the catheter along with direct visualization of the neuraxial structure and spread of LA, but there is a learning curve for this.

The procedure time in group UT was more than that in group LT, but the difference was not statistically significant. The findings of our study are in accordance with those of a study conducted by Willschke et al. [2]. In a study by Pak and Gulati [11], the mean procedure time was longer than that in our study. The longer procedure time may have been due to difficulty in discerning the ultrasonic anatomy by curvilinear, low-frequency transducers in adults.

The number of attempts, bone contacts, needle redirections, ease of catheter insertion, dural puncture, and failure rate was significantly lower in group UT than in group LT. In pediatric patients due to lack of ossification of posterior elements of the spinal canal, an acoustic window is created for the US beam to demonstrate the anatomy better. Furthermore, the shallow epidural depth in children allows a linear, high-frequency linear probe to show good image resolution and better image quality. Real-time visualization of the entire trajectory of the epidural needle during the procedure facilitates ease, accuracy, and safety [9,13–15].

A systemic review by Lam et al. [6] also demonstrated the efficacy of the US technique in terms of the reduced number of attempts, bone contacts, needle redirections, and ease of performing similar to our study. Despite the relative ease of insertion of the epidural needle under sonographic view, 30% of bone contacts were still encountered, which could be attributed to the non-visualization of the incompletely ossified bony structures, which may be missed by US imaging.

The visualization of the dura is best appreciated in younger children, and as the age advances, this visibility may gradually become difficult. The uncertainty over the depth of the epidural space has prompted few investigators to derive formulas to predict skin to the epidural distance in the pediatric population based on their age, weight, and height [16,17]. In our study, the correlation of skin-to-epidural distance with patient weight was also determined. The skin-to-epidural distance showed a good correlation between the age of 1–6 years and the body weight of the child.

Many methods of epidural space confirmations [18], such as LOR to air or saline or using devices like an epidural balloon, epidrum, episure, hanging drop method, epidurography, electric stimulation [19,20], or electrocardiography or pressure waveform guided system [21] have been mentioned in the literature, but direct visualization of the catheter with the US and downward displacement of the dura while injecting saline or LA is the most reliable method to date.

The use of US can also mitigate complications such as dural puncture and injury to the spinal cord, encountered during traditional epidural placement in pediatric patients [2,11,14,15]. In our study, the success rate of epidural catheter placement was 100%. Dural puncture occurred in four patients and block failure occurred in eight cases in group LT, while none occurred in group UT. Bloody tap occurred in one patient in group UT and none in group LT. This reflects an increased margin of safety for pediatric epidural placement with the use of the US. Eight children in the landmark group required additional postoperative analgesia, suggesting a higher success rate of real-time ultrasound-guided epidural insertion.

Despite the advantages of real-time US techniques, knowledge of ultrasonic anatomy and training is required, and pediatric anesthesiologists should acquire the necessary skills before actual practice.

There were some limitations to our study. The investigator was not blinded to the technique, leaving room for operator bias. The drawing conclusions on rare complications, such as a bloody tap and neural injuries, may not be accurate as they require a larger sample size.

We conclude that the use of US significantly reduced needle redirection, number of attempts, bone contact, and complications. There was no statistically significant difference in the time to access the epidural space between the US and landmark technique groups.

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CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

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Complex regional pain syndrome (CRPS) is a painful disorder, characterized by pain following an inciting injury and a variable convergence of signs and symptoms of sensory, vasomotor, sudomotor, trophic, and motor dysfunction [1]. CRPS appears to be caused by various components of inflammatory factors, autoimmune factors, neuronal plasticity, and autoimmune dysregulation. Inexplicable pain, limb edema, skin color changes, and elevated skin temperature can manifest after trauma and surgery due to an exaggerated inflammatory response [2]. Although neurogenic inflammation is a normal process after nerve injury, tissue injury in CRPS with or without nerve injury appears to induce an exaggerated neuroinflammatory response, including the release of proinflammatory neuropeptides. Proinflammatory mediators can cause the activation of nociceptors that may lead to allodynia and hyperalgesia, which are the well-known characteristics of CRPS that result from peripheral sensitization [3,4].

As frequently observed in herpes zoster or stroke patients, many disorders of the peripheral and central nervous systems cause both neuropathic itch (NI) and neuropathic pain (NP). Sensory loss and gain of function can be concomitant-
ly observed in both these conditions [5]. In NP, the hyper-sensitive sensory states are termed allodynia and hyperalgesia whereas the corresponding terms used in NI are alloknesis and hyperknesis. Over the past few years, studies have attempted to describe the pathophysiology of itch and its neuropathic origin. Therefore, in the light of this research, our understanding of pruritus suggests that the skin is not the only reason for the sensation of itch. Damage to the nervous system may interfere with the pruritic afferent pathways allowing painful and noxious sensations to be perceived as pruritic [5].

Although the concept of NI has been emerging, few studies have covered its pathophysiology. Unfortunately, common treatments for pruritus are not often effective for pruritus of such origins. Furthermore, NI affects a patient’s quality of life to an extent similar to NP. Herein, we discuss the atypical presentation of NI in a patient with CRPS and the treatment modalities used to improve his symptoms.

**CASE REPORT**

We obtained written informed consent from the patient after surgery to publish this report.

A 23-year-old male presented with uncontrolled, chronic pruritus of his left foot and ankle. When he first visited the clinic, he was limping and had reduced range of motion, swelling, and sweating and flushing of the skin over the affected area. Interestingly, he was mainly concerned with the severe itching sensation and did not complain of pain. Six months before his first visit to our clinic, he had undergone open reduction and internal fixation of his left foot due to recurrent left first metatarsal fracture. To start with, the initial injury was a left great toe fracture, prompting a cast application. From the time of injury, the patient only complained of itching, rather than pain, over the affected foot. Due to the accompanying itch, he had kicked his foot against a hard wall in frustration and developed a comminuted toe fracture. Therefore, an additional surgical correction was performed. A plaster cast was applied for 3 months after the surgical correction due to the complex nature of the recurrent metatarsal fracture. Immediately after removal of the plaster cast, he developed uncontrolled pruritus and discomfort, skin color change, and swelling over the surgical site, which lasted for more than 3 months.

This patient had a history of congenital heart disease, with a functional single ventricle with transposition of the great arteries and pulmonary atresia, and had undergone three open heart surgeries by 5 years of age. At 11 days after birth, he underwent central shunt operation as his first cardiac surgery. Two weeks postoperatively, he experienced a sudden cardiac arrest for unknown reasons, and was revived. However, this had resulted in the development of ischemic brain damage (Fig. 1). The follow-up brain magnetic resonance imaging had shown multiple chronic cerebral infarctions at both the parieto-occipital lobes and left anterior watershed zone. It also showed thinning of the posterior portion of the corpus callosum and multifocal small lacunar infarctions in the left cerebellum. The ischemic stroke caused mental retardation and repeated seizures for years afterwards.

We and a consultant dermatologist did not find skin lesions could cause itching except for edema and change in skin color at the affected area. There was no change in the medication administered during the period when the patient started complaining of symptoms. In addition, itching caused by infection could be ruled out with the physical examination and normal laboratory findings. Physical examination revealed edema, change and asymmetry in skin color, sweating, and decreased range of motion at the affected foot and ankle. Moreover, he complained of severe itching when the affected foot and ankle were rubbed using a soft brush (alloknesis), and pinprick-evoked itch was also observed (hyperknesis).

Simple X-ray showed osteopenia at the affected foot and ankle. The temperature difference between both feet was up to 2.42°C in thermography. We found sympathetic postganglionic sudomotor dysfunction or sweat gland abnormality in the left distal leg and foot by quantitative sudomotor axon reflex test (QSART) test. In addition, a 3-phase bone scan test found diffusely increased perfusion and blood pool and delayed bone uptake in the left ankle and foot suggesting CRPS [6] (Fig. 2). Unfortunately, the energy dispersive X-ray analysis test and electrodiagnostic study were not performed because the patient did not cooperate. Although the patient did not complain of pain at all, these findings with his the symptoms and signs over the affected foot and ankle partially met the diagnostic criteria for CRPS as per the International Association for the Study of Pain (Budapest criteria) [1], and met the criteria for CRPS-NOS (not otherwise specified) [7] with itching.

We initiated his treatment carefully, with sub-anesthetic doses of intravenous (IV) ketamine therapy (0.1–0.3 mg/kg) administered in the outpatient pain clinic, along with prescribed oral doses of pregabalin (75 mg, twice a day) and
Fig. 1. Magnetic resonance imaging of the brain shows multiple chronic cerebral infarctions at both the parieto-occipital lobes and left anterior watershed zone and thinning of the posterior portion of the corpus callosum (A). Multifocal small lacunar infarctions are also seen in the left cerebellum (B).

Fig. 2. The three-phase bone scan shows diffusely increased perfusion, blood pool, and delayed bone uptake in the left foot and ankle. $^{99m}$Tc-DPD: $^{99m}$Tc-3, 3-diphosphono-1, 2-propanodicarboxylic acid, IV: intravenous.
naproxen (500 mg, twice a day) to control his symptoms. One month later, his gait had improved, and the edema and profuse sweating had resolved. Although he experienced a few side effects, such as urinary retention and generalized edema, he could relatively tolerate them. With the same treatment every month, the pruritus improved gradually and completely subsided by the sixth month, along with the skin discoloration. Subsequently, we discontinued the IV ketamine therapy and prescribed reduced doses of pregabalin only. Therefore, the patient was successfully treated with medications used for the treatment of NP.

**DISCUSSION**

There could be three explanations for the questionable symptoms observed in this case. First, delayed removal of the plaster cast may have triggered the itching and skin color change. It could also have caused muscle atrophy, deep vein thrombosis, joint stiffness due to prolonged immobilization, gait abnormalities, and calf muscle weakness [8]. This could explain some of his symptoms, but they do not usually last for more than 1 month; if they do, physicians are required to look for other causes for these symptoms. Another possibility of itching was the atypical presentation of CRPS. Fracture of an extremity is a common inciting event of CRPS type 1. According to a previous report, 7% of patients with a single fracture of the wrist, scaphoid, ankle, or metatarsal bone develop CRPS type 1 [3]. With the obvious inciting events, the patient showed skin color changes, edema, and abnormal sudomotor activity, without the presence of other conditions that could account for the dysfunction. Except for the fact that the continuous pain and allodynia were substituted by continuous severe itching and alloknesis, results of the imaging test, QSART test, and 3-phase bone scan and physical evidence pointed to an atypical presentation of CRPS-NOS with itch. His successful treatment with medications used for NP supports this diagnosis. Lastly, due to his cerebrovascular disease, it is possible that the abnormal pruritus may have been caused by a lesion in the afferent sensory pathway, rather than by a cutaneous lesion or a peripheral stimulus. An unusual itch with a neurologic origin is called an NI and is defined as an itch caused by a pathology located at any point along the afferent pathway of the nervous system [5].

About 30% of patients with NI have a peripheral neuropathic cause, including post-herpetic itch, brachioradial pruritus, natalgia paresthetica, trigeminal trophic syndrome, and itch caused by burns or keloids [9]. It has been reported that 15% of itches arise from central nervous system disorders [10]. Spinal cord disorders including inflammatory transverse myelitis, neoplasms, cavernous hemangiomas, and post-traumatic Brown-Sequard syndrome have also been implicated for the same [9,11]. Ischemic stroke of the subcortical area or brainstem is the most common central cause of NI [10]. As shown in Fig. 1, the patient was previously diagnosed with multiple hypoxic ischemic encephalopathy. Since NI can occur in patients with central nervous system disorders, we also cannot rule out the possibility of NI due to cerebrovascular disease.

The diagnostic criteria for NI has yet to be definitively established. Currently, its diagnosis is primarily based on clinical characteristics specific to NI syndromes, with history taking as an important process to exclude dermatologic or systemic causes, as well as detect neuropathic causes [9]. Sensory tests, electrodiagnostic tests, autonomic function tests, imaging studies, and skin biopsies may also help detect and localize potential neuropathic causes [9]. In the present case, due to the patient’s non-cooperation, we could not perform an electrodiagnostic test and skin biopsy; however, results from the sensory test, 3-phase bone scan, and QSART test suggested that his itching was neuropathic in origin.

Similar to the circumstances of NI diagnosis, there is also no specific treatment for this condition [9]. Generally, management of NI begins with non-pharmacological measures used for itch, followed by other therapies in a stepwise approach, wherein the choice of treatment is usually based on the size and localization of the pruritus [12,13]. In particular, treatment of itching caused by neuropathy is often based on NP management [9]. Moreover, preventing and treating secondary scratch-induced skin lesions is also important to reduce further itching and infection. Since antihistamines, corticosteroids, and most pain medications were largely ineffective in treating NI, we decided to systematically administer inhibitors of neuronal excitability, and thus the patient was treated using medications for CRPS with NP. More specifically, monthly IV sub-anesthetic ketamine doses with daily oral pregabalin and naproxen were administered to the patient for 6 months. Naproxen was prescribed in this case to reduce further itching and infection. Since antihistamines, corticosteroids, and most pain medications were largely ineffective in treating NI, we decided to systematically administer inhibitors of neuronal excitability, and thus the patient was treated using medications for CRPS with NP. More specifically, monthly IV sub-anesthetic ketamine doses with daily oral pregabalin and naproxen were administered to the patient for 6 months. Naproxen was prescribed in this case to reduce the release of inflammatory mediators that may affect NP and/or NI. Although he experienced a few side effects, such as urinary retention and generalized edema, the pruritus was successfully treated.

In conclusion, when a patient complains of unexplained itching not resolved by general itching treatments, a probable neuropathy should also be considered among its various
Neuropathic itching of CRPS

causes. Careful history taking and evaluation of symptoms, with some neurologic and radiologic tests to detect neuropathic causes, can help identify NI. Although there is no established treatment for NI, treatment according to NP can improve these symptoms.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

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Patients of trigeminal neuralgia (TN) present a sudden severe, electric shock like, stabbing, and recurrent pain in the division area of the trigeminal nerve. The facial pain mostly demonstrates unilateral location with a cutaneous trigger zone. The peak age of onset is 50 to 60 years old. TN shows higher prevalence in women, ranging from 0.03–0.3% [1,2]. Although the reported incidence of TN is low, the severe and disabling pain nature of TN significantly affect the quality of life with resultant psychologic distress, and may even lead to suicide [3].

Carbamazepine is known to demonstrate an excellent pain relief for TN. However, 10% of TN shows minimal response to oral medication. In addition, various side effects of carbamazepine including dizziness, loss of coordination, vertigo, and liver toxicity limit the popular use of such medication [4]. Various effective treatments including microvascular decompression (MVD), radiofrequency thermoablation, glycerol rhizolysis and percutaneous balloon microcompression are useful options for such intractable cases. Among such procedures, radiofrequency thermoablation demonstrates an excellent treatment outcome with a success rate of 80% to 97%, although it shows reoccurrence in some of TN patients [5,6].

For the diagnosis of TN, characteristic clinical feature is
most important. With such clinical feature, magnetic resonance imaging (MRI) study of the brain is also recommended to rule out secondary TN [4,7].

We encountered a patient with severe gum and lower molar teeth pain of TN who was confirmed with anterior communicating artery saccular aneurysm by MRI and MR angiography (MRA). Here, we report this case as gasserian ganglion thermoablation was performed safely without any rupture of the saccular aneurysm. Before the preparation of this case report, written informed consent for publication was obtained from the patient.

CASE REPORT

An 85-year-old female with a height of 152 cm and a weight of 52 kg, who presented severe left-sided lower teeth and gum pain, visited our pain clinic. Severe pain started 2 years ago. Her pain showed abrupt onset and termination with an electric shock like sensation. Duration of pain was within 1–2 min. Pain was usually provoked by washing face, brushing teeth, eating and mouth opening. Initially, she was evaluated at a dental clinic because her main symptom was in gum, lower molar teeth and mandibular area. Since, any problem was not found during dental examination, she was referred to the neurology department. She was diagnosed as TN at the neurology department, and medication was started with gabapentin 900 mg/day, celecoxib 200 mg/day and amitriptyline 10 mg/day with minimal responses. Oral intake was very poor due to inadequate pain treatment. Her underlying disease was diabetes mellitus and hypertension.

According to her characteristic pain nature described above, we assessed her as TN. Carbamazepine 200 mg/day was prescribed since she was not taking such medication previously. In addition, ultrasound-guided mental nerve blockade was performed with 0.2% ropivacaine 0.5 ml using a hockey stick probe (Logiq S8, GE Healthcare, USA) (Fig. 1). MRI and MRA were ordered to rule out possible secondary TN, and to evaluate any vascular anomaly or vascular compression of the trigeminal nerve.

Mental nerve blockade was performed twice with one week interval and carbamazepine medication was maintained for 16 days. She showed mild pain relief in lower teeth and gum after initiation of medication with mental nerve blockade. However, she demonstrated severe general weakness, dizziness, vertigo and poor oral intake. We assumed such symptoms to be side effects of carbamazepine. When carbamazepine medication was stopped, various symptoms observed after medication disappeared. Although partial pain relief was achieved even after termination of carbamazepine, maintaining normal daily life was impossible due to the reoccurrence of pain.

Gasserian ganglion thermoablation was planned to relieve intractable pain. Her MRI demonstrated mild brain atrophy, but otherwise normal findings. However, MRA showed saccular aneurysm (5.1 mm × 2.4 mm) in the inferior aspect of the anterior communicating artery (Fig. 2). Due to the risk of abrupt rupture of the aneurysm during the procedure of gasserian ganglion thermoablation, we recommended delayed thermoablation after performing cerebral angiography or coiling. However, cerebral angiography or coiling was not possible until at least 3 weeks later due to overloaded schedules. Patient’s intractable pain and poor general condition were too severe to wait for 3 weeks.

After explaining of possible rupture of the cerebral aneurysm, gasserian ganglion thermoablation was performed carefully under intravenous sedation anesthesia.

Before the procedure of thermoablation, light sedation was maintained with intravenous midazolam at 0.02 mg/kg and sufentanil 5 μg, so that the patient could respond properly during electrical stimulation. Patient was monitored with electrocardiography, blood pressure, and pulse oximetry. Facial mask was applied to supply oxygen (3 L/min). During thermoablation, we paid special attention to the changes of blood pressure, to minimize the risk of rupture of cerebral aneurysm. Her initial systolic blood pressure and heart rate was 155 mmHg and 76 beats/min, respectively. Patient lay in the supine position with neck slightly extended, and chin up. The
C-arm was tilted caudally 30 to 35 degrees, and rotated to the left side 20 to 25 degrees obliquely, to visualize the foramen ovale (FO). Skin entry was done at 2–3 cm lateral to the angle of the mouth. A radiofrequency cannula of 22-gauge, 10-cm, and 2 mm active tip was used. After confirming the clear visualization of the FO, the cannula was inserted in a coaxial manner into the fluoroscopic beam towards the FO.

When the cannula reached just in front of the FO in lateral view, nicardipine 1 mg was injected to prevent abrupt increase of blood pressure. Systolic blood pressure before and after puncture of FO was 145 mmHg and 135 mmHg, respectively.

After puncturing of the FO, the cannula was advanced 2–3 mm further and the location of cannula tip was confirmed. Once the cannula position was verified with C-arm, the electrical stimulation of 0.1 V at 50 Hz frequency was in concordance with the location of the pain. The final position of the cannula tip was modified minutely, according to the effect of the stimulation (Fig. 3A, B). After successful concordant electrical stimulation in the mandibular area, radiofrequency was performed at 70°C for 60 seconds for one time. Just after finishing radiofrequency procedure, vital sign was stable except for the sinus tachycardia (112 beats/min). Patient was observed in the recovery area with vital sign monitoring. After taking a rest for an hour, she was in full awake state with

![Fig. 2. Magnetic resonance angiography of brain showing saccular aneurysm (arrow) in inferior aspect of the anterior communicating artery (5.1 mm × 2.4 mm).](image)

![Fig. 3. Oblique (A) and lateral view (B) when the cannula tip reached the final location of mandibular division of the gasserian ganglion after electrical stimulation.](image)
stable vital sign. She visited our pain clinic 2 weeks later, and her pain had disappeared completely with mild hypoesthesia around the chin.

**DISCUSSION**

Gasserian ganglion thermoablation in a patient with cerebral artery aneurysm is very challenging, due to the unexpected risk of aneurysm rupture. Cerebral aneurysm is found dominantly at artery bifurcations and hemodynamic instability or stresses play the most important role in the initiation, development, and rupture of aneurysm [8]. Hence, the risk of rupture of cerebral artery aneurysm should be assessed since unwanted hemodynamic responses during gasserian ganglion thermoablation might be encountered frequently [9,10]. Among procedure steps of thermoablation, FO puncture led to significant increase in heart rate (42/48, 88%) and mean arterial pressure (48/48, 100%). Also, the heating stimulation of radiofrequency thermocoagulation obviously increased the mean arterial pressure and heart rate [9]. According to previous reports [9,10] and our past experiences of thermoablation, we considered the moment of FO puncture and heating of gasserian ganglion would be the most critical event of unwanted increase in arterial pressure. Therefore, antihypertensive medication of nicardipine 1 mg was injected just before puncturing of the FO to prevent abrupt increase of arterial pressure. As a result, the procedure was finished safely maintaining stable hemodynamics.

For antihypertensive medication, nicardipine was chosen because it shows fast onset of antihypertensive action with reflex increase in heart rate [11]. We thought that reflex increase in the heart rate of nicardipine would be beneficial, since sudden bradycardia can be found during gasserian ganglion thermoablation owing to trigeminocardiac reflex. Trigeminocardiac reflex can be found during percutaneous procedure to treat trigeminal neuralgia. It presents transient bradycardia or even sinus arrest [10,12]. Our patient did not show any bradycardia during the procedure.

Neurovascular conflict is the leading cause of TN, accounting for 80–90% of cases, although some patients of TN do not present any neurovascular conflict. An aberrant loop of artery or vein close to the trigeminal nerve root can result in such neurovascular conflict. The most common vessel resulting in neurovascular conflict is superior cerebellar artery (66–88%) and less often, the anterior inferior cerebellar artery (7.5–25%) [7,13]. Although it is not frequent, aneurysm of the posterior cerebral artery can result in symptom of TN [13]. Similarly, giant posterior communicating artery aneurysm projecting to posterior fossa caused TN and surgical clipping of the aneurysm completely resolved severe facial pain [14]. We do not think that the anterior communicating artery aneurysm of this patient resulted in the symptom of TN, since the trigeminal nerve and Meckel’s cave are located in the posterior cranial fossa.

For patients with TN refractory to medical therapy, gasserian ganglion thermoablation, gamma knife, and MVD may be considered. In younger patients of TN, MVD is generally accepted as the treatment of choice. Previous studies indicated that MVD provided improved quality of life with long term pain relief. However, for elderly patients, gasserian ganglion thermoablation is preferred over MVD due to the increased morbidity and mortality associated with MVD [15].

The recurrence rate of thermoablation is 15% after 1 year of thermoablation, while MVD shows 8.4% after 2 years of surgery [16,17].

For the purpose of identifying secondary TN due to compression by tumor or other mass lesion, brain MRI is strongly recommended in TN [7]. In pain clinics of our institution, we recommend MRI and MRA for better workup of other possible vascular lesion. In this case, if we did not evaluate with MRA, gasserian ganglion thermoablation might be performed without knowing the existence of cerebral aneurysm. The importance of MRA in patients of TN should be evaluated, since cerebral aneurysm itself might be a cause of TN. Also, by knowing the existence of cerebral aneurysm previously, we can take a step to minimize the hemodynamic changes during thermoablation.

Intravenous sedation anesthesia with vital sign monitoring should always be performed during gasserian ganglion thermoablation since this procedure is very painful and challenging. Propofol or midazolam as anxiolytic medications and opioids are used for sedation anesthesia [5,9]. If a patient combines TN with a cerebral aneurysm, the process of careful vital sign monitoring is an inevitable step.

In conclusion, we could perform gasserian ganglion thermoablation in a patient with anterior communicating artery aneurysm safely with careful vital sign monitoring using antihypertensive medication.

**CONFLICTS OF INTEREST**

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

All data generated or analyzed during this study are included in this published article. This is a case report.

AUTHOR CONTRIBUTIONS

Writing - original draft: Yong Ho Lee, Ji Hee Hong. Writing - review & editing: Yong Ho Lee, Ji Hee Hong. Investigation: Yong Ho Lee, Ji Hee Hong, Hye Kyung Shin. Supervision: Ji Hee Hong.

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Postherpetic neuralgia (PHN) is a neuropathic pain resulting from herpes zoster infection. Herpes zoster infection usually presents as an acutely painful vesicular rash that affects the dermatome. It usually resolves within a few weeks; however, it can be complicated by persistent neuropathic pain. A systemic review in 2014 reported that the estimated incidence of herpes zoster ranged between 3–5/1,000 persons per year in Asia, Europe, and North America and increases both with age and with impaired immunity. When neuropathic pain persists for more than 30–90 days after the appearance of the acute herpes zoster rash, it is called PHN [1].

The incidence of PHN after herpes zoster is 10% in people over 40 years of age, 20–50% in those over 60 years, and rarely seen in people less than 30 years of age. This proportion increases with age, with more severe prodrome, rash, and pain during the acute phase of herpes zoster infection [2].

Pharmacological treatments for PHN include topical therapy and systemic medication with anticonvulsants, antidepressants, topical lidocaine, and opioids [3]. However, few PHN patients experience more than 50% pain reduction, and adverse effects are common, particularly in older patients [4]. In some cases of PHN, patients experience severe pain despite multi-drug medication, nerve block, and/or radiofrequency treatment. In these intractable cases, neuro-
surgical procedures such as electrical stimulation of the spinal cord, nerve roots, peripheral nerves, and brain can be considered [5].

However, effective thoracic spinal cord stimulation is particularly difficult compared to the cervical and lumbar regions due to challenges in targeting the tight dermatome level and cerebrospinal fluid (CSF) layer thickness [3]. In addition, it was effective in select cases. In this case, we stimulated thoracic dorsal root ganglion (DRG) stimulation combined with spinal cord stimulation (SCS) for intractable PHN and obtained good results.

**CASE REPORT**

Written informed consent was obtained from the patient for publication of this report. The patient was 54 years of age and male with no medical history. He had herpes zoster in the left back, chest, axillar, and upper arm (left T1–3 dermatomes), and pain was sustained on the affected site for 7 years. His pain score was 9–10 (0, no pain; 10, the worst pain imaginable). His pain was very severe and he had allodynia and hyperalgesia in the left axilla and upper arm. The pain was stabbing and electric shock-like. He received medical therapy with pregabalin 600 mg/day, milnacipran 100 mg/day, tramadol 200 mg/day, nortriptyline 10 mg/day, fentanyl patch 62 μg/h, and interventional therapy with epidural block, nerve root block, and radiofrequency treatment several times. However, he experienced pain relief for only a short term or not at all. Therefore, we decided to perform an SCS trial.

For the SCS trial, the skin was incised at the left T6–8 level and 15-gauge Tuohy needle was inserted using the paramedian approach via the left T4–5 interlaminar space. After the epidural space was confirmed with loss of resistance and C-arm fluoroscopy, an eight-electrode lead (Vectlis surescan MRI lead, Medtronic, USA) was first installed within the left C4 level under C-arm fluoroscopy. The best position of the lead tip was the upper C6 level, which could cover the widest pain site with paresthesia. Even though we changed the lead tip position from C3 to C6, it stimulated only a small part of the pain site, such as the chest, except for the most painful site such as the axillar and upper arm. Therefore, we installed another lead to T1 and T2 DRG for trial after skin incision at the right T3–4 level. The needle was inserted via the T1–2 and T2–3 interlaminar spaces. T2 DRG stimulation did not fully provoke paresthesia in the pain site, and some stimulation overlapped with that of SCS. After additional T1 DRG stimulation (2.2 mA, 500 ms, and 40 Hz) with spinal cord stimulation (4.4 mA, 500 ms, and 40 Hz), the patient received adequate paresthesia at the entire pain site, including the axilla and upper arm. During a 1-week trial period, his pain was relieved by more than 50% (pain score changed from 9–10 to 4). DRG stimulation combined with SCS could stimulate almost his pain lesion, including the most severe pain site. We implanted a permanent implantable pulse generator (IPG, Restore sensor Surescan MRI, Medtronic) in the subcutaneous pocket of the right upper chest (Fig. 1). The stimulator worked properly during hospitalization and had no complications. He was discharged from the hospital after 2 weeks and was able to cut off the fentanyl patch. After 2 months, his pain score was 3–4, and DRG stimulation with SCS was effective.

**DISCUSSION**

To our knowledge, this is the first report of DRG stimulation in Korea. There are few case reports of DRG stimulation for PHNs.

SCS can be a treatment option for patients with intractable PHN. It is sometimes difficult to obtain proper stimulation by SCS for PHNs. Although the thoracic level is the most common zoster-affected dermatome, appropriate stimulation can be difficult because the depth of the CSF is greatest at the thoracic level. Moreover, medical costs are high for the

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**Fig. 1.** X-ray of the patient with dual leads.
SCS [3]. Several methods have been used to identify patients who are likely to benefit from SCS. One study suggested patients with little or no sensory loss in the affected area [6], and another study suggested patients with persistent pain, regardless of epidural infusion [7]. Both studies showed significant pain reduction in PHN after SCS, and these findings might indicate that patients with PHN caused by central sensitization and those with preserved neuronal and dorsal column function would respond well to SCS. However, patients with marked sensory loss and constant pain without allodynia would not benefit from SCS, as deafferentation and degeneration of the dorsal column might be the dominant mechanism. Therefore, it is important to select patients who would benefit from SCS for PHN. The patient in this case had minimal sensory loss. We expected SCS with proper stimulation at the pain lesion to have a good effect. However, the SCS did not provide overall stimulation to the pain area. There was no stimulation to the most severe pain sites, such as the axilla and upper arm.

The limitations of SCS include incomplete or inconsistent coverage for certain body areas, and peripheral nerve stimulation is limited by surgical procedures and lack of selectivity for sensory and motor fibers [8]. Because DRG stimulation directly stimulates specific DRG, it can obtain proper stimulation in thoracic lesions. Therefore, it can compensate for the shortcomings of spinal cord stimulation, which is difficult to stimulate at a specific thoracic dermatome in PHN. Although further investigation of DRG stimulation for PHN is needed, it can provide proper stimulation for thoracic lesions. The central mechanisms of PHN include necrosis and scarring of neurons in the DRG and inflammation involving both the anterior and posterior horns of the spinal cord. However, PHN also involves a peripheral mechanism; therefore, peripheral nerve stimulation may be a possible treatment [9]. Yanamoto and Murakawa [10] showed that SCS with spinal nerve root stimulation method is expected to be useful for selective SCS in cases with failure to acquire stable stimulation by dorsal cord stimulation. Adrian et al. [11] showed that dorsal nerve root stimulation relieves pain, improves quality of life and functionality, and allows for medication reduction to a comparable degree as SCS and similar results in VAS scores for the SCS and dorsal nerve root stimulation group at all time points in the study. Both groups achieved a > 50% VAS reduction at 12 months. In PHN, peripheral nerve stimulation including the DRG may be a viable option, even at higher cervical spinal segments [12]. Theoretically, DRG stimulation offers several advantages over SCS. It is established that the action of successful neuromodulation should be proximal to the site of the neural lesion. DRG stimulation would provoke stimulation much more exclusively in the pain site and corresponding segment, avoiding adjacent stimulation. It could be expected that a lower stimulation power would be necessary. It seems that DRG stimulation can be an effective option for patients who already have failed SCS trials or those who are not good candidates for SCS.

However, there are mixed results in the DRG stimulation of PHN treatment [10,12]. No comprehensive overview has been published so far, and no consensus exists regarding the recommendations for DRG stimulation in PHN. Simulation of the affected ganglion itself may provoke immediate and unbearable pain, and the effect of the DRG may not last long [13].

This study has some limitations. First, in this case, DRG stimulation was performed due to insufficient SCS stimulation; therefore, the effectiveness or efficacy of DRG stimulation alone cannot be verified. However, this requires further evaluation. Second, this is a case report, and there is no randomized controlled trial and no consensus regarding SCS and DRG stimulation. Third, this case is only a short-term result. Long-term follow-up and further evaluation are required.

DRG stimulation combined with SCS may be a treatment option for intractable PHN without significant complications and inconvenience. DRG stimulation may compensate for the shortcomings of spinal cord stimulation, which is difficult to stimulate at a specific thoracic dermatome.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available.

AUTHOR CONTRIBUTIONS

REFERENCES

INTRODUCTION

Recently new instruments have been developed for viewing the larynx with video assistance for safe and accurate endotracheal intubation [1]. Among various instruments, video stylets are popular due to their portability, convenience of preparation, and safety [2,3]. The Optiscope™ (Clarus Medical LLC, USA) is a video stylet made of rigid fiberoptic attached to an LCD monitor with two light sources, allowing intubation to be performed while visualizing the patient’s larynx through the monitor [1,4]. The monitor of the Optiscope™ is fixed to the handle, thus providing the anesthesiologist a more comfortable and desirable posture during intubation [1]. Previous studies have compared the Optiscope™ with other intubation devices and revealed that the Optiscope™ helps reduce the cervical spine motion compared to videolaryngoscopes, and allows for shorter intubation time than flexible fiberoptic bronchoscopes [2,5]. The widely performed con-

The effects of backward, upward, rightward pressure maneuver for intubation using the Optiscope™: a retrospective study

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Background: The Optiscope™ and the backward, upward, rightward pressure (BURP) maneuver are widely used in clinical practice because the BURP maneuver facilitates intubation by improving visualization of the larynx. However, the effect of the BURP maneuver is unclear when using the Optiscope™. Therefore, we retrospectively investigated the effect of the BURP maneuver on intubation using the Optiscope™.

Methods: Sixty-eight patients intubated with the Optiscope™ were enrolled. We used the BURP maneuver in Group A (n = 33) and the conventional maneuver (which does not use the BURP maneuver) in Group B (n = 35). BURP application status was a binary variable representing whether the BURP maneuver was used during the intubation. A multiple linear regression analysis was performed to assess the effects of the BURP application status on intubation time controlling for body mass index, preoperative dental injury status, obstructive sleep apnea history, thyromental distance, sternomental distance, interincisor distance, history of neck rotation restriction, and Mallampati classification.

Results: There was no difference in the intubation time between the two groups. According to the regression model (R² = 0.308, P = 0.007), the BURP maneuver (Group A) decreased the intubation time by 6.089 seconds (95% confidence interval 1.303–10.875, P = 0.014) compared to Group B.

Conclusions: The BURP maneuver reduced intubation time when using the Optiscope™.

Keywords: Intubation device; Intubation time; Maneuver; Rigid fiberooscope.
Conventional maneuver when using the Optiscope™ consists of a single non-dominant handed chin lift while the Optiscope™ is inserted with the dominant hand [6].

Alongside new instruments, anesthesiologists perform various maneuvers to manage difficult airways. Applying BURP (backward, upward, and rightward pressure on the thyroid cartilage) maneuver (Fig. 1) is well explained by Knill [7]. The BURP maneuver is a reliable method for improving the management of complex laryngoscopy procedures by improving the visualization of the larynx [8,9]. The Optiscope™ and the BURP maneuver are independently used widely in different clinical practices and have proven beneficial. However, only a few studies have identified the correlation of the BURP maneuver when using the Optiscope™ for intubation.

This study compares the intubation time and other intubation data between the conventional maneuver and the BURP maneuver retrospectively while using the Optiscope™ in both cases. The clinical factors affecting intubation time are also evaluated statistically.

**MATERIALS AND METHODS**

**Ethics and approval**

Ethical approval for this retrospective study (no. 2021-01-008-002) was provided by the institutional review board. Written informed consent for enrollment in the study was renounced because of the retrospective nature of this study.

**Subjects**

All patients who underwent operation under general anesthesia and were intubated by the chief resident with the Optiscope™ at our medical center from October 2020 to February 2021 were eligible for this study. The anesthesiology chief resident who performed all the intubations in this study had performed over 50 successful tracheal intubations using the Optiscope™ with more than 3 years’ of experience. Patients intubated by other residents and staff anesthesiologists were excluded to minimize inter-intubator variability. Patients with upper airway abnormalities, such as tumor, trauma, inflammation or foreign body, were excluded. Patients with risk of aspiration, history of difficult intubation, or American Society of Anesthesiologists (ASA) physical status classification of ≥ 4 were also excluded.

Patients were assigned to 2 groups depending on the execution status of the BURP maneuver (Group A-BURP maneuver, Group B-conventional maneuver). The staff anesthesiologists assisted the chief resident in intubating patients by performing the BURP maneuver or conventional maneuver. A current staff anesthesiologist at our institute routinely uses the BURP maneuver whenever intubation is attempted regardless of any circumstances including the performing device, and patient characteristics. Thus these patients were assigned to group A. The other staff anesthesiologists do not perform the BURP maneuver, therefore categorizing remaining patients into group B.

**Data collection**

In this study, demographic data and the ASA physical status were collected as general data. Airway related variables consisted of the presence of preoperative dental injuries, diagnosis of obstructive sleep apnea history (OSA hx.), thyromental distance (TMD), sternomental distance (SMD), neck circumference (NC), interincisor distance, presence of neck rotation of motion restriction history (ROM hx.), and the

![Fig. 1. BURP maneuver. BURP: Backward, Upward, Rightward Pressure.](image-url)
Mallampati classification. The sternomental distance was considered the distance from the upper border of the manubrium to the tip of the mandible. It was measured with the head fully extended on the neck with the mouth closed. Intubation data consisting of the degree of manual mask ventilation, the total number of attempts, and intubation time were collected. The degree of manual mask ventilation was categorized into three groups (easy, moderate, and difficult), and converted into quantitative variables 1, 2, and 3, respectively, for statistical analysis. The primary outcome of this study was the intubation time. The intubation time was defined as the time interval between the removal of the ventilation mask from the patient’s face to just after the connection of the endotracheal tube with the breathing circuit. In each group, the intubation time was limited to 90 seconds per attempt. Whenever the intubation time reached 90 seconds or the SpO2 < 90%, the attempt was ceased and manual ventilation was performed for 1 min with 100% oxygen [10]. Failed tracheal intubation was defined as failure to secure the airway with three consecutive attempts [4,10]. Upon failing to intubate, alternative devices such as fiberoptic bronchoscope or Pentax-AWS® were used, and the corresponding suspect was excluded. Postoperatively, sore throat pain (11 Visual analog scale score), oral cavity bleeding, hoarseness, and dental injury were checked by a post-anesthesia care unit nurse who was blinded to the group assignment. The 11 visual analog scale score ranges from 0 to 10, with 0 representing no pain and 10 representing the worst imaginable pain.

**General anesthesia protocol**

All procedures other than the execution of the BURP maneuver were identical between the two groups. Patients entered the operating room without any premedication. Following routine monitoring, including electrocardiography, pulse oximetry, noninvasive blood pressure measurement was performed. After pre-oxygenation with 100% oxygen via facemask for 3 min, general anesthesia was induced with propofol (2 mg/kg) and sevoflurane. Rocuronium 0.6 mg/kg was administered after the loss of consciousness to facilitate intubation with neuromuscular relaxation. Subsequently, 0.2 mg of glycopyrrrolate was administered to reduce oral secretion. After a minimum of 120 s from rocuronium administration, intubation was performed with the Optiscope™. In group A (BURP group) a staff anesthesiologist performed the BURP maneuver on the thyroid cartilage. The Optiscope™ was prepared with a tracheal tube (internal diameter 7.5 mm for males and 7.0 mm for females) coated by an anti-fog agent at the end tip of the camera, and the stylet lubricated where the tube was placed. The Optiscope™ was bent at a 45° angle 5 cm from the distal end. The Optiscope™ was then inserted into the posterior pharynx using the chin lift with the non-dominant hand. After identifying the epiglottis, the distal tip of the Optiscope™ was advanced under the epiglottis into the vocal cord and the tube was further advanced until the cuff passed the glottis. Successful intubation was confirmed based on the auscultation of both lung fields and the appearance of continuous end-tidal carbon dioxide monitoring using a ventilator.

**Statistical analysis**

Continuous variables were compared using the Student’s t-test, assuming that each variable demonstrated normal distribution following the central limit theorem with a subject number larger than 30. Categorical variables were compared using Fisher’s exact test.

The following variables were each coded, converting them to categorical variables. ASA and Mallampati classifications were coded into their inherent numbers (1, 2, 3 for ASA and 1, 2, 3, 4 for Mallampati). Pre-op dental injury, OSA hx., Neck ROM hx., were coded into 0, or 1, where 0 meant an existent history, while 1 meant no history. Post-op. bleeding, post-op. hoarseness, and post-op. dental injuries were also coded into 0 or 1, where 0 meant no complication and 1 meant the occurrence of complication. Sex was also coded into 0 or 1, where 0 represented male and 1 represented female.

Categorical variables are presented as numbers (percent), and continuous variables are presented as mean ± SD.

All statistical analyses were conducted using IBM SPSS Statistics (version 25.0, IBM Corp., USA).

Multiple linear regression analysis was conducted to identify the effect of each variable on intubation time. The BURP maneuver application status was coded into a categorical variable for this analysis, with group A being coded 0 and group B being 1.

In our study, analysis with a value of P < 0.05 was defined as statistically significant.

**RESULTS**

Three hundred thirty-four patients were screened and 260
patients who underwent intubation using a device other than the Optiscope™ were excluded; therefore, 74 patients were enrolled. One patient with a difficult intubation history, another with an airway anomaly of severe tracheal deviation, 3 patients with an ASA classification equal to or above class 4, and 1 patient with an increased risk of aspiration were excluded. The data were analyzed for the remaining 68 patients.

Baseline general demographic and airway characteristics, including age, sex, height, weight, body mass index, ASA classification, preoperative presence of dental injury, OSA hx., TMD, SMD, NC, interincisor distance, neck ROM history and Mallampati class are listed in Table 1. There was no significant difference in general demographic and airway characteristics between both groups.

The intubation time alongside other intubation variables did not differ between the two groups (Table 2).

Table 3 summarizes the effect of certain variables on intubation time, as identified by multiple regression analysis and proven to be statistically significant (P = 0.007). The variables in this model were chosen with a difference less than 0.1 between R² and adjusted R². Applying the BURP maneuver reduced the intubation time by 6.089 seconds compared to the conventional maneuver (P = 0.014). Other variables that proved significant were OSA hx. (P = 0.009), TMD (P = 0.047), SMD (P = 0.002), and Mallampati class (P = 0.042). Among those, SMD was most significant with a P value of 0.002.

**DISCUSSION**

This clinical study was performed to identify the effect of the BURP maneuver when using the Optiscope™ for intubation. There was no significant difference in intubation time between the two groups when compared using the Student’s t-test (Table 2). However, after controlling certain variables and identifying each variable’s effect on intubation time using multiple linear regression analysis, applying BURP was found to shorten intubation time by 6.089 seconds (Table 3).

There may be few possibilities behind this outcome. First, the anesthesiologist performing intubation in our study was right-handed. Thus, he used his left hand (non-dominant hand) for the chin lift while advancing the Optiscope™ with

| Table 1. Demographic Data and Airway Assessment Data, between Group A (BURP Maneuver; Backward, Upward, and Rightward Pressure), and Group B (Conventional Maneuver) |
|---------------------|---------------------|---------------------|---------------------|
| Variable            | Group A (n = 33)    | Group B (n = 35)    | P value             |
| Age (yr)            | 59.82 ± 13.9        | 63.14 ± 13.6        | 0.325               |
| Sex, male           | 16 (48.5)           | 17 (48.6)           | 0.994               |
| Height (cm)         | 161.12 ± 8.09       | 160.51 ± 9.9        | 0.785               |
| Weight (kg)         | 65.76 ± 16.02       | 64.46 ± 12.16       | 0.707               |
| BMI (kg/m²)         | 25.05 ± 4.72        | 25.06 ± 4.80        | 0.707               |
| ASA classification   |                     |                     | 0.063               |
| 1                   | 1 (3.0)             | 1 (2.9)             |                     |
| 2                   | 24 (72.7)           | 32 (91.4)           |                     |
| 3                   | 8 (24.2)            | 2 (5.7)             |                     |
| Pre op. dental injury| 1 (3.0)             | 3 (8.6)             | 0.614               |
| OSA hx.             | 7 (21.2)            | 7 (20.0)            | 0.902               |
| TMD (cm)            | 9.39 ± 1.47         | 9.58 ± 2.32         | 0.685               |
| SMD (cm)            | 17.18 ± 1.86        | 16.41 ± 2.56        | 0.161               |
| NC (cm)             | 38.28 ± 4.99        | 36.62 ± 4.73        | 0.164               |
| IID (cm)            | 4.56 ± 0.77         | 4.82 ± 0.76         | 0.157               |
| Neck ROM hx.        | 1 (3.0)             | 2 (5.7)             | NA                  |
| Mallampati classification | 1 | 6 (18.2) | 11 (31.4) |
|                      |                     |                     |                     |
|                      |                     |                     |                     |
|                      |                     |                     |                     |

Values are presented as mean ± SD or number (%). BMI: body mass index, ASA: American Society of Anesthesiology, Pre-op.: preoperative, OSA hx.: obstructive sleep apnea history, TMD: thyromental distance, SMD: sternomental distance, NC: neck circumference, IID: interincisor distance, ROM hx.: rotation of motion history, NA: not applicable.
his right hand via the proportionally right side of the oral cavity. Knill [7] proposed that the moderate rightward displacement of the BURP may improve the view by placing the glottis in a more open visual pathway along the right side of the oral cavity. This effect may have further opened the oral pathway for advancing the Optiscope™ on the right side of the oral cavity, resulting in a shorter intubation time. Also, a study comparing Glidescope® video laryngoscope and direct laryngoscope in pediatric patients revealed that with the BURP maneuver, the Glidescope® was able to enhance the Cormack and Lehane grade of 3 or 4 view to a grade 1 or 2 view [11]. Although the shape of the Glidescope® resembles the standard laryngoscope more than the Optiscope™, we propose a hypothesis that the BURP maneuver also provided better glottic exposure when used with the Optiscope™. We expected that longer SMD would facilitate intubation. Previous studies have suggested short SMD as a predictor of difficult laryngoscopy [12–14]. In addition, SMD is an indicator for neck mobility and extension [14]. Full extension of the neck makes the alignment of the oropharyngeal axes more horizontal creating an ideal environment for laryngoscopy [4]. Thus we hypothesized that longer SMD would shorten intubation time when using the Optiscope™. However, multiple linear regression analysis showed that longer SMD was associated with longer intubation time in the current study. This outcome may be due to several reasons.

Firstly, Khan et al. [15] reported that SMD ≤ 13 cm was the cutoff point for difficult intubation. Other studies defined

**Table 2. Comparison of Intubation Data between Group A (BURP Maneuver; Backward, Upward, and Rightward Pressure) and Group B (Conventional Maneuver)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (n = 33)</th>
<th>Group B (n = 35)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mask ventilation</td>
<td></td>
<td></td>
<td>0.228</td>
</tr>
<tr>
<td>1</td>
<td>28 (84.8)</td>
<td>32 (91.4)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3 (9.1)</td>
<td>3 (8.6)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2 (6.1)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Intubation attempt</td>
<td></td>
<td></td>
<td>0.171</td>
</tr>
<tr>
<td>1</td>
<td>31 (93.9)</td>
<td>30 (85.7)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2 (6.1)</td>
<td>3 (8.6)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0 (0.0)</td>
<td>2 (5.7)</td>
<td></td>
</tr>
<tr>
<td>Intubation time (s)</td>
<td>36.23 ± 8.98</td>
<td>38.92 ± 10.97</td>
<td>0.275</td>
</tr>
<tr>
<td>Throat pain (VAS score)</td>
<td>1.36</td>
<td>1.51</td>
<td>0.732</td>
</tr>
<tr>
<td>Post-op. bleeding</td>
<td>3 (9.1)</td>
<td>1 (2.9)</td>
<td>0.349</td>
</tr>
<tr>
<td>Post-op. hoarseness</td>
<td>2 (6.1)</td>
<td>3 (8.6)</td>
<td>NA</td>
</tr>
<tr>
<td>Post-op. dental injury</td>
<td>0</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

Values are presented as number (%) or mean ± SD. VAS: visual analog scale, Post-op.: postoperative, NA: not applicable.

**Table 3. Multiple Regression Analysis with Intubation Time as an Outcome Variable**

<table>
<thead>
<tr>
<th>Model</th>
<th>Unstandardized coefficient</th>
<th>95% CI for B</th>
<th>t</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (constant)</td>
<td>25.142</td>
<td>18.62</td>
<td>-12.130 to 62.415</td>
<td>1.350</td>
</tr>
<tr>
<td>BURP status (0-group A 1-group B)</td>
<td>6.089</td>
<td>2.391</td>
<td>1.30 to 10.875</td>
<td>2.547</td>
</tr>
<tr>
<td>BMI</td>
<td>-0.443</td>
<td>0.246</td>
<td>-0.936 to 0.049</td>
<td>-1.802</td>
</tr>
<tr>
<td>Pre-op. dental injury</td>
<td>-1.389</td>
<td>5.093</td>
<td>-11.583 to 8.805</td>
<td>-0.273</td>
</tr>
<tr>
<td>OSA hx.</td>
<td>-7.805</td>
<td>2.897</td>
<td>-13.605 to -2.005</td>
<td>-2.694</td>
</tr>
<tr>
<td>TMD</td>
<td>-1.531</td>
<td>0.753</td>
<td>-3.039 to -0.024</td>
<td>-2.033</td>
</tr>
<tr>
<td>SMD</td>
<td>2.129</td>
<td>0.668</td>
<td>0.792 to 3.465</td>
<td>3.189</td>
</tr>
<tr>
<td>IID</td>
<td>-1.197</td>
<td>1.816</td>
<td>-4.833 to 2.438</td>
<td>-0.659</td>
</tr>
<tr>
<td>Neck ROM hx.</td>
<td>4.259</td>
<td>6.113</td>
<td>-7.977 to 16.496</td>
<td>0.697</td>
</tr>
<tr>
<td>Mallampati classification</td>
<td>3.384</td>
<td>1.629</td>
<td>0.124 to 6.644</td>
<td>2.078</td>
</tr>
</tbody>
</table>

Dependent variable: intubation time R value: 0.555, R²: 0.308, adjusted R²: 0.200, P value: 0.007. CI: confidence interval, SE: standard error, BURP: backward, upward, and rightward pressure, BMI: body mass index, Pre-op.: preoperative, OSA: obstructive sleep apnea, TMD: thyromental distance, SMD: sternomental distance, IID: interincisor distance, ROM: rotation of motion. *Statistically significant at P < 0.05.
the cutoff point of SMD for difficult intubation as \( \leq 12.5 \text{ cm} \) [13] and 13.5 cm [12]. However, in our study, the mean of SMD was 17.18 and 16.41 for Group A, and Group B, respectively. This distance is far off from the cutoff point indicated for difficult intubation in previous studies, which might have affected the outcome.

Secondly, a previous study demonstrated that the area under the curve of 0.66 for SMD was predictive of difficult intubation using the Optiscope™ [4]. This study found that the discrimination power mentioned previously is less than acceptable, suggesting that the importance of SMD as a predictor of difficult intubation with the Optiscope™ might be clinically insignificant. Thus, while SMD remains a strong predictor of difficult intubation using the laryngoscope, it becomes uncertain when using the Optiscope™.

There are several limitations to this study. First, the retrospective nature of this study suggests that this study had poor control over other undetected exposure factors and co-variates [16]. Second, this was a single-center study with relatively small group size. Due to the Coronavirus disease (COVID-19) pandemic and the subsequent conversion of our institute to a semi-COVID 19 special hospital during 2020, the total number of elective surgeries was significantly reduced. The number of surgeries has not been restored to full capacity yet, making it difficult to accumulate a concrete subject number. Thus a large multicenter study with a definite subject number is needed. Third, the intubation time in our study is defined by the time between removing the facial mask from the patient and just after the connection of the tube with the circuit. Other studies that measured the intubation time of various instruments usually defined it as the interval between insertion of the device into the oral cavity and their extrication after intubation [1,2,10]. This difference might be why the average intubation time in the current study is much longer than in previous studies, which might have affected the study results. Fourth, our view that BURP maneuver possibly shortens intubation time when using the Optiscope™ remains only a hypothesis since the intubation time did not differ between the two groups using the Student t-test (Table 2) despite the strong evidence from multiple linear regression (Table 3). The precise statistical explanation would be that there was no significant difference in intubation time between the two groups initially. However, after controlling other variables, the intubation time was prolonged by 6.089 seconds compared to the BURP maneuver when using the Optiscope™.

Despite these limitations, the change in intubation time depending on the BURP maneuver status can prove valuable in clinical practices such as the rapid sequence intubation where intubation time is critical [17].

In conclusion, after controlling other variables, the BURP maneuver reduced intubation time compared to the conventional maneuver when using the Optiscope™. However, this remains only a possibility with domains of further evaluation and verification. Moreover, the findings from the present study suggest that the BURP maneuver, when applied with the Optiscope™, can be optional and even beneficial in certain situations.

**CONFLICTS OF INTEREST**

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

**DATA AVAILABILITY STATEMENT**

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

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BURP maneuver using the Optiscope™


Tracheal intubation is essential for maintaining the airway during general anesthesia. When performing endotracheal intubation, air leakage is one of the most common complications. The lack of ventilation caused by endotracheal tube cuff tears accounts for 5.9% to 11% of air leakage complications [1,2]. A damaged cuff can lead to a variety of complications, ranging from minor issues, such as air bubbles in the oral cavity, to fatal respiratory complications. Since immediate reintubation may entail risks associated with hypoxia and airway maintenance failure, damage to the endotracheal tube cuff during endotracheal intubation is an important issue that requires caution [3].

For orthognathic surgery, nasotracheal intubation, namely endotracheal intubation through the nasal cavity, is usually performed. Among patients who undergo orthognathic surgery, the skeletal anchorage system (SAS) is implemented in some patients for orthodontic correction. The micro-screws used for orthodontic correction are also called SAS screws, orthodontic anchoring screws, mini-screws, and micro-implants [4]. In this case, they are referred to as orthodontic micro-implants. Micro-implants placed in the middle of the palate can play the role of indenting the molar teeth or
tilting the molar to the buccal side [4].

In this report, we present the first case of repetitive endotracheal tube cuff damage caused by orthodontic micro-implants during nasotracheal intubation.

**CASE REPORT**

Institutional Review Board waived the requirement of written consent for the publication of this case (no. CAUH-2101-016-19352).

A 34-year-old female patient (height, 168 cm; weight, 59 kg) was scheduled to undergo orthognathic surgery under general anesthesia for malocclusion and facial asymmetry. The patient had no medical history or specific findings other than orthodontic findings. Preoperative imaging examinations were performed, including facial and intraoral surface anatomy photography, panoramic X-ray photography, and cone-beam computed tomography, which showed no specific findings in either the nasal or nasopharyngeal regions (Fig. 1). Pulse oximetry, noninvasive blood pressure monitoring, and electrocardiography monitoring were initiated after the patient entered the operating room. Before the induction of anesthesia, her blood pressure was 110/70 mmHg, heart rate was 70 beats per minute, and pulse oxygen saturation was 99%.

Before the induction of anesthesia, the nasal tube (Nasal RAE, COVIDIEN™, Ireland) with an inner diameter of 6.5 mm was assessed preoperatively for any leakages on the cuff by immersing the tube of the endotracheal tube in a 1-L bottle of normal saline solution. Approximately 10 ml of air was injected into the cuff, but no air bubbles were observed. The anterior part of the endotracheal tube was also immersed in normal saline solution at 37°C for 5 min to soften the nasal tube.

For the induction of anesthesia, 100 μg of fentanyl, 40 mg of 2% lidocaine, 120 mg of 1% propofol, and 40 mg of rocuronium were administered after sufficient oxygenation through 100% oxygen. Nasotracheal intubation was performed via the right nasal cavity. In passing the tube through the nasal cavity, the anesthesiologist perceived slight stiffness without bleeding or other difficulties. After passage through the nasal cavity, a laryngoscope and Magill forceps were used for tracheal intubation. Due to the risk of rupture of the cuff, the anesthesiologist intended not to handle the cuff of the nasotracheal tube using the Magill forceps. Tracheal intubation was performed without any particular difficulty (Cormack–Lehane grade I). After nasotracheal intubation, clear symmetric breathing sounds were heard in both lungs, and the cuff did not leak immediately after injecting air into the cuff. Ten minutes after mechanical ventilation, positive pressure ventilation was applied, and the gap between the inspiratory volume and expiratory volume began to increase. There was leakage of anesthetic gas into the oral cavity, and a leakage sound was heard in the oral cavity. Re-intubation was attempted under the suspicion of cuff rupture. A nasotracheal tube with an inner diameter of 6.0 mm, which was one size smaller than the size of the previous tube, was assessed again for tube leakage and re-intubated through the right nasal cavity.

In the process of passing through the nasal cavity, as in the first attempt, the anesthesiologist perceived slight stiffness, and the tube was assessed using a laryngoscope and intubated into the vocal cords without using Magill forceps. However, immediately after intubation, a cuff tear was observed, and the tracheal tube was removed. The anesthesiologist repositioned the tube from the right to the left nasal cavity, and a nasal tube with an internal diameter of 6.0 mm was reinserted. Unlike on the right side, the nasotracheal tube passed through the left nasal cavity smoothly without any perception of stiffness. After air injection, no findings of air leakage in the endotracheal tube were observed, both

---

**Fig. 1.** Preoperative skull radiography. Preoperative skull radiography showed no remarkable findings.
lung auscultations were symmetric and clear, no sounds from the outflow of oral auscultation were heard, and the tidal volume was properly obtained through positive mechanical ventilation. Subsequently, the surgery proceeded well without any leakage, and maintenance of anesthesia was performed using 50% nitrous oxide and oxygen mixed fresh gas and 6–7 vol% desflurane.

During the dental surgery, the micro-implant screw, which was fixed at a position 3 mm from the central line to the right from the single-stage ceiling, was found by the surgeon (Fig. 2). On incision of the maxilla, the surgeon confirmed that the tip had protruded approximately 1–2 mm in the nasal cavity. The cause of the cuff tear of the nasotracheal tube during repeated intubation via the right nasal trachea was finally confirmed. Subsequently, the surgery was completed without any complications.

The screw, which was an orthodontic micro-implant, is used for dental orthodontics. Since the micro-implant was inserted between the imaging test and surgery, we did not detect the position of the micro-implant before the surgery. Radiography and computed tomography performed on the 1st day after the surgery revealed findings leading to the suspicion of orthodontic micro-implants (Figs. 3, 4).

**DISCUSSION**

Nasotracheal intubation is generally performed when the oral route cannot be used in patients who have undergone...
head and neck, oral, or open impairment surgery. It is also performed as an alternative to tracheostomy when long-term intubation maintenance is required in the intensive care unit [5,6]. In particular, nasotracheal intubation facilitates securing a surgical field of view in orthognathic surgery. However, nasotracheal intubation is associated with a higher risk of cuff damage because the passage of the nasal cavity is narrow and there are more structures compared to the oral cavity. Abnormal structures that can affect nasotracheal intubation include concha bullosa, septal curvature, septal spurs, nasal polyps, and other anatomical variations [7]. Therefore, intubation is performed by using a route that contains fewer abnormal structures that may affect nasotracheal intubation. This is because nasotracheal intubation may not be successful in cases of a narrow nasal cavity, and abnormal structures may damage the tube cuff. In addition, cuff tears may occur because of the Magill forces used for intubation through the nasal cavity. Therefore, an anesthesiologist must take care not to handle the tube cuff when intubating via the vocal cords and trachea in the oropharynx [8,9].

The nasal cavity is divided into two sides by the nasal wall. The lower wall is composed of the oral cavity and hard palate, and the upper wall is composed of the middle wall of the maxillary sinus and three nasal bones. When performing nasotracheal intubation, the nasal tube passes through the nasal canal via two routes: the upper and lower routes [10]. In the upper route, the tube passes through the space between the middle turbinate and inferior turbinate, and in the lower route, it passes through the space between the bottom of the nasal cavity and inferior turbinate [11]. The lower route is known to be safer because it does not pass near the middle turbinate, which is rich in vascular structures [4,12]. In our case, we suggest that the right nasotracheal intubation had entered through the lower route of the nasal canal both times, and the intubation was perceived as slightly stiff as it passed through a narrow space. In this case, the anesthesiologist detected the rupture and leakage of the cuff and performed reintubation. In the second trial, a tube that was one size smaller was used, and in the third trial, the intubation was repositioned from the right to the left to prevent respiratory complications related to hypoxia.

In some cases, orthognathic surgery may be performed with a micro-implant inserted for further correction. In this situation, there is the possibility of a nasotracheal tube cuff tear by the micro-implant. Micro-implants, which are usually used for orthodontics, are 1.2 mm in diameter and have a screw 6–8 mm in length. In our case, a micro-implant with a diameter of 1.4 mm and length of 6 mm was inserted in the part that had deviated to the right by 3 to 3.5 mm from the middle of the upper palate. The location of micro-implants varies, but it is possible in most of the areas with alveolar bone of the maxilla or mandible, as well as alveolar bones such as the buccal or labial bone, palatal alveolar bone, maxillary nodule of maxilla, mid-maxillary palatal bone, posterior teeth, and body part of the maxilla [13,14]. Micro-implants placed in the middle of the palate in this way can play a role in indenting the molar teeth or tilting the molar to the buccal side [4].

Although the intranasal screw does not protrude after normal orthodontic treatment, there may be some complications following micro-implant placement, such as inflammation, infection, root contact, fractures, and swelling [13]. Therefore, additional orthodontic treatment should be avoided after preoperative imaging tests. We suggest that it is necessary to confirm that there are no problems in securing airways. All procedures require close communication with the attending physician. If there is leakage of the tube and rupture of the cuff after intubation through the nasal cavity, it is necessary to determine whether there are abnormal C that might cause problems in the tracheal intubation passage through the nasal cavity. In particular, it is necessary to carefully examine patients with fixed micro-implants, as in this case. In other cases, the presence of a nasal spur may damage the cuff, similar to the above case.

Although corrective micro-implants were placed by other dentists during the period between preoperative evaluation and surgery in this case, we regret that we did not confirm the orthodontic micro-implant that was fixed to the hard palate prior to nasotracheal intubation.

Although the timing of preoperative evaluation depends on the patient’s schedule, preoperative evaluation including preoperative X-ray is generally performed after micro-implants procedure. In this case, due to the patient’s schedule, micro-implant procedure was performed 5 days after preoperative evaluation. Surgery was performed 3 days after the micro-implant procedure. As the time interval between micro-implants procedure and orthognathic surgery was too short, and it X-ray cannot clearly distinguish whether micro-implant was protruded out of the tissue or not, post-implant X-ray was not taken.

Not all patients with orthognathic surgery got micro-implants procedure before surgery. The micro-implant inserted into the palate acts as an anchor for pulling or pushing a...
tooth. Recently, in patients with narrow maxillary, the uses of mini-screw assisted rapid palatal expansion (MARPE) are increasing. In this patient, MARPE was performed to expand the maxilla thus widen the nasal airway. In general, the micro-implant procedure does not make a problem for intubation because it is located within the tissue in most cases. This is a rare case in which the direction of micro-implant insertion was misaligned, and the tip of micro-implant was protruded out of tissue.

In order to prevent problems such as our case, we suggest to check whether the patients undergoing orthognathic surgery was performed micro-implants or not, and nasal cavity using nasal endoscopy before surgery if micro-implants was performed. To check the oral cavity before nasal intubation and intubate endotracheal tube to the other side of micro-implant also would be the help to prevent problems.

In our case, endotracheal tube cuff leakage was not identified during the preoperative evaluation and was resolved through additional alternatives. In the case of intubation through the nasal cavity, it is necessary to proceed with caution because one may encounter various situations.

CONFLICTS OF INTEREST

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

DATA AVAILABILITY STATEMENT

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

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REFERENCES

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Enacted: May 15, 2006
Recently revised (13th): September 7, 2021

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- The datasets generated during and/or analyzed during the current study are not publicly available due [REASON WHY DATA ARE NOT PUBLIC] but are available from the corresponding author on reasonable request.
- The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.
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ed in this published article [and its supplementary information files].

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

III. Research and Publication Ethics Guidelines

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

1. Conflict-of-interest statement

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

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

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

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

2. Statement of informed consent

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

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

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

4. Protection of human and animal rights

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

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

5. Registration of the clinical research

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

6. Reporting guidelines

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

7. Author and authorship

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

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

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

8. Plagiarism and duplicate publication

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

1) Intellectual theft
Deliberate copying of large blocks of text without attribution

2) Intellectual sloth
Copying of “generic” text, e.g., a description of a standard technique, without clear attribution

3) Plagiarism for scientific English
Copying of verbatim text, often from multiple sources

4) Technical plagiarism
Use of verbatim text without identifying it as a direct quotation but citing the source

5) Self-“plagiarism”

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

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

IV. Manuscript Preparation

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

- 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 Previous presentation in conferences
   Title of the conference, date of presentation, and the location of the conference may be described.

   ③ Funding statement
   Disclosure of all financial support for the work, including departmental or institutional funding/sup- port.

   ④ 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.

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

Materials and Methods
The materials and methods section should include sufficient details regarding the design, subjects, and methods of the research, 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. 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

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, end-point. Usually, the mean difference and standard deviation (SD) are typical parameters in estimating the effect size. The power must be equal to or greater than 80 percent. In the case of multiple comparisons, an adjusted level of significance is acceptable.

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

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

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

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

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.

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

- The format for references follows the descriptions below. Otherwise, it follows the NLM Style Guide for Authors, Editors, and Publishers (Patrias, K. Citing medicine: the NLM style guide for authors, editors, and publishers [Internet]. 2nd ed. Wendling, DL, technical editor. Bethesda (MD): National Library of Medicine (US); 2007 [updated 2015 Oct 2; cited Year Month Day]. Available at: www.ncbi.nlm.nih.gov/books/NBK7256/).
- If necessary, the Editorial Board may request original documents for the references.
- Six authors can be listed. If there are more than 6 authors, only list 6 names with “et al.”
- Provide the start and final page numbers of the cited reference.
- Abstracts of conferences may not be included in the references. The American Society of Anesthesiologists (ASA) refresher course lecture is not acceptable as a reference.
- Description format
  A. Regular journal
  Author name. Title of article. Name of journal published year; volume: start page-final page.
  Journal article volume with supplement
  Journal article issue with supplement
  B. Monographs
  - If reference page is only 1 page, mark ‘p’.
  - Note if it is beyond the 2nd edition.
  - Translated documents cannot be used as references. The original documents should be provided as references.
  C. Chapter
  Any separate author of a chapter should be provided.
  D. Electronic documents
  E. Online journal article
  F. Advance access article

Tables
- Only one table is to be drawn per page in the order cited in the text.
- The title of the table is to be in English and written
at the top of the table in the form of a phrase.

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

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

(3) Figures and Photographs

1 APM encourages authors to use color to increase the clarity of figures. Please note that color figures are used without charge.

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

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

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

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

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

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

8 Pathological samples should be pictured with a measuring stick.

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

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

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

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

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

5 The maximum number of video clips is 20.

6 The video clip(s) should be playable on Microsoft Windows OS. The video clip(s) should be tested for playback before submission, preferably on computers not used for their creation, to check for any compatibility issues.

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

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

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

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

   (1) Cover page: Same as that for clinical and experimental studies.
   (2) Abstract: All case reports should contain a structured abstract that is written only in English. Provide an abstract of no more than 150 words. It should contain 3 subsections: Background, Case, and Conclusions. A list of keywords, with a minimum of 3 and maximum of 10 items, should be included at the end of the abstract.
   (3) Introduction: Should not be separately divided. Briefly describe the case and background without a title.
   (4) Case report: Describe only the clinical information that is directly related to the diagnosis and anesthetic management.
   (5) Discussion: Briefly discuss the case, and state conclusions at the end of the case. Do not structure the conclusion section separately.
   (6) References: The number of references should be less than 15. However, if necessary, the number of reference can be added in accordance with the decision of the editorial committee.
   (7) Tables and figures: Proportional to those for clinical and experimental studies.

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

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

   (1) Cover pages should be formatted in the same way as those of clinical research papers. The corresponding author should be the first author. A maximum of five authors is allowable.
   (2) The body text should not exceed 1,000 words and should have no more than 5 references. A figure or a table may be used.
   (3) Letters may be edited by the Editorial Board, and if necessary, responses by the author of the subject paper may be provided.

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

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

   (1) The title should contain no more than 8 words. No more than 2 authors should be listed.
   (2) The legend should contain no more than 250 words.
   (3) If there is more than one panel, please label them Panel A, Panel B, etc.
   (4) The legends to the images and videos should briefly present relevant clinical information, including a short description of the patient’s history, relevant physical and laboratory findings, clinical course, response to treatment (if any), and condition at the last follow-up.