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Erector spinae plane block in children: a narrative review

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In addition to publishing original articles, KJA features reviews, editorials, case reports, and letters to the editor. KJA also features statistical rounds to provide its readers with educational fundamentals and practical implications for clinical and experimental statistics. Additionally, KJA gladly publishes negative results, which will benefit clinical practice and promote further research activity.

The primary considerations for publication are clarity, uniqueness, and advancement in design, performance, and knowledge.

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Current evidence of ultrasound-guided fascial plane blocks for cardiac surgery: a narrative literature review

Boohwi Hong¹,²*, Chahyun Oh¹*, Yumin Jo¹, Soomin Lee¹, Seyeon Park³, Yoon-Hee Kim¹

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근막면 차단술은 심장 수술 후 다중모드 진통에 유용한 요소이다. 근막면 차단술은 신경축 혈종 및 기흉 등 고전적 흉부 신경차단술과 관련된 심각한 합병증의 위험을 피하면서 효과적인 진통을 제공할 수 있다. 본 서술적 문헌고찰은 심장 수술에 사용되는 근막면 차단술인 흉골연늑간면, 흉근사이면, 흉근전거근면, 전거근면, 척추기립근면, 척추후궁후면 차단술을 다루었으며, 해당 차단술들의 해부학적 고려사항, 기전, 근거 문헌을 검토하였다. 또한, 피하 이식형 제세동기의 삽입수술을 위한 근막면 차단술도 고찰하였다.

Keywords: Analgesia; Cardiac surgical procedures; Fascia; Implantable defibrillators; Nerve block; Postoperative pain; Thoracic wall.
Erector spinae plane block in children: a narrative review

Monica Lucente, Giulia Ragonesi, Marco Sanguigni, Fabio Sbaraglia, Alessandro Vergari, Rosa Lamacchia, Demetrio Del Prete, Marco Rossi

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Erector spinae plane block (ESPB) is a technique used for pain control in children. The ESPB technique is performed by injecting local anesthetic into the erector spinae muscle plane. This technique has been shown to be effective for postoperative pain control in children.

Keywords: Analgesia; Anesthesia; Child; Conduction anesthesia; Nerve block; Newborn infant; Review.
Effect of equipotent doses of propofol and sevoflurane on endoplasmic reticulum stress during breast cancer surgery

Chung-Sik Oh¹,², Seung Wan Hong¹, Sarah Park¹, Yubi Kwon¹, Seong-Hyop Kim¹,²,³

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 배경: 암 환자 수술 중 프로포폴을 사용하는 것이 흡입 마취제를 사용하는 것 보다, 암 환자의 예후, 재발의 측면에서 우월하다는 선행 연구가 많다. 본 연구는 유방암 수술 중 프로포폴 및 세보플루란 마취 후 암세포 사멸 기전 중 하나로 알려진 소포체(endoplasmic reticulum, ER) 스트레스의 변화를 비교하였다.

방법: 유방암 수술을 받는 환자 53명을 프로포폴(נ = 28) 및 세보플루란(נ = 25) 마취군에 무작위 배정하였다. 마취를 유도하기 직전 그리고 수술 후 1시간과 24시간 시점에 혈액 검체를 채취했다. 인간 유방암 세포주를 환자 혈장으로 배양 및 처리하였으며, 암 세포주 및 림프구에 대한 C/EBP 상동 단백질(CHOP)의 빈도를 측정했다. 혈장 내 호중구 vs. 림프구 비율을 두 군에서 평가했다.

결과: 유방암 세포주에 대한 CHOP 발현은 군 간 차이가 없었지만(P = 0.108), 시간이 경과함에 따라 유의하게 감소했다(P = 0.027). 림프구에 대한 CHOP 발현은 군 간 유사하였으며(P = 0.485), 호중구 vs. 림프구 비율(P = 0.501)도 마찬가지였다.

결론: 유방암 수술 중 프로포폴 및 세보플루란 마취 후 암세포 및 림프구에서 소포체 스트레스의 변화에는 큰 차이가 없었다. 암세포 사멸과 관계된 것으로 알려진 소포체 스트레스는, 암환자 수술 중 사용하는 마취제의 종류에 큰 영향을 받지 않는다.

Keywords: Anesthesia; Apoptosis; Breast neoplasms; Endoplasmic reticulum; Propofol; Sevoflurane.

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Accuracy of suprascapular notch cross-sectional area by MRI in the diagnosis of suprascapular nerve entrapment syndrome: a retrospective pilot study

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Feasibility and efficacy of erector spinae plane block versus transversus abdominis plane block in laparoscopic bariatric surgery: a randomized comparative trial

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Keywords: Analgesia; Anesthesia; Bariatric surgery; Nerve block; Opioid analgesics; Pain clinics.
Determination of the 95% effective dose of remimazolam to achieve loss of consciousness during anesthesia induction in different age groups

Juyeon Oh¹, Sung Yong Park¹, Sook Young Lee¹, Ju Yeol Song¹, Ga Yun Lee¹, Ji Hyun Park², Han Bum Joe¹

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Keywords: General anesthesia; Hypnotics and sedatives; Intravenous anesthesia; Remimazolam; Unconsciousness; Vital signs.
Dexmedetomidine attenuates subarachnoid hemorrhage-induced acute lung injury through regulating autophagy and TLR/NFκB signaling pathway

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Keywords: Acute lung injury; Autophagy; Dexmedetomidine; Inflammation; Subarachnoid hemorrhage; Toll-like receptors.
For several decades after its introduction in 1934, thiopental was the most widely used intravenous anesthetic induction agent. However, propofol replaced thiopental in the 1990s owing to its various comparative advantages, including quicker recovery, shorter context-sensitive half-time, and antipruritic and antiemetic effects. Target-controlled infusion pumps with pharmacokinetic models and electroencephalogram-based anesthesia depth-monitoring devices have accelerated this trend. Numerous studies have provided further evidence for the safety and efficacy of propofol in various clinical situations [1–4].

Thirty years after the introduction of propofol, remimazolam, an ultra-short-acting benzodiazepine, was introduced as a novel intravenous anesthetic agent [5]. Remimazolam acts on the inactive metabolites by non-specific tissue esterases. Because remimazolam has a high clearance, small steady-state volume of distribution, and short context-sensitive half-time [5], it may not require dose adjustments in patients with renal or hepatic impairment [6]. Additionally, remimazolam has advantages over propofol, particularly in terms of safety, including less hemodynamic instability and respiratory depression, no pain on injection, and a known reversible agent, flumazenil [7–9].

However, many hurdles must be overcome before remimazolam can be widely used for general anesthesia. First, although remimazolam has been approved for general anesthesia in Japan and South Korea, it has not yet been approved for this purpose in other countries [5]. Second, commercially available infusion pumps and pharmacokinetic models for the target-controlled infusion of remimazolam are limited. Third, anesthesia depth monitoring indices, such as the bispectral index (Medtronic, Ireland) or patient state index (Masimo, USA), are not well correlated with loss of consciousness in general anesthesia with remimazolam [10,11]. Fourth, interactions with other drugs used for general anesthesia, particularly opioid analgesics, have not been studied sufficiently. Fifth, few studies have been conducted on the clinical outcomes after general anesthesia using remimazolam [12–15]. Sixth, no consensus has been reached on the doses of remimazolam for induction and maintenance of general anesthesia.

However, studies have been conducted recently to determine the induction dose of remimazolam for general anesthesia. Dai et al. [9] conducted a study to determine the appropriate single bolus injection dose of remimazolam (0.2, 0.3, or 0.4 mg/kg) for anesthesia induction within 1 min. They randomly assigned 189 patients to four groups (the remimazolam 0.2, 0.3, and 0.4 mg/kg groups and the propofol group) and reported a 94% success rate for loss of consciousness in the remimazolam 0.3 mg/kg group. In another study, Chae et al. [11] used a parametric time-to-event model to estimate the effective dose of remimazolam required to achieve a 95% success rate (ED95) for loss of consciousness within 5 min. They randomly assigned 120 patients to six different dose groups (0.02, 0.07, 0.12, 0.17, 0.22, and 0.27 mg/kg) and found the estimated ED95 to be 0.33, 0.25, 0.19, and 0.14 mg/kg for patients aged 20, 40, 60, and 80 years, respectively.
From the results, they proposed the following induction doses for remimazolam: 0.25–0.33 for patients aged < 40 years, 0.19–0.25 for those aged 40–60 years, and 0.14–0.19 mg/kg for those aged 60–80 years.

In this issue of the *Korean Journal of Anesthesiology*, another study aimed to determine the induction dose of remimazolam for general anesthesia was reported by Oh et al. [16]. Unlike previous studies, the authors of this study determined the ED95 of remimazolam for loss of consciousness within 3 min using the biased coin up-and-down method. This method is a type of sequential design for clinical trials that enables accurate estimation of the effective dose for a specific success rate without repeatedly exposing subjects to the same dose [17]. They enrolled 40 patients each in the young (20–39 years), middle-aged (40–59 years), and elderly (60–79 years) groups and found the ED95 of remimazolam for loss of consciousness within 3 min to be 0.37 mg/kg (95% CI [0.28, 0.39]) in the young group, 0.37 mg/kg (95% CI [0.27, 0.39]) in the middle-aged group, and 0.25 mg/kg (95% CI [0.20, 0.29]) in the elderly group. The discrepancies in the ED95 between the studies conducted by Chae et al. [11] and Oh et al. [16] in the middle-aged group (0.19–0.25 vs. 0.27–0.39 mg/kg) and elderly group (0.14–0.19 vs. 0.20–0.29 mg/kg) may be due to differences in the maximum observation period for loss of consciousness between the studies (5 min for Chae et al. vs. 3 min for Oh et al.). In general, slower induction with a smaller dose of induction agent is purposed for reducing side effects. However, it is notable that none of the patients experienced hypotension or bradycardia that required rescue medications during the 3 min observation period in the study conducted by Oh et al. [16].

Although remimazolam has potential advantages over propofol, the current evidence is still insufficient, especially regarding general anesthesia. Therefore, whether remimazolam could be widely used for general anesthesia in the future remains uncertain. Well-designed clinical studies and reports of clinical experiences are needed to confirm the safety and efficacy of remimazolam for general anesthesia in various clinical situations.

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**Conflicts of Interest**

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

**References**


Current evidence of ultrasound-guided fascial plane blocks for cardiac surgery: a narrative literature review

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Fascial plane blocks are useful for multimodal analgesia after cardiac surgery since they can provide effective analgesia without the serious risks associated with conventional techniques such as neuraxial hematoma and pneumothorax. This narrative review covers blocks performed at the parasternal intercostal, interpectoral, pectoserratus, serratus anterior, erector spinae, and retrolaminar planes, which are targets for fascial plane blocks in cardiac surgery. Brief anatomical considerations, mechanisms, and currently available evidence are reviewed. Additionally, recent evidence on fascial plane blocks for subcutaneous-implantable cardioverter-defibrillator implantation are also reviewed.

Keywords: Analgesia; Cardiac surgical procedures; Fascia; Implantable defibrillators; Nerve block; Postoperative pain; Thoracic wall.

Introduction

Cardiac surgeries are mainly performed via sternotomy and have been conventionally managed using high doses of opioids to attenuate undesirable physiologic responses [1]. However, such high opioid doses are associated with unwanted risks such as prolonged mechanical ventilation and a longer intensive care unit or hospital stay. These practices have recently been changing with the introduction of concepts of enhanced recovery after surgery [2] and fast-tracking [3,4], which aim to achieve both quick and high-quality recovery. As these goals can conflict with a high-dose opioid regimen, perioperative analgesic protocols should ideally involve alternatives or supplements for opioids. Effective pain control contributes not only to an improvement in patient comfort and satisfaction but also clinical outcomes [3–8].

Cardiac surgery has become increasingly less invasive with advancements in surgical instruments and techniques, such as minimal invasive direct coronary artery bypass (MIDCAB) graft surgery and anterior thoracotomy for valve surgery [9]. As the rationale for applying these less invasive techniques is to alleviate physiological deterioration due to extensive surgical wounds and accompanying pain and thereby enhance recovery, immediate or early extubation is often attempted in these patients. In contrast to classical cardiac surgical patients who were heavily sedated with high doses of sedatives and opioids in the early postoperative period, these patients have to confront this stressful time without the assistance of mechanical ventilation and with minimal use of sedatives and opioids. To effectively accomplish this, numerous regional analgesic techniques have been introduced as essential components of an effective multimodal analgesic pro-
tocol [10–16].

Among the various thoracic regional techniques, fascial plane blocks are emerging as an effective alternative to conventional techniques such as paravertebral, epidural, or spinal blocks [17–19]. Fascial plane blocks involve the injection of a local anesthetic between the muscles through which the peripheral nerve travels [20]. For these techniques, the nerve itself is not targeted and the needle is not directed toward the neural axis; therefore, the risks of serious complications such as neural injury and neuraxial hematoma can be prevented or at least reduced. As most cardiac surgical patients receive heparin, avoiding neuraxial needling is especially appealing. The additional benefit that these blocks are relatively simple to perform has resulted in its widespread use.

In this article, the current evidence provided by randomized controlled trials (RCTs) on various ultrasound-guided fascial plane blocks for cardiac surgery are reviewed.

Method of the narrative review

We performed a literature search for articles assessing chest wall nerve blocks for cardiac surgery in PubMed, Embase, and Cochrane Library. The search was conducted from June 22, 2022 to June 26, 2022. In this review, the PICO (Populations of interest, Intervention, Comparators, and Outcomes) was as follows: (P) adults or pediatric patients undergoing cardiac surgery, (I) regional analgesia, (C) a comparative intervention such as no blockade or systemic analgesia, and (O) various clinical outcomes including pain score and analgesic consumption. The exclusion criteria were as follows: non-English language articles, non-RCTs, and duplicate or irrelevant articles. The search terms used included: (P) “Cardiac surgical procedures [Mesh] or “Heart surgery” or “Minimal invasive cardiac surgery” or “Anterior thoracotomy”; (I) limited to “PECS block,” or “Pectoral nerve block” or “Serratus plane block” or “Parasternal block” or “Transversus thoracis plane block” or “Erector spinae plane block” or “Retrolaminar block,” which are the most commonly performed thoracic fascial plane blocks.

We screened 1,223 records that were identified in the literature search. After removing duplicates, 1,026 distinct citations were retrieved, of which 991 (96.5%) were excluded during the initial screening phase. The primary reasons for exclusion were non-RCT designs and not meeting the inclusion criteria. After reviewing the full texts, 20 studies remained. Two additional cardiac surgery RCTs and three studies on subcutaneous-implantable cardioverter-defibrillator (S-ICD) implantation were included after a manual search was conducted. Consequently, 25 studies were included in this review; 22 for cardiac surgery (Table 1) and three for S-ICD implantation.

Nomenclature

Recently, the American Society of Regional Anesthesia and Pain Medicine (ASRA) and European Society of Regional Anesthesia and Pain Therapy (ESRA) conducted an international study aimed at achieving consensus on the nomenclature of abdominal, paraspinal, and chest wall anesthetic techniques [21]. The names and anatomical definitions of various regional techniques were standardized by expert consensus. The suggested nomenclature was designed to make identifying the target injection point for each procedure easy. In this review, the descriptions will primarily be based on the new names. However, to show respect to the authors that first published studies of these techniques, the original nomenclatures are introduced at the beginning of each section. Table 2 summarizes the detailed injection points of the fascial plane blocks described in this article.

Fascial plane blocks for cardiac surgery

Parasternal intercostal plane block

The parasternal intercostal plane (PIP) block targets the anterior cutaneous branches of the intercostal nerves, which innervate the anteromedial chest wall. These nerves penetrate the intercostal muscles and pectoralis major muscle at each thoracic level. The block is divided into a superficial and deep PIP block according to the injection plane (beyond or below the internal intercostal muscle). Since the midline of the chest and abdominal wall slightly overlap on both sides, bilateral injection is required for complete coverage of the sternal area [22]. PIP blocks were performed for sternotomies in all the studies included in this section.

Superficial PIP block

The superficial PIP block was first introduced by Torre et al. in 2014 under the name “pecto-intercostal fascial plane block” [23]. Placing the ultrasound parasagittally on the lateral border of the sternum and using an in-plane technique allows for the fascial plane between the pectoralis major and internal intercostal muscles to be hydro-dissected and, once the needle is advanced along the dissection, allows for multi-level spread of the injectate (Fig. 1). Although this technique can be performed in the surgical field under direct vision at sternal closure, it is distinct from the ultrasound-guided approach since the spreading of the local anesthetic cannot be observed.

Bloc et al. [5] assessed the effect of preoperative superficial PIP
<table>
<thead>
<tr>
<th>Author/year</th>
<th>Surgery/approach</th>
<th>Block</th>
<th>Local anesthetics</th>
<th>Sample size</th>
<th>Primary outcome</th>
<th>Other results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fujii et al. 2019</td>
<td>CABG, valve/sternotomy</td>
<td>Deep PIP</td>
<td>0.3% or 0.5% ropivacaine, 20 ml</td>
<td>C (n = 8) B (n = 9)</td>
<td>High patient recruitment (95%)</td>
<td>No statistical analysis</td>
</tr>
<tr>
<td>Bloc et al. 2021</td>
<td>CABG/sternotomy</td>
<td>Superficial PIP</td>
<td>0.25% ropivacaine, 15 × 4 ml</td>
<td>C (n = 17) B (n = 18)</td>
<td>Reduced intraoperative OC</td>
<td>Reduced postoperative proinflammatory cytokines</td>
</tr>
<tr>
<td>Aydin et al. 2020</td>
<td>CABG, valve/sternotomy</td>
<td>Deep PIP</td>
<td>0.25% bupivacaine, 20 ml</td>
<td>C (n = 24) B (n = 25)</td>
<td>Reduced 24 h post-operation OC</td>
<td>Reduced pain score and PONV incidence</td>
</tr>
<tr>
<td>Hamed et al. 2022</td>
<td>CABG, valve/sternotomy</td>
<td>Superficial PIP</td>
<td>0.25% bupivacaine, 20 ml</td>
<td>C (n = 35) B (n = 35)</td>
<td>Reduced 24-h OC</td>
<td>Longer first analgesic request time, reduced wound pain score</td>
</tr>
<tr>
<td>Khera et al. 2021</td>
<td>CABG, valve/sternotomy</td>
<td>Superficial PIP</td>
<td>0.25% bupivacaine, 20 ml</td>
<td>C (n = 36) B (n = 37)</td>
<td>No difference in the 48-h OC</td>
<td>No difference in the incidence of postoperative delirium</td>
</tr>
<tr>
<td>Zhang et al. 2021</td>
<td>Open cardiac surgery</td>
<td>Deep PIP</td>
<td>0.4% ropivacaine, 20 ml</td>
<td>C (n = 40) B (n = 40)</td>
<td>Less perioperative OC</td>
<td>Improved sleep quality, reduced time to extubation and ICU stay</td>
</tr>
<tr>
<td>Abdelbaser and</td>
<td>Pediatric/sternotomy</td>
<td>Deep PIP</td>
<td>0.25% bupivacaine, 0.2–0.4 ml/kg</td>
<td>C (n = 30) B (n = 30)</td>
<td>Decreased 24-h perioperative OC</td>
<td>Lower intraoperative HR and MAP, longer time to first rescue analgesia, shorter time to extubate and ICU stay</td>
</tr>
<tr>
<td>mageed 2020</td>
<td>Pediatric/sternotomy</td>
<td>Deep PIP</td>
<td>0.2% ropivacaine, 0.75 ml/kg</td>
<td>C (n = 50) B (n = 50)</td>
<td>Lower MOPS</td>
<td>Less OC, reduced time to extubate and ICU and hospital stay</td>
</tr>
<tr>
<td>Zhang et al. 2020</td>
<td>Pediatric/sternotomy</td>
<td>Deep PIP</td>
<td>0.2% ropivacaine, 1.5 mg/kg</td>
<td>C (n = 51) B (n = 50)</td>
<td>Lower MOPS at 24 h post-operation</td>
<td>Lower perioperative OC, reduced time to extubate, time to initial flatus, and length of ICU and hospital stay</td>
</tr>
<tr>
<td>Zhang et al. 2022</td>
<td>Pediatric/sternotomy</td>
<td>Superficial PIP</td>
<td>0.2% ropivacaine, 1.5 mg/kg</td>
<td>C (n = 50) B (n = 50)</td>
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<tr>
<td>Athar et al. 2021</td>
<td>CABG, valve/sternotomy</td>
<td>ESP</td>
<td>0.25% levobupivacaine, 20 ml</td>
<td>C (n = 15) B (n = 15)</td>
<td>Reduced OC in 24 h post-operation</td>
<td>Prolonged time to first rescue analgesia, shorter duration of mechanical ventilation</td>
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<tr>
<td>Krishna et al. 2019</td>
<td>CABG, valve, ASD/unspeci-</td>
<td>ESP</td>
<td>0.375% ropivacaine, 3 mg/kg</td>
<td>C (n = 53) B (n = 53)</td>
<td>Reduced postoperative pain</td>
<td>Higher mean duration of analgesia</td>
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<tr>
<td>fied</td>
<td>Pediatric/sternotomy</td>
<td>ESP</td>
<td>0.25% ropivacaine, 3 ml/kg</td>
<td>C (n = 52) B (n = 52)</td>
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<tr>
<td>Wasy et al. 2021</td>
<td>CABG/sternotomy</td>
<td>Continuous ESP</td>
<td>0.25% ropivacaine, 15 ml</td>
<td>C (n = 20) B (n = 20)</td>
<td>Lower pain score to 48 h after extubation</td>
<td>Reduced total perioperative OC, higher peak inspiratory flow, shorter duration of ventilation and ICU stay</td>
</tr>
<tr>
<td>Gado et al. 2022</td>
<td>Pediatric/sternotomy</td>
<td>ESP</td>
<td>0.25% bupivacaine, 0.4 ml/kg</td>
<td>C (n = 48) B (n = 50)</td>
<td>Lower intraoperative OC</td>
<td>Delayed first rescue analgesia</td>
</tr>
<tr>
<td>Kaushal et al. 2020</td>
<td>Pediatric/sternotomy</td>
<td>ESP</td>
<td>0.2% ropivacaine, 1.5 mg/kg</td>
<td>C (n = 40) B (n = 40)</td>
<td>Reduced pain score to 10 h post-operation</td>
<td>Less postoperative OC, longer time to first rescue dose, lower postoperative sedation scores and ICU stay</td>
</tr>
<tr>
<td>Karacaer et al. 2022</td>
<td>Pediatric/sternotomy</td>
<td>ESP</td>
<td>0.25% ropivacaine, 0.5 ml/kg</td>
<td>C (n = 20) B (n = 20)</td>
<td>Lower OC in first 24 h post-operation</td>
<td>No significant difference in pain score</td>
</tr>
<tr>
<td>Macaire et al. 2020</td>
<td>Pediatric/sternotomy</td>
<td>Continuous ESP</td>
<td>0.1% or 0.2% ropivacaine, 0.5 ml/kg/side</td>
<td>C (n = 23) B (n = 27)</td>
<td>Decreased OC during first 48 h post-operation</td>
<td>Reduced pain scores, no differences in times to extubation and drain removal or length of hospital stay</td>
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</table>

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<table>
<thead>
<tr>
<th>Author/year</th>
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<th>Block</th>
<th>Local anesthetics</th>
<th>Sample size</th>
<th>Primary outcome</th>
<th>Other results</th>
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<tr>
<td>Abdelbaser et al. 2022</td>
<td>Pediatric/sternotomy</td>
<td>Retrolaminar</td>
<td>0.25% bupivacaine, 0.4 ml/kg</td>
<td>C (n = 28)</td>
<td>Reduced perioperative OC</td>
<td>Lower pain score, shorter time to extubation</td>
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<tr>
<td>IPP/PSP/SAP 55</td>
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<td></td>
<td></td>
<td>B (n = 29)</td>
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<tr>
<td>Kaushal et al. 2019 [59]</td>
<td>Pediatric/thoracotomy</td>
<td>SAP, IPP-PSP, INB</td>
<td>0.2% ropivacaine, 3 mg/kg</td>
<td>SAP (n = 36)</td>
<td>Mean MOPS at 6, 8, 10, 12 h were lower with the SAP and IPP-PSP block</td>
<td>Reduced postoperative OC for the SAP, IPP-PSP block</td>
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<td>IPP (n = 36)</td>
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<td>INB (n = 36)</td>
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<tr>
<td>Kamal et al. 2022 [60]</td>
<td>Pediatric/sternotomy</td>
<td>IPP-PSP</td>
<td>0.25% bupivacaine, 0.5 ml/kg</td>
<td>C (n = 20)</td>
<td>Lower pain score at 6 h post-operation</td>
<td>Longer interval to first rescue analgesia, lower PAED score, shorter ICU stay</td>
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<td>B (n = 20)</td>
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<tr>
<td>Kumar et al. 2018 [61]</td>
<td>CABG, valve/sternotomy</td>
<td>IPP-PSP</td>
<td>0.25% bupivacaine, 60 ml</td>
<td>C (n = 20)</td>
<td>Shorter duration of ventilator support</td>
<td>Lower pain score, higher peak inspiratory flow rates, less rescue analgesia administered</td>
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<td>B (n = 20)</td>
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<tr>
<td>Gautam et al. 2020 [64]</td>
<td>MIDCAB/left anterior thoracotomy</td>
<td>Continuous deep SAP</td>
<td>0.2% ropivacaine, 20 ml (1 μg/ml fentanyl), 8 ml/h infusion</td>
<td>C (n = 20)</td>
<td>Reduced pain scores</td>
<td>Reduced postoperative 48-h OC</td>
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<td>B (n = 24)</td>
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<tr>
<td>Combined</td>
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<tr>
<td>Gawęda et al. 2020 [63]</td>
<td>Valve/mini-thoracotomy approach</td>
<td>ESP, ESP + IPP-PSP</td>
<td>0.375% ropivacaine, 0.2 ml/kg</td>
<td>ESP (n = 15)</td>
<td>ESP + IPP-PSP block reduced OC and pain score</td>
<td>Increased patient satisfaction in ESP + IPP-PSP group</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>ESP + IPP-PSP (n = 15)</td>
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</table>

blocks on the intraoperative opioid requirement to maintain hemodynamic stability during sternotomy for coronary artery bypass graft (CABG) surgery. The maximal concentration of remifentanil was reduced in the block group (median 4.2 ng/ml vs 7.0 ng/ml in block and placebo groups, respectively) and significant reductions in postoperative proinflammatory cytokines were observed. Hamed et al. [24] evaluated the analgesic efficacy of the superficial PIP block after various open heart surgeries with a median sternotomy. The 24-hour cumulative morphine consumption was significantly reduced compared with the control group, although the effect size was small (−3.54 mg, 95% CI [−6.55, −0.53]). However, the quality of oxygenation (evaluated using PaO₂ and the ratio of PaO₂/inspired fraction of O₂) in the postoperative period was improved in the block group. Khera et al. [25] also showed improved pain scores with the superficial PIP block compared to placebo, although the reduction in postoperative opioid consumption was not significant.

### Deep PIP block

The anterior cutaneous nerve runs over the transversus thoracis muscle, traverses the intercostal and pectoralis major muscles near the sternal border, and enters the superficial plane. This allows for an injection to be performed on a more proximal and deeper plane. This technique was first described in 2015 as the “transversus thoracis plane block” [26]. Ultrasound scanning can be performed parallel to the lateral sternal border parasagittally or parallel to the intercostal space transversely (Fig. 1 and 2, respectively). The transversus thoracis muscle is a thin structure located just below the sternum and just above the pleura, making it difficult to be clearly distinguished on ultrasound imaging. Because the internal mammary artery (IMA) and vein run over this muscle, to avoid inadvertent puncture, these vessels should be visualized and used as a landmark (Fig. 1 and 2) [27]. Color-flow doppler is useful for probing the IMA, which is usually observed under translucent costal cartilage on an ultrasound image. The downward displacement of the pleura by the injectate can be used

<table>
<thead>
<tr>
<th>Blocks</th>
<th>Injection points</th>
</tr>
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<tbody>
<tr>
<td>Superficial PIP</td>
<td>Superficial to the internal intercostal muscles and ribs and deep to the pectoralis major muscle</td>
</tr>
<tr>
<td>Deep PIP block</td>
<td>Between the internal intercostal and the transversus thoracis muscles</td>
</tr>
<tr>
<td>IPP block</td>
<td>Between the pectoralis major and pectoralis minor muscles</td>
</tr>
<tr>
<td>PSP block</td>
<td>Between the pectoralis minor and serratus anterior muscles</td>
</tr>
<tr>
<td>Superficial SAP</td>
<td>Superficial to the serratus anterior muscles</td>
</tr>
<tr>
<td>Deep SAP block</td>
<td>Between the posterior surface of the serratus anterior muscle and the periosteum of the rib</td>
</tr>
<tr>
<td>ESP block</td>
<td>Between the erector spinae muscles and the transverse process</td>
</tr>
<tr>
<td>Retrolaminar block</td>
<td>Between the erector spinae muscles and the lamina</td>
</tr>
</tbody>
</table>

**Table 2. Injection Points of the Fascial Plane Blocks for Cardiac Surgery**

**Fig. 1.** Sonoanatomy (A) and color doppler image of internal mammary artery (B) captured during parasagittal approach of superficial parasternal intercostal plane (PIP) block. (A) The fascial plane between the pectoralis major and internal intercostal muscles (PIP) is indicated as a red solid line. Cartilages were captured as echolucent structures. (B) The internal mammary artery is captured as a red-colored tubular structure on the long axis view.

**Fig. 2.** Ultrasound image of internal mammary artery captured during parasagittal approach of superficial parasternal intercostal plane (PIP) block. (A) The fascial plane between the pectoralis major and internal intercostal muscles (PIP) is indicated as a red solid line. Cartilages were captured as echolucent structures. (B) The internal mammary artery is captured as a red-colored tubular structure on the long axis view.
as an indication of appropriate ultrasound endpoint. Because the needle angle has to be stiffer in the parasagittal approach than in the transverse approach due to the narrow needle path (i.e., between the ribs), the transverse approach can be a little easier and safer for a deep PIP block. However, no study has compared the two approaches directly.

Fujii et al. [28] evaluated the safety and analgesic effect of the deep PIP block 12 h after cardiac surgery and found high rates of patient recruitment, adherence, and satisfaction. Aydin et al. [29] showed that a preoperative deep PIP block had a significant opioid sparing effect during the first 24 h postoperatively; however, compared with the placebo group, the improved pain score was only significant until 12 h post-operation. In a study conducted by Zhang et al. [30], the deep PIP block was found to provide not only an effective analgesia but also other positive clinical outcomes such as a shorter time to extubation, time to first bowel movement, and ICU and hospital stay.

The superficial PIP block is considered a safer technique than the deep PIP block as the former is performed further from vascular structures, the pleura, and the heart. However, since these are emerging techniques, reports about complications are scarce and further research is therefore warranted.

**Use of PIP blocks in pediatric patients**

In pediatric patients, a multi-level blockade can be achieved with a single injection of these PIP blocks, while adults require multi-level injections. In this section, recent RCTs of pediatric patients that show that PIP blocks could reduce intra- and/or postoperative opioid consumption and improve clinical outcomes will be discussed.

Abdelbaser et al. [31] revealed that the deep PIP block almost halved the opioid consumption in the first 24 h postoperatively and significantly lowered objective pain scores compared to the control group in pediatric cardiac surgery performed via a median sternotomy. Zhang et al. investigated deep [6] and superficial PIP blocks [32] through two RCTs. The block groups showed significantly lower pain scores in the first 24 h after extubation than the placebo group. But the pain scores were comparable between the groups at 48 h post-operation. In these studies, both blockades could also reduce the duration of mechanical ventilation and length of ICU stay, which are clinically meaningful outcomes.

**Erector spinae plane block**

The erector spinae plane (ESP) block has been used in various surgeries since it is both simple and safe to perform [33]. It was first introduced as a novel analgesic technique for thoracic neuropathic pain in a case report by Forero et al. in 2016 [34]. Usually, the clinician places the probe in the paraspinal area parasagittally and searches for a bony structure. Once the bony shape is identified, the clinician slides the probe in the medial and lateral directions to distinguish the round shape of the rib and the squared-off shape of the transverse process (Fig. 3A). While the pleura is clearly visible during rib scanning, this is not the case for transverse process scanning. The edge of the transverse process is the preferred target for needle placement, though slight advancement deeper off the edge may be needed to achieve the proper spreading of injectate into the plane between the erector spinae muscle...
and the transverse process [18].

The mechanism of the ESP block that mediates chest wall coverage (besides the back) appears to be the spread of the local anesthetic close to the paravertebral space where the dorsal and ventral rami of the spinal nerve diverge. Although there is plenty of evidence showing the analgesic effect of the ESP block in various types of surgery including breast, thoracic, and abdominal surgery, its use in cardiac surgery is still limited [35–39]. The ESP block has some advantages in terms of safety and simplicity over the thoracic paravertebral or epidural blocks, which are associated with risks such as hematomas, neural injury, or pneumothorax and are technically challenging.

In their study assessing the efficacy of a single-shot ESP block in adult cardiac surgery, Athar et al. [8] found superior analgesia with a decrease in opioid consumption of 64.5% and a greater reduction in the duration of mechanical ventilation and the sedation score at 6 h post-extubation compared with the sham block. Krishna et al. [40] compared the single-shot ESP block with a conventional analgesic regimen in cardiac surgeries with cardiopulmonary bypass, which included intravenous paracetamol and tramadol. Interestingly, the analgesic effect of the ESP block was almost perfect in the immediate postoperative period, as shown by a median NRS score of 0 until the sixth hour post-extubation.

The studies described above evaluated the efficacy of a single-shot ESP block. As the gradual anterior spread of the block to the thoracic paravertebral space is considered a determinant factor for consistent coverage of the anterolateral chest wall [41], a continuous block may provide a greater analgesic effect by gradual diffusion of local anesthetic over a prolonged period of time. Wasfy et al. [42] evaluated a continuous bilateral ESP block in CABG surgery and found a reduction in the postoperative opioid consumption and pain scores in the block group until 48 h post-extubation. Additionally, they found improved peak inspiratory flow and a reduction in the duration of mechanical ventilation and ICU stay.

Recently, the pathways through which the injectate spreads to the paravertebral space has been further elaborated for the ESP block [43–45]. The superior costotransverse ligament (SCTL) incompletely forms the posterior wall of the thoracic paravertebral space and through the slits (including the costotransverse foramen), the retro-SCTL space broadly communicates with the paravertebral space. Thus, the so-called intertransverse process (ITP) blocks that involve administering the injection a little closer to the communicating channels (between the retro-SCTL and paravertebral spaces) than the ESP block have been introduced under various names [46]. Future research evaluating the usefulness of ITP blocks in cardiac surgery is needed.

Use of ESP block in pediatric patients

In 2017, Chin et al. [47] reported a successful perioperative pain management using ESP block in a pediatric patient who underwent oncological thoracic surgery. Since then, the ESP block

Fig. 3. Sonoanatomy of erector spinae plane (ESP) (A) and retrolaminar (B) blocks. (A) Note the transverse process of the spine captured as bright squared-off bony structures underneath the erector spinae muscle. The edge of the transverse process is the preferred target for needle placement and slight advancement deeper off the edge may be needed to achieve proper spread of the injectate into the plane between the erector spinae muscle and the transverse process. (B) Note the flat structures (lamina) with small notches and the overlying erector spinae muscle. Using an in-plane technique, the needle can be introduced until the tip contacts with the lamina. Optimal needle positioning can be confirmed by observing the proper spread of injectate throughout the plane between the lamina and the erector spinae muscle.
has been applied in a wide range of pediatric clinical scenarios [48].

Kaushal et al. [7] evaluated the efficacy of the ESP block in pedi-

diatric patients with acyanotic congenital heart disease under-

going cardiac surgery via a midline sternotomy. Pain scores were

significantly reduced by the blockade until 10 h post-extubation.

Additionally, rescue opioid consumption and the duration of the

ICU stay were reduced with lower sedation scores in the ESP

block group. Conversely, Karacaer et al. [49] noted no significant

differences between the ESP block and control groups in terms of

the pain score, sedation score, extubation time, and length of ICU

stay. Gado [50] assessed the efficacy and safety of bilateral ESP

blocks in pediatric patients undergoing cardiac surgeries through

a median sternotomy. Perioperative opioid consumption was re-

duced in the ESP block group compared with the control group

with comparable postoperative complications such as vomiting,

itching, and respiratory depression. Macaire et al. [51] performed

a bilateral continuous ESP block in pediatric cardiac surgery per-

formed via median sternotomy. Significantly less total morphine

consumption during the first 48 h postoperatively and improved

pain scores were noted in the block group compared with the

control group. A protocol consisting of programmed intermittent

bolus injections through bilateral catheters (alternatively) was

used to avoid systemic toxicity associated with local anesthetics in

the study. The plasma ropivacaine concentrations at 1 and 48 h af-

ter the initiation of the blockade were below known safe levels.

Retrolaminar block

The retrolaminar block first appeared in 2013 in a case report

on pain management of a patient with multiple rib fractures [52].

Similar to the ESP block, the retrolaminar block is performed in

the parasagittal plane. Sliding the probe from the lateral to medi-

dal direction, the rib, transverse process, and lamina can be distin-

guished by their distinctive bony contours which are round, rect-

angular, and flat structures with small notches, respectively (Fig.

3B). Using an in-plane technique, the needle can be introduced

until the tip contacts with the flat structure (i.e., lamina). Optimal

needle positioning can be confirmed by observing the proper

spreading of injectate throughout the plane between the lamina

and erector spinae muscle.

Although this blockade is different from the ESP block in that

the injection point is the plane between the erector spinae muscles

and the lamina [21], the mechanism of this block is similar to that

to the ESP block [53]. Currently, the analgesic efficacy of the so-
called “paravertebral by proxy” techniques (ESP, retrolaminar, and

ITP blocks) is mainly explained by how much the injectate

spreads anteriorly to the paravertebral space [54].

Only one recent RCT [55] to date has reported on an ultra-

sound-guided bilateral thoracic retrolaminar block in pediatric

open cardiac surgery. Perioperative fentanyl consumption was

significantly lower in the block group compared with the control

group. Additionally, the block enabled early extubation and a

shortened ICU stay.

Interpectoral plane, pectoserratus plane, and serratus

anterior plane blocks

PECS I (currently the interpectoral plane [IPP] block), PECS II

(currently the IPP combined with the pectoserratus plane [PSP]

block), and the serratus anterior plane (SAP) blocks were first in-

troduced by Blanco et al. [56–58]. The IPP block targets the medi-
al and lateral pectoral nerves and is performed by injecting local

anesthetic within the fascial plane between the pectoralis major

and minor muscles [56]. The PSP block targets the lateral cutane-
ous nerve within the fascial plane between the pectoralis minor

and serratus muscles (Fig. 4A). Since the PECS II block actually

consists of two blocks (the IPP and PSP), it is sometimes errone-
ously described as the PECS I + PECS II block [57]. Thus, in this

review, the PECS II block is described as the IPP-PSP block to

avoid confusion. The SAP block was introduced as a modification

of the PECS blocks, involving an injection that is more lateral and

posterior in order to provide analgesia for most of the hemithorax

[58]. It is further divided into the superficial and deep SAP blocks,

depending on whether the injection is performed at the plane

above or below the serratus anterior muscle (Fig. 4B). Therefore,

the target plane for the PSP and superficial SAP blocks is actually

the same, though the injection is either performed in the area un-
der the pectoralis minor muscle (PSP) or not (superficial SAP).

Kaushal et al. [59] compared the efficacy of the ultra-

sound-guided deep SAP block, IPP-PSP block, and intercostal

nerve block for the management of post-thoracotomy pain in pe-
diatric cardiac surgery. These blocks showed comparable efficacy

in terms of pain scores in the early postoperative period (1 to 4 h),

but a more prolonged analgesic effect was found in the SAP and

PSP groups.

The mechanism by which the IPP or PSP block mediates the

analgesic effect after sternotomy is unclear. Although these blocks

are not expected to cover the anterior cutaneous branches of the

intercostal nerves, several studies have reported effective analgesia

of the PSP in pediatric cardiac surgery involving median sternoto-

my [60,61]. In pediatric patients, while the local anesthetic inject-
ed in the anterolateral chest wall may spread to the anteromedial

side given the relatively small size of the chest wall, direct evidence
is currently lacking. It can hardly be expected, however, that the analgesic effect of these blocks would be sufficient for adult patients post-sternotomy [62].

Kamal et al. [60] compared the analgesic effect of the bilateral IPP-PSP block to conventional intravenous analgesia (control) for post-sternotomy pain after pediatric cardiac surgery. The block group reported lower pain scores and postoperative opioid requirements than the control. Furthermore, emergence agitation and the duration of the ICU stay were also lower in the study group. Kumar et al. [61] performed a bilateral IPP-PSP block in cardiac surgeries performed via a midline sternotomy. The block group required a shorter duration of ventilator support in comparison to the parenteral analgesia group, and the analgesic effects and inspiratory function also improved.

A study conducted by Gawęda et al. [63] provides interesting insight into the distinct mechanism of the IPP-PSP block. In that study, patients undergoing mitral/tricuspid valve repair via mini-thoracotomy were randomized into either the ESP or ESP with IPP-PSP block groups. The ESP with IPP-PSP block group showed better analgesic outcomes and patient satisfaction. In theory, the most distinctive nerves that could be blocked by the IPP-PSP block that are not covered by the ESP block are the pectoral nerves. As the pectoral nerves are motor nerves, the analgesic effect expected from the blockade of these nerves would mainly be due to a reduction in pectoral muscle spasm. The additional analgesic effect provided by the IPP-PSP block in the study could be partially explained by this mechanism.

The SAP block is performed more posterolaterally on the chest wall than the IPP or PSP blocks [58]. Sufficient hydro-dissection of the fascial plane provides a multi-level blockade of the lateral cutaneous branches of the intercostal nerves. This technique can be performed in a supine or lateral decubitus position and thus is flexible according to the planned surgical positioning (e.g., supine position for MIDCAB or lateral decubitus position for lung surgery) (Fig. 4B). Although significant analgesic effects have been shown for thoracoscopic surgery, the SAP block appears to have less of an analgesic effect than the paravertebral or ESP blocks [38]. In the only RCT using the SAP block in cardiac surgery to date, Gautam et al. [64] evaluated the role of a continuous deep SAP block for postoperative pain relief in patients undergoing MIDCAB surgery via left anterior thoracotomy. Although reduced pain scores and postoperative opioid consumption were reported for the SAP block group, fentanyl was included in the infusate (1 μg/ml, infused at 8 ml/h after 20 ml of bolus dose), and thus the efficacy of the SAP block itself in the study is uncertain.

Fascial plane blocks for subcutaneous-implantable cardioverter-defibrillator implantation

A proper regional analgesia for S-ICD implantation should cover two areas of the chest wall, one for a pocket creation between the serratus anterior and latissimus dorsi muscles and another for parasternal tunneling of the lead. A well-established guideline addressing regional techniques for S-ICD implantation is still lacking and only a recommendation led by U.S. physicians published in 2018 exists to date [65]. A few recent studies on the SAP and
PIP blocks, however, have been conducted. Shariat et al. [66] investigated the efficacy of a deep PIP block combined with a superficial SAP block for S-ICD implantation. Compared with the wound infiltration group, intraoperative fentanyl requirements were significantly lower in the block group. However, as the administration of intraoperative fentanyl was based on the subjective discretion of a non-blinded anesthesiologist, the validity of the positive result of the study is uncertain. A larger, double-blinded RCT [67] has been conducted that compares the analgesic efficacy of the regional techniques consisting of the ultrasound-guided deep PIP block and deep SAP block versus local infiltration in 80 S-ICD placements. The pain scores assessed by the Critical-Care Pain Observation Tool during the procedure were significantly lower in the block group compared with the local infiltration group. The authors conducted another similar study using the same techniques in pediatric patients [68]. The block group showed favorable analgesic outcomes and shorter extubation time and length of PACU stay compared with the control group (sham block).

Conclusions

Evidence suggests that fascial plane blocks can provide effective analgesia for cardiac surgery. Some studies additionally provide evidence of improved postoperative pulmonary mechanics and reduced length of ICU or hospital stays. However, the followings should be considered when interpreting the results of the previous studies and applying them to clinical practice:
1. The coverage of the blockade should correspond to the target surgical site. Specifically, sternal coverage of the IPP and PSP block is not guaranteed in adult patients.
2. The consistency of the blockade may depend on several factors. The efficacy of paravertebral by proxies can be influenced by the degree of paravertebral spread of the injectate. Additionally, a lack of delicate control during needle tip placement can impair proper spreading of the injectate into the target plane and thus hinder block consistency.
3. The somatic blockade does not guarantee complete analgesia for cardiac surgery; therefore, it may be more effective in combination for multimodal analgesia.
4. Although the included studies in this review showed positive outcomes for various cardiac surgeries, functional or long term clinical outcomes are limited [69].

A comprehensive conclusion regarding the efficacy of ultrasound-guided fascial plane blocks in cardiac surgery cannot be made since more studies comparing various techniques are needed. Nevertheless, most fascial plane blocks for cardiac surgery show effective analgesia and low procedure-related risks. Therefore, the application of these emerging ultrasound-guided fascial plane block techniques in cardiac surgery is worthy of consideration.

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Conflicts of Interest

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

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Yumin Jo (Writing – original draft; Writing – review & editing)
Soomin Lee (Writing – original draft; Writing – review & editing)
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Erector spinae plane block in children: a narrative review

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The erector spinae plane block (ESPB) is a novel technique used in both adult and pediatric patients. Its use in children has mostly been described in terms of perioperative pain management for various types of surgery. After its introduction, anesthesiologists began using ESPBs in various surgical settings. As adequate analgesia along with a low complication rate were reported, interest in this technique dramatically increased. Many studies in adults and children, including randomized controlled trials, have been published, resulting in the emergence of different clinical indications, with various technical and pharmacological approaches currently evident in the literature. This narrative review aims to analyze the current evidence in order to guide practitioners towards a more homogeneous approach to ESPBs in children, with a major focus on clinical applications. The ESPB is an efficient, safe, and relatively easy technique to administer. It can be applied in a wide range of surgeries, includes thoracic, abdominal, hip, and femur surgery. Its usefulness is evident in the context of enhanced recovery after surgery protocols and multimodal analgesia. Single-shot, intermittent bolus, and continuous infusion techniques have been described, and non-inferiority has been observed when compared with other locoregional techniques. Even though both the efficacy and safety of the procedure are widely accepted, current evidence is predominantly based on case reports, with very few well-designed observational studies. Consequently, the level of evidence is still poor, and more well-designed double-blind, randomized, placebo-controlled trials are needed to refine the procedure for different clinical applications in the pediatric population.

Keywords: Analgesia; Anesthesia; Child; Conduction anesthesia; Nerve block; Newborn infant; Review.

Introduction

The erector spinae plane block (ESPB), which was first described by Forero in 2016 [1] for the treatment of thoracic neuropathic pain, was applied in the pediatric population for postoperative pain management as early as 2017 [2]. Subsequent interest in this technique has rapidly expanded and expertise has increased, with applications not only for the management of perioperative analgesia but also for non-surgical pain management in the pediatric population (Table 1).

Despite more extensive series and observational evidence in the current literature, very few rigorous, well-designed trials have been conducted (Table 2). While these include a few randomized controlled studies, the protocols and indications used have been highly variable. The efficacy and safety of ESPBs in perioperative pain management have been explored in many case reports and observational studies compared with other loco-re-
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<tr>
<td>Muñoz et al. 2017 [2]</td>
<td>1</td>
<td>7 years</td>
<td>Chest wall surgery</td>
<td>Postoperative</td>
<td>Single shot T8 14 ml bupivacaine 0.5% with epinephrine 5 μg/ml</td>
<td>None reported</td>
</tr>
<tr>
<td>Adler et al. 2019 [4]</td>
<td>1</td>
<td>3 weeks</td>
<td>Thoracic surgery</td>
<td>Preoperative catheter placement</td>
<td>Initial postoperative bolus through catheter 0.1% (0.25 mg/kg/h) ropivacaine in infusion for 48 h</td>
<td>None</td>
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<tr>
<td>Darling et al. 2018 [14]</td>
<td>1</td>
<td>11 years</td>
<td>Iliac crest autograft</td>
<td>Preoperative Postoperative</td>
<td>Single shot catheter tip at L2 15 ml 0.5% ropivacaine intraoperative 11 ml 0.2% ropivacaine every 2 h on postoperative days 0–5 Catheter removed after 48 h</td>
<td>None reported</td>
</tr>
<tr>
<td>Balaban et al. 2019 [15]</td>
<td>1</td>
<td>6 years</td>
<td>Femur fixation</td>
<td>Postoperative</td>
<td>Single shot T5 20 ml 0.25% bupivacaine</td>
<td>None reported</td>
</tr>
<tr>
<td>Bosinci et al. 2021 [16]</td>
<td>2</td>
<td>2 years</td>
<td>Hip surgery</td>
<td>Preoperative</td>
<td>Single shot T4 Lidocaine 2% 2 ml and levobupivacaine 0.25% 14 ml</td>
<td>None reported</td>
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<tr>
<td></td>
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<td>CAME single shot lidocaine 2% 4 ml and levobupivacaine 0.25% 17 ml then continuous infusion levobupivacaine 0.125% 4–8 ml/h via infusion pump Catheter removed at 72 h</td>
<td>None reported</td>
</tr>
<tr>
<td>Hernandez et al. 2018 [17]</td>
<td>1</td>
<td>3 years</td>
<td>Thoracic surgery</td>
<td>Preoperative</td>
<td>Single shot T1 0.1 ml/kg bupivacaine 0.25% 0.1 ml/kg lidocaine 1%</td>
<td>None reported</td>
</tr>
<tr>
<td>Altparmak et al. 2019 [20]</td>
<td>1</td>
<td>2 days</td>
<td>Thoracic surgery</td>
<td>Preoperative (32 weeks PCA)</td>
<td>Single shot T4 T6 0.5 ml 0.25% bupivacaine (x2)</td>
<td>None reported</td>
</tr>
<tr>
<td>Gomez-Menendez et al. 2019 [21]</td>
<td>1</td>
<td>13 months</td>
<td>Thoracic surgery</td>
<td>Preoperative</td>
<td>Single shot T4 5 ml bupivacaine 0.25%</td>
<td>None reported</td>
</tr>
<tr>
<td>Hagen et al. 2019 [22]</td>
<td>7</td>
<td>37 days–9 years</td>
<td>Thoracic surgery</td>
<td>Preoperative</td>
<td>Single shot 0.5% bupivacaine + dexamethasone (1 bilateral)</td>
<td>None reported</td>
</tr>
<tr>
<td>Wyatt and Elattary 2019 [23]</td>
<td>1</td>
<td>17 years</td>
<td>Thoracic surgery</td>
<td>Preoperative</td>
<td>Single shot T5 with catheter placement 25 ml 0.5% ropivacaine Continuous infusion through catheter 0.2% ropivacaine 8 ml/h during surgery 0.1% ropivacaine 10 ml/h postoperative Rescue bolus 4 ml bupivacaine 0.25% mixed + 1 ml lidocaine 2% upon arrival in ICU; Catheter removed at 96 h</td>
<td>None reported</td>
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<tr>
<td>Aytulu et al. 2020 [24]</td>
<td>1</td>
<td>5 years</td>
<td>Chest tube insertion</td>
<td>Preoperative</td>
<td>Single shot T6-T7 7 ml 0.5% bupivacaine</td>
<td>None reported</td>
</tr>
<tr>
<td>Çiftçi and Ekin 2020 [25]</td>
<td>1</td>
<td>12 years</td>
<td>Thoracic surgery</td>
<td>Preoperative</td>
<td>Single shot T5 15 ml 0.25% bupivacaine</td>
<td>None reported</td>
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<tr>
<td>Gupta et al. 2020 [26]</td>
<td>1</td>
<td>2 years</td>
<td>Thoracic surgery</td>
<td>Preoperative</td>
<td>Single shot T5 8 ml 0.375% ropivacaine + 10 μg clonidine</td>
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<tr>
<td>Swenson Schalkwyk et al. 2020 [27]</td>
<td>1</td>
<td>2 days</td>
<td>Thoracic surgery</td>
<td>Preoperative</td>
<td>Catheter T5-T6 with hydrodissection + 2 ml 3% chloroprocaine 1 ml 0.1% at surgery Continuous infusion: 1.5% chloroprocaine at 0.25 ml/kg/h Catheter removed at 140 h</td>
<td>None</td>
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<tr>
<td>Wong et al. 2018 [28]</td>
<td>17 years</td>
<td>Cardiac surgery</td>
<td>Preoperative catheter placement and bolus; postoperative PIB</td>
<td>Bilateral catheters tip T7 10 ml 0.5% ropivacaine (x2) preoperative, then postoperative alternating catheter boluses of 10 ml 0.1% ropivacaine every 60 min Catheter removal at 72 h</td>
<td>None reported</td>
<td></td>
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<tr>
<td>Moore et al. 2018 [29]</td>
<td>1 year</td>
<td>Abdominal surgery</td>
<td>Preoperative catheter placement and bolus; postoperative continuous infusion</td>
<td>Bilateral catheters T8-T10 1 ml 0.2% ropivacaine followed by 0.5 ml/h 0.2% ropivacaine intraoperative Postoperative 0.5 ml/h 0.1% ropivacaine until catheter removal 72 h postop</td>
<td>None reported</td>
<td></td>
</tr>
<tr>
<td>Aksu and Gürkan 2018 [30]</td>
<td>2</td>
<td>6 months 7 years</td>
<td>Nephrectomy</td>
<td>Preoperative</td>
<td>Single shot T12 0.5 ml/kg 0.25% bupivacaine</td>
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<td>Thomas and Tulgar 2018 [31]</td>
<td>1</td>
<td>11 years</td>
<td>Abdominal surgery</td>
<td>Preoperative</td>
<td>Single shot bilateral T9 0.25% bupivacaine 0.5 ml/kg (x2)</td>
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<tr>
<td>Munshey et al. 2018 [32]</td>
<td>1</td>
<td>11 months</td>
<td>Open pyeloplasty</td>
<td>Preoperative</td>
<td>Catheter tip T8 Bolus 0.3 ml/kg ropivacaine 0.2% every hour during surgery; then 0.3 ml/kg ropivacaine 0.5% at end of surgery; Catheter removed at 48 h</td>
<td>None reported</td>
</tr>
<tr>
<td>Aksu and Gürkan 2019 [33]</td>
<td>3</td>
<td>8, 11, 13 years</td>
<td>Laparoscopy</td>
<td>Preoperative</td>
<td>Single shot bilateral T7 0.5 ml/kg 0.25% bupivacaine (max 20 ml) (x2)</td>
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<tr>
<td>Ince et al. 2019 [34]</td>
<td>1</td>
<td>13 years</td>
<td>Abdominal surgery</td>
<td>Preoperative</td>
<td>Single shot bilateral L2-3 LA not specified</td>
<td>None reported</td>
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<tr>
<td>Karaca and Pınar 2019 [35]</td>
<td>4</td>
<td>10–14 years</td>
<td>Abdominal surgery</td>
<td>Preoperative</td>
<td>Bilateral single-shot T7 Total 2.5 mg/kg bupivacaine</td>
<td>None</td>
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<tr>
<td>Aydin et al. 2020 [36]</td>
<td>1</td>
<td>9 months</td>
<td>Abdominal surgery</td>
<td>Postoperative</td>
<td>Single shot T10 + T11 Bupivacaine 0.25% (3 ml T10 + 3 ml T11)</td>
<td>None</td>
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<tr>
<td>Ekinci et al. 2020 [37]</td>
<td>1</td>
<td>2 years</td>
<td>Shock wave lithotripsy</td>
<td>Preoperative</td>
<td>Single shot T10 6 ml 0.25% bupivacaine</td>
<td>None reported</td>
</tr>
<tr>
<td>Tsui et al. 2020 [38]</td>
<td>1</td>
<td>16 years</td>
<td>Spinal surgery</td>
<td>Intraoperative surgical catheter placement</td>
<td>Bilateral catheter tips at T6 20 ml lidocaine 0.5% (x2) at end of surgery Postoperative boluses 20-22 ml 0.5% lidocaine alternating right and left side every 60 min; Catheter removed at 48 h</td>
<td>None reported</td>
</tr>
<tr>
<td>Aksu and Gürkan 2020 [39]</td>
<td>1</td>
<td>6 months</td>
<td>Genital surgery</td>
<td>Preoperative</td>
<td>Single-shot median sacral 8 ml of 0.25% bupivacaine</td>
<td>None</td>
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<tr>
<td>Ince et al. 2020 [40]</td>
<td>1</td>
<td>4 years</td>
<td>Hip surgery</td>
<td>Preoperative</td>
<td>Single shot L4 ESPB in combination with pericapsular nerve block 0.25% bupivacaine (total 20 ml 0.25% bupivacaine)</td>
<td>None</td>
</tr>
<tr>
<td>Baca et al. 2019 [41]</td>
<td>1</td>
<td>15 years</td>
<td>Palliative pain</td>
<td>Catheters placed under general anesthesia in hospital before release to home care</td>
<td>Bilateral tunneled catheters T8 (advanced to T12) Single shot 11 ml 0.5% ropivacaine PIB 10 ml 0.2% ropivacaine every 2 h alternating sides Catheter removed after 7 days</td>
<td>None</td>
</tr>
<tr>
<td>Kupeli et al. 2021 [42]</td>
<td>9</td>
<td>2–10 years</td>
<td>Multiple surgery</td>
<td>Preoperative</td>
<td>Preoperative single shot upon catheter placement, 0.25% levobupivacaine 0.4 ml/kg Postoperative continuous infusion through perineural catheter 1–5 ml/h 0.125% levobupivacaine Level T5 for thoracotomy; T8 for nephrectomy; T12–L2 for appendectomy and inguinal hernia; L1–2 for orchidopexy and ureterocele; and L4 for hip surgery Catheters removed within 24 h after surgery</td>
<td>None reported</td>
</tr>
<tr>
<td>Le et al. 2020 [43]</td>
<td>1</td>
<td>17 years</td>
<td>Ravitch procedure</td>
<td>Preoperative</td>
<td>Bilateral catheters T5 20 ml 0.2% ropivacaine preoperative Continuous infusion 6–8 ml/h ropivacaine 0.15% Rescue bolus 6 ml ropivacaine 0.15% on each side on postoperative day 1 Catheters removed at 72 h</td>
<td>None reported</td>
</tr>
<tr>
<td>Bonfiglio et al. 2021 [44]</td>
<td>1</td>
<td>19 years</td>
<td>Thoracoscopy</td>
<td>Preoperative catheter placement and bolus; postoperative continuous infusion + patient-controlled infusion</td>
<td>Single shot T4 18 ml of 0.25% levobupivacaine + 30 μg of dexmedetomidine Continuous infusion 0.125% levobupivacaine 10 ml/h + PCI 5 ml with 60-min lockout Catheter removed on postoperative day 3</td>
<td>None reported</td>
</tr>
<tr>
<td>Bakshi et al. 2020 [45]</td>
<td>2</td>
<td>3 years</td>
<td>Spine surgery</td>
<td>Preoperative catheter placement; catheter placement on postoperative day 4</td>
<td>Intermittent bolus 6 ml 0.25% levobupivacaine every 8 h for 4 days Intermittent bolus of 5 ml 0.25% bupivacaine every 8 h for 4 days</td>
<td>None</td>
</tr>
<tr>
<td>Patel et al. 2019 [46]</td>
<td>1</td>
<td>6 years</td>
<td>Thoracic surgery</td>
<td>Preoperative</td>
<td>Single shot T5 10 ml of 0.5% ropivacaine Continuous infusion through catheter 0.2 mg/kg/h ropivacaine Catheter removed at 96 h</td>
<td>None reported</td>
</tr>
<tr>
<td>De la Cuadra-Fontaine et al. 2018 [47]</td>
<td>1</td>
<td>3 years</td>
<td>Thoracic surgery</td>
<td>Preoperative catheter placement and bolus; postoperative continuous infusion + patient-controlled infusion</td>
<td>Single shot T9 8 ml of 0.25% levobupivacaine;Continuous infusion 0.1% levobupivacaine 3 ml/h + PCA 1.5 ml with 30-min lockout Catheter removed at 96 h</td>
<td>None reported</td>
</tr>
<tr>
<td>Basaran and Akkoyun 2020 [48]</td>
<td>1</td>
<td>1 days</td>
<td>Abdominal surgery</td>
<td>Preoperative</td>
<td>Single shot bilateral T7 0.5 ml 0.25% bupivacaine (x2)</td>
<td>None reported</td>
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<thead>
<tr>
<th>Case reports</th>
<th>Cases</th>
<th>Age</th>
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<th>Block-related adverse events</th>
</tr>
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<tbody>
<tr>
<td>Aksu and Gürkan 2019</td>
<td>2</td>
<td>11 years</td>
<td>Abdominal surgery</td>
<td>Preoperative</td>
<td>Single shot T11 bilateral 0.25% bupivacaine 0.5 ml/kg</td>
<td>None</td>
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<tr>
<td></td>
<td>2</td>
<td>2 years</td>
<td>Inguinal hernia repair</td>
<td>Preoperative</td>
<td>Single shot lumbar ESPB 0.25% bupivacaine 0.5 ml/kg (does not specify vertebral level)</td>
<td>None</td>
</tr>
<tr>
<td>Cesur et al. 2019</td>
<td>5</td>
<td>3–12 years</td>
<td>Inguinal hernia repair</td>
<td>Preoperative</td>
<td>Single shot 0.25% bupivacaine with a volume of 0.5 ml/kg (vertebral level not specified)</td>
<td>None reported</td>
</tr>
<tr>
<td>Hernandez et al. 2018</td>
<td>1</td>
<td>2 months</td>
<td>Inguinal hernia repair</td>
<td>Preoperative</td>
<td>Single-shot T6 0.2 ml/kg bupivacaine 0.25% 0.2 ml/kg lidocaine 1%</td>
<td>None</td>
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<td>Elkoundi et al. 2019</td>
<td>1</td>
<td>4 years</td>
<td>Hip surgery</td>
<td>Preoperative</td>
<td>Single shot L2 0.3 ml/kg 0.25% bupivacaine</td>
<td>None reported</td>
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<tr>
<td>Uysal et al. 2020</td>
<td>1</td>
<td>5 months</td>
<td>Diaphragmatic hernia</td>
<td>Postoperative</td>
<td>Single shot (twice) T6 T10 0.5 ml/kg 0.25% bupivacaine</td>
<td>None</td>
</tr>
<tr>
<td>Paladini et al. 2019</td>
<td>1</td>
<td>5 months</td>
<td>Thoracic surgery</td>
<td>Preoperative</td>
<td>Single shot T4 (twice) 4 ml 0.2% levobupivacaine after induction 4 ml 0.1% levobupivacaine before emergence</td>
<td>None</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Postoperative</td>
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<tr>
<td>Kaplan et al. 2018</td>
<td>1</td>
<td>7 months</td>
<td>Thoracic surgery</td>
<td>Preoperative</td>
<td>Single shot T6 2 ml of 0.2% ropivacaine for hydrodissection and catheter placement, then continuous infusion through catheter 0.2% ropivacaine 1 ml/h Catheter removed at 72 h</td>
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<tr>
<td>Gurbuz et al. 2021</td>
<td>2</td>
<td>1 day</td>
<td>Thoraco-abdominal surgery</td>
<td>Postoperative; preoperative</td>
<td>Single shot T4; T8 0.75 ml 0.2% bupivacaine</td>
<td>Bradycardia 10 min after block (treated with atropine) in 1 case</td>
</tr>
<tr>
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<td></td>
<td>25 days</td>
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<th>Cases</th>
<th>Age</th>
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<tr>
<td>Kaushal et al. 2020 [5]</td>
<td>80</td>
<td>Mean age 28.5 months</td>
<td>Prospective randomized single-blind comparative trial</td>
<td>Cardiac surgery</td>
<td>Preoperative</td>
<td>Single shot bilateral T3 1.5 mg/kg 0.2% ropivacaine (x2) vs. no block</td>
<td>None</td>
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<tr>
<td>Macaire et al. 2020 [6]</td>
<td>50</td>
<td>Mean age 25 months</td>
<td>Prospective randomized double blind controlled trial</td>
<td>Cardiac surgery</td>
<td>Preoperative followed by postoperative programmed intermittent bolus regimen</td>
<td>Induction single shot in bilateral T3-T4 catheter 0.1%–0.2% ropivacaine followed by postoperative PIB 0.1%–0.2% ropivacaine for 48 h vs. sham PIB with saline for 48 h</td>
<td>Accidental catheter removal or displacement</td>
</tr>
<tr>
<td>Aksu et al. 2019 [7]</td>
<td>57</td>
<td>1–7 years</td>
<td>Prospective double blind randomized trial</td>
<td>Pelvic small surgery</td>
<td>Preoperative</td>
<td>Single shot L1 ESPB vs. single shot quadratus lumborum block 0.5 ml/kg 0.25% bupivacaine</td>
<td>None</td>
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<tr>
<td>Mostafa et al. 2019 [8]</td>
<td>60</td>
<td>3–10 years</td>
<td>Prospective randomized control trial</td>
<td>Open splenectomy</td>
<td>Preoperative</td>
<td>Single shot bilateral T7 0.3 ml/kg 0.25% bupivacaine (x2) vs. bilateral sham ESPB 0.3 ml/kg normal saline (x2)</td>
<td>None</td>
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<tr>
<td>Singh et al. 2020 [9]</td>
<td>40</td>
<td>2–10 years</td>
<td>Prospective randomized control trial</td>
<td>Lower abdominal surgery</td>
<td>Preoperative</td>
<td>Single shot bilateral L1 0.5 ml/kg 0.25% bupivacaine (x2) vs. no block</td>
<td>None</td>
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<tr>
<td>El-Emam et al. 2019 [10]</td>
<td>60</td>
<td>6 months–3 years</td>
<td>Prospective randomized control trial</td>
<td>Unilateral inguinal hernia repair</td>
<td>Preoperative</td>
<td>Single shot L1 level ESPB vs. iliinguinal/iliohypogastric nerve block, 0.5 ml/kg 0.125% bupivacaine + fentanyl 1 μg/ml injectate</td>
<td>None</td>
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<tr>
<td>Jambotkar and Malde 2021 [19]</td>
<td>30</td>
<td>1–12 years</td>
<td>Prospective observational study</td>
<td>Thoracotomy</td>
<td>Preoperative</td>
<td>Single shot T4 0.25% bupivacaine 0.3 ml/kg</td>
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<tr>
<td>Aksu and Gurkan 2019 [69]</td>
<td>141</td>
<td>0.25–17 years</td>
<td>Retrospective cohort study</td>
<td>Thoracic, abdominal and pelvic surgery</td>
<td>Preoperative</td>
<td>Unilateral (112) or bilateral (29) single shot T4 to S4 0.25% bupivacaine 0.5 ml/kg (max 20 ml)</td>
<td>None</td>
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<tr>
<td>Munshey et al. 2020 [73]</td>
<td>22</td>
<td>11 months–17 years</td>
<td>Retrospective cohort study</td>
<td>Thoracic, abdominal, hip surgery</td>
<td>Preoperative (postoperative for one patient) followed by intraoperative and postoperative programmed intermittent bolus regimen</td>
<td>Catheter ESPB (17 unilateral, 5 bilateral; 22 thoracic, 5 lumbar) with median loading dose 0.4 ml/kg ropivacaine 0.5%, intraoperative bolus of 0.3 ml/kg/h ropivacaine 0.2%, postoperative programmed intermittent bolus maximum 0.5 mg/kg/h</td>
<td>Local edema and tenderness</td>
</tr>
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ESPB: erector spinae plane block, PIB: programmed intermittent bolus.
regional procedures (Tables 1 and 2). However, the position, timing, and pharmacological approach are highly variable across operators and no standardized protocols are available.

The level of evidence is still limited, and a general consensus on these aspects is lacking. The purpose of this narrative review is therefore to provide an overview of the state of ESPBs in children, highlighting critical aspects and future perspectives to guide practitioners towards a more homogeneous approach.

Clinical indications

ESPBs have been proposed for a wide variety of potential applications, especially as part of a multimodal perioperative analgesia regimen to promote enhanced recovery after surgery (ERAS) in numerous kinds of procedures, ranging from chest and abdominal to inguinal and lower limb surgeries. In fact, analgesia can be attained in a broad range of anatomical areas depending on the vertebral level of local anesthetic (LA) injection, with extensive craniocaudal spread providing anesthesia coverage to multiple dermatomes [3]. Consequently, this technique allows for the operator to achieve analgesia in the desired region with an injection that is remote from the surgical incision area [2].

While ESPBs could be synergistic with other locoregional techniques, to date, it has mostly been reported as an alternative to other approaches. For example, the ESPB has been used as an alternative to the thoracic epidural, a classic technique for cardiothoracic surgeries involving a midline sternotomy or thoracotomy, as it is considered safer because it is injected farther from important structures, such as the spinal cord, pleura, and vascular structures [4]. Bilateral ESPBs at the T3-T4 level have been shown to provide improved postoperative analgesia compared to no block in children undergoing cardiac surgeries involving a midline sternotomy [5,6].

Several reports have described the use of ESPBs for perioperative pain management during lower body surgeries. The non-inferiority of the ESPB to the quadratus lumbarum block in pediatric lower abdominal surgeries has been shown [7]. Bilateral ESPBs can provide superior intraoperative and postoperative analgesia compared to sham blocks for splenectomies involving a midline incision [8] and compared to no block for lower abdominal surgeries [9]. ESPBs have also been shown to provide more effective and longer-lasting postoperative analgesia than ilioinguinal/iliohypogastric blocks in unilateral inguinal hernia repairs [10].

Despite the fact that caudal epidurals are one of the most extensively used regional blocks in children undergoing hip and lower abdominal surgeries [11,12], no studies have compared caudal epidurals to ESPBs in pediatric patients. Additionally, no comparisons between ESPBs and psoas compartment blocks in hip surgery have been conducted, even though the effectiveness of both techniques have been confirmed [13–16].

A reduction in the use of intraoperative and postoperative analgesics for opioid-sparing general anesthesia has also been demonstrated with ESPBs [5,6,8]. Anecdotal evidence in the form of case studies and small case series have been reported for numerous applications of the ESPB as part of a multimodal opioid-sparing analgesia regimen, including for thoracotomy, thoracoscopic surgery, thoracic wall surgery [2,3,4,18–27], sternotomy [28], abdominal surgery [29–37] spinal surgery [38], genital surgery [39] and hip joint and proximal femur surgery [14–16,40].

Outside the operating room, ESPBs have been successfully employed for pain control in pediatric oncological palliative care [41].

Beyond the use of ESPBs as a routine technique in the pediatric anesthesiologist’s arsenal, it has also been applied in the management of particularly complex cases. Due to the craniocaudal spread of ESPBs, it can be injected at a remote point from the vertebral level of the incision site [42], and thus may be used when there is an incision site infection or as a valid alternative to neuraxial anesthesia in the case of spinal deformities, previous spinal surgery, or neuraxial spread of neoplastic disease [43–45]. ESPB catheters have also been used successfully when epidural and paravertebral catheters are not possible due to coagulopathy [46]. The high safety profile of the ESPB in terms of the hemodynamic impact has led to its consideration by clinicians who are reluctant to use epidural anesthesia in patients with heart defects [47]. Additionally, during the perioperative period of an emergency laparotomy, analgesia has been provided by ESPBs even in very low birth weight premature infants, despite their small size [48].

Anatomy, technique, and diffusion of the anesthetic solution

Accurate knowledge of pediatric anatomy is essential for performing an ESPB and achieving an adequate sensory blockade. Anatomical differences between adult and pediatric patients, such as the muscles, fascia, and connective tissues under the skin, which are usually thinner and less rigid in pediatric patients, must be taken into account. Therefore, neonatal/pediatric probe, shorter needle, and lower drug volume should be considered.

Regardless of the vertebral level, the target of this fascial plane block is the erector spinae fasciae plane. This is a virtual space located under the erector spinae muscles that communicates with the paravertebral space where the dorsal rami of the spinal cord is located (Fig. 1).
The erector spinae muscles constitute the intermediate layer of the deep muscles of the vertebral column, arising from the posterior part of the iliac crest, sacrum, and lumbar spinous processes. It encompasses the spinalis, longissimus dorsi, and iliocostalis muscles. These muscles are located posterolaterally to the vertebral column, lying between the vertebral spinous processes medially and angles of the ribs laterally.

During sonography, the probe should initially be placed at the midline of the spine with a transverse orientation to visualize the spinous processes. Moving laterally, the transverse processes can then be located. Maintaining the probe in a transverse orientation, an out-of-plane approach can be used, with the needle placed in a craniocaudal or caudocranial direction. Otherwise, after a 90° rotation of the probe, an in-plane approach is also possible.

The structures are visualized from superficial to deep as follows: the trapezius, rhomboid, and erector spinae muscles and the transverse process of the respective vertebra.

The needle must be advanced to the tip of the transverse process, after which the LA can be injected to hydrodissect the plane deep to the erector spinae muscle to verify the proper injectate location before injecting the residual volume. Alternatively, if the patient’s weight allows for only very small volumes of LA, normal saline may be used for this initial hydrodissection to spare the LA allowance.

The distance between the skin and tip of the transverse process is very small in pediatric patients and can vary considerably according to age and body mass index. Therefore, small-sized needle devices and a stable position are required to perform the block.

The above mentioned approach, which is mostly conducted in the prone position in children, is similar to that used in the first reports of ESPBs conducted on two adult patients in the sitting position [1]. As this technique has been increasingly applied in the pediatric population and refined for the particular needs of these patients, several other approaches have been developed. In 2018, an ESPB administered with the patient in the lateral decubitus position was described by placing the ultrasound probe transversely to obtain a midline view of the spinous and transverse processes of the vertebral and erector spinae muscles, using an out-of-plane technique [49].

The Aksu approach for lumbar ESPBs has also been described in pediatric patients, in which an in-plane technique in the lateral decubitus position is applied, thus eliminating the need to turn the anesthetized patient prone and then back to a supine position for surgery [50]. The major disadvantage of this approach is the inability to visualize the craniocaudal spread of the LA, which is only possible when the probe is turned to the sagittal position after the block is performed [51].

Regardless of the technical approach, LAs injected into the erector spinae fascial plane are meant to spread through the paravertebral space, not only at the level of the injection site but also cranially and caudally to reach distant dermatomes.

However, the exact diffusion pathway remains controversial. The dorsal rami emerges from the paravertebral space and moves through the inter-transverse connective tissue complex. The ven-
tral rami continues from the paravertebral to the intercostal space, becoming the intercostal nerves. The involvement of the ventral rami is contested since no solid evidence is available on the actual route of spread of the injected drugs.

Different methods have been adopted to study the spread of LAs; however, most are described in adult patients whose tissues are much more rigid and stiffer than those of children. Sonography, while clearly a limited technique, is useful for studying the cephalocaudal distribution of the injectate and is feasible in the pediatric population. Munoz et al. [2] observed the spread of LA from T5 to T11 after an 8-ml injection of solution was performed at T8 in a 7-year-old patient. Additionally, the distribution of a 3.2-ml solution from T1 to T9 was documented via ultrasound in a 3-year-old patient after an ESPB was performed at T1 [17]. In another case report, the same author visualized the spread of 1 ml of solution between T4 and L1 following an ESPB performed at T6 in a 2-month-old infant [52]. A wide distribution was also observed between L1 and L4 following the administration of 4.5 ml of solution at L2 in a 4-year-old patient [53].

A cadaveric study that analyzed the spread of a methylene blue dye solution in two embalmed preterm stillborn neonates weighing 1.6 and 0.6 kg was also conducted. The first cadaver received a unilateral 0.5-ml injection of solution at the T5 level, and superficial cephalocaudal diffusion from T2 to T12 was observed, with deeper staining of the ventral and dorsal roots and ganglia between T3 and T6. In the second cadaver, in which a 0.2-ml injection was performed at the T8 level, superficial staining spread from T7 to L1 and dorsal and ventral roots/ganglia were involved from T7 to T11. In both cases, the paravertebral and epidural spaces as well as the dura mater surrounding the spinal cord were stained [54].

CT scanning with multi-slice and three-dimensional (3D) technology has been used to assess the spread of iodinated contrast dye in a fresh unembalmed preterm neonatal cadaver weighing 2.7 kg. The first injection (2.3 ml) was performed at the T8 level on the right side and a second injection (2.3 ml) on the opposite side was performed at the T10 level. 3D reconstruction revealed diffusion of the dye from T6 to T9 on the right side and from T9 to T11/T12 on the left side. Contrast dye was seen in the paravertebral space but not in the epidural space, spreading over the costotransverse ligament and reaching the intercostal space. The lack of spread to the epidural space could be explained by in vivo factors, such as intrathoracic pressure changes and the absence of muscle tone and tissue tension. The study suggested a volume of 0.3–0.4 ml per dermatome, with involvement of 3 to 4 dermatomes with the ESPB [55].

The paucity of data available regarding injectate spread in children requires that adult studies be referenced. However, considerable differences in diffusion patterns in adult and pediatric patients must be recognized in relation to multiple factors, such as the developmental formation of the vertebral curvature, more elastic pediatric spine, and less dense ligaments and cartilaginous laminae [54]. Drug distribution in the adult population has been observed in MRI and cadaveric studies, which suggest different possibilities for lateral and anterior diffusion of LAs. Beyond anatomy, the vertebral level [56] and drug volume [57] are also relevant factors in the spread of injected LA. Analyses of cadaveric samples have revealed anterior and posterior diffusion of the injectate with different percentages at different vertebral levels, with inconclusive results. Paravertebral, intercostal, and epidural spread have been described, but these findings are not consistent among the available studies [56–68]. Given these variabilities in adult MRI and cadaveric studies, the results are inconclusive and presumably related to the site of injection, volume of solution, and physical characteristics of the tissues.

Although this technique is clearly effective, given its many successful clinical applications, evidence regarding the precise diffusion of the injected solution in children is not entirely clear, with only two studies on neonatal cadavers [54,55] and several case series reporting data from in vivo sonographic imaging.

**Choice and dosage of local anesthetics**

The pharmacological approaches described in the current literature are highly inconsistent, as the procedure has multiple applications and the specific pharmacological approach associated with the variety of clinical contexts is variable.

Bupivacaine, ropivacaine, and levobupivacaine at different concentrations and volumes have been most commonly used for ESPBs in pediatric patients, with no significant differences in postoperative pain management between them.

In the first documented application of the ESPB in children in the literature, a single shot injection of 14 ml of 0.5% bupivacaine performed at T8 was administered to a 7-year-old boy undergoing surgery for the treatment of a tumor of the eleventh rib [2].

Most of the pediatric ESPBs currently described in the literature are performed with 0.25% bupivacaine, with volumes ranging from 0.3 to 0.6 ml/kg [19,20,25,30,31,33,36,69,70]. A 1 : 1 solution of 0.25% bupivacaine and 1% lidocaine with a total volume of 0.2 ml/kg was administered via ESPB as a single shot injection to a 3-year-old girl weighing 16 kg undergoing surgical resection of dorsal lipoma. The patient was discharged 4 h after surgery with full pain control [17]. The same solution at a dosage of 0.4 ml/kg was administered as a single shot ESPB in a...
2-month-old infant before inguinal hernia repair [53].
The use of levobupivacaine 0.2% (4 ml) for thoracic surgery in a 5-month-old female was also reported [71] to enhance recovery after surgery.

The first continuous ESPB in the literature was administered to a 3-year-old boy, who received an 8-ml initial injection of 0.25% levobupivacaine through a catheter placed at the T9 level at the end of a thoracotomy. Two hours later, a patient-controlled analgesia pump with 0.1% levobupivacaine (3 ml/h continuous infusion) was started, with a standing order of 1.5-ml rescue boluses at 30-min lockout intervals. On the fourth postoperative day, the infusion was stopped. Only two 1.5-ml rescue boluses were administered and no other medications were required to control pain [47].

A 7-month-old infant received 0.2% ropivacaine through a catheter placed at the T6 level (1 ml/h) prior to an upper lobectomy for a congenital pulmonary airway malformation. The catheter was removed on the third postoperative day, and pain scores showed adequate analgesia [72].

A retrospective review of a single center on various surgeries described the efficacy of ESPBs with 0.5% ropivacaine in children, with an initial loading dose of 0.4 ml/kg followed by intermittent boluses of 0.2%–0.3% at 0.3 ml/kg administered hourly [73].

Pharmacokinetic variability must be taken into account for all fascial plane blocks. In contrast to peripheral nerve blocks, where anesthetics are precisely deposited around a specific nerve, a consistent level of intensity of the sensory blockade cannot be expected for fascial plane blocks. Moreover, differences in tissue laxity in pediatric patients could contribute to increased variability. Consequently, it is difficult to replicate the same sensory block in different children, even when administered by the same practitioner.

More studies are thus necessary to guide the type, dosage, and duration of LA and adjuvant administrations to create specific protocols for the various clinical applications of pediatric ESPBs.

Safety profile and adverse events

Regional anesthesia is generally considered safe in the pediatric population, although caution must be exercised, especially when applying these techniques to infants [74]. Furthermore, these techniques can be safely utilized under general anesthesia [75]. In particular, ESPBs appear to be exceptionally safe, as the injection site is very superficial and ultrasound guidance allows for visualization of vital structures such as the neuraxis, pleura, and vascular structures as the needle is inserted. Additionally, it is widely accepted that ESPBs can be conducted safely in patients with coagulopathy [46]. While the standard contraindications and possible complications of any peripheral block, including LA systemic toxicity (LAST), allergic reactions, or motor block, may occur with ESPBs, the available literature documents a promising safety profile in children, with most studies reporting no adverse events or complications such as epidural hematoma, which may occur with neuraxial blocks.

Some minor adverse events such as catheter occlusion, displacement, and unintentional removal have been reported [6,73]. Rare cases of bradycardia or possible LAST have also been reported, but quickly reversed [76,77]. While injection site infections may be a contraindication to peripheral nerve blocks, the possibility of injecting LAs at a site distant from the target in a fascial plane block may allow operators to safely implement ESPBs even in cases of surgical site infection. One other potential complication of ESPBs is a pneumothorax [78]; however, a literature search yielded no documented episodes, and experienced operators hold that ultrasound guidance, fine needle skills, and preventative techniques can minimize this risk [49].

Conclusions

Despite significant interest in ESPBs in the pediatric anesthesia community due to its versatility, low learning curve and safety profile, the available evidence is still anecdotal and non-homogeneous with few rigorous trials, yielding low-quality evidence and no clear protocol to follow. Taken together, the available data suggest that ESPBs may be a valid technique to improve intra- and postoperative pain control and reduce opioid use in pediatric thoracic, abdominal, inguinal, hip, and femur surgeries. Additionally, multiple authors have considered this procedure a valid alternative to other loco-regional techniques and epidural anesthesia. The choice of LA is quite variable among practitioners, with reports of single shot or continuous infusions for different surgeries, and the distribution of injected solutions remains controversial. Hence, more well-designed randomized controlled trials are needed to clarify specific approaches for performing ESPBs for different clinical procedures in the pediatric population.

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None.

Conflicts of Interest

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

Monica Lucente (Conceptualization; Data curation; Writing – original draft)
Giulia Ragonesi (Data curation; Funding acquisition; Writing – original draft; Writing – review & editing)
Marco Sanguigni (Data curation; Software; Writing – original draft)
Fabio Sbaraglia (Conceptualization; Methodology; Supervision; Writing – review & editing)
Alessandro Vergari (Resources; Validation; Visualization; Writing – review & editing)
Rosa Lamacchia (Resources; Writing – review & editing)
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Effect of equipotent doses of propofol and sevoflurane on endoplasmic reticulum stress during breast cancer surgery

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Background: Numerous studies suggest that intravenous propofol is superior to inhaled volatile anesthetic. This study compared the changes in the endoplasmic reticulum (ER) stress of cancer cells and lymphocytes after propofol- and sevoflurane-based anesthesia during breast cancer surgery.

Methods: We randomized 53 patients undergoing breast cancer surgery to propofol (n = 28) and sevoflurane (n = 25) anesthesia groups. Blood samples were obtained immediately before inducing anesthesia, and 1 and 24 h postoperatively. Human breast cancer cell lines were cultured and treated with patient plasma, and the frequency of C/EBP homologous protein (CHOP) on the cancer cell lines and lymphocytes was measured. The neutrophil-to-lymphocyte ratio in plasma was evaluated in both groups.

Results: The CHOP expression on breast cancer cell lines did not differ between the groups (P = 0.108), although it decreased significantly over time (P = 0.027). The CHOP expression on lymphocytes was comparable between the groups (P = 0.485), and was the neutrophil-to-lymphocyte ratio (P = 0.501).

Conclusions: Propofol-based anesthesia did not induce greater ER stress than sevoflurane-based anesthesia during breast cancer surgery. The ER stress of cancer cells did not differ according to the type of anesthesia during breast cancer surgery.

Keywords: Anesthesia; Apoptosis; Breast neoplasms; Endoplasmic reticulum; Propofol; Sevoflurane.

Introduction

The endoplasmic reticulum (ER) synthesizes transmembrane proteins and lipids, and stores calcium [1]. Conditions such as hypoxia and inflammation impose stress on cells. They enhance ER stress to induce apoptosis for normal cellular homeostasis [2]. Numerous diseases such as multiple myeloma, neurodegenerative disease, and diabetes are associated with ER stress, and cancer is associated with alteration of ER stress [3,4].

Propofol is considered superior to sevoflurane for attenuating cancer progression compared to inhaled volatile anesthetics, although this is controversial [5–8]. The effects of propofol on cancer are derived from its anti-inflammatory properties, while sevoflurane causes immunosuppression and promotes cancer progression [7]. Propofol exerts a neuroprotective effect by reducing ER stress of normal neurons, unlike the neurotoxic vola-
tile anesthetics that enhance ER stress [9,10]. However, few studies have compared changes in ER stress after propofol- and volatile anesthetic-based anesthesia in a cancer environment.

We hypothesized that propofol would induce greater ER stress in cancer cells than sevoflurane. The study was designed to compare the changes in ER stress of cancer cells and lymphocytes between propofol- and sevoflurane-based anesthesia in patients undergoing breast cancer surgery.

Materials and Methods

Study population

The study was approved by the Institutional Review Board (Konkuk University Medical Center, Seoul, Korea; KUH1160108) and registered at Clinicaltrials.gov (NCT03561831), and was conducted in accordance with the Helsinki Declaration–2013. Informed consent was obtained from all patients before the operation. Female Koreans with American Society of Anesthesiologists class I to II physical status, who were scheduled to undergo breast cancer surgery, were enrolled in this study. Patients were excluded based on the following criteria: age < 20 years old, abnormal pre-operative laboratory results, history of cancer, history of propofol or sevoflurane allergy, or other concurrent surgery. On entering the operating room, each patient was randomly allocated to propofol-based (Propofol) or sevoflurane-based (Sevoflurane) anesthesia groups. A random-permuted block design was used for randomization. The medical team involved in the patient care was blind to the study. All data were collected by trained observers who were also blind to the study and did not participate in patient care.

Anesthesia

The anesthesia techniques were standardized. No patient received pre-anesthetic medication. Anesthesia was induced after routine non-invasive monitoring, including the bispectral index (BIS). For the Propofol group, an initial effect-site propofol concentration of 4.0 µg/ml was administered intravenously under a modified Marsh model \( (k_{\text{e0}} 1.21/\text{min}) \) using a target-controlled infusion (TCI) device (Orchestra® Base Primea; Fresenius Vial, France). For the Sevoflurane group, thiopental sodium (5 mg/kg) was administered intravenously to induce anesthesia. After loss of consciousness, mask ventilation was confirmed and rocuronium 0.6 mg/kg was administered intravenously. Remifentanil (5.0 ng/ml) was intravenously administered under the Minto model [11], and maintained until the end of surgery. After tracheal intubation, propofol or sevoflurane was titrated to maintain a BIS of 40 to 60. The mean systemic blood pressure was maintained within 20% of the baseline or > 60 mmHg during anesthesia. At the end of the surgery, the administration of propofol or sevoflurane with remifentanil was stopped and ketorolac 0.5 mg/kg was given intravenously for postoperative analgesia. Residual neuromuscular paralysis was antagonized with neostigmine 0.03 mg/kg and glycopyrrolate 0.008 mg/kg with neuromuscular transmission monitoring. Intravenous patient-controlled analgesia (PCA) was available on demand for patients undergoing radical mastectomies. The total PCA volume was 200 ml, consisting of fentanyl (2,000 µg; 40 ml), ramosetron (0.6 mg; 4 ml), and normal saline (156 ml). The PCA device (Gemstar Pump™; Hospira, USA) was programmed to deliver 0.03 ml/kg/h as the basal infusion rate and 0.05 ml/kg on demand, with a 15 min lock-out time. After tracheal extubation, patients were transferred to the post-anesthesia care unit (PACU). Postoperative medical treatment and decision making were under the control of the surgeon responsible, in accordance with standard institutional regimens.

Blood samples

Venous blood samples were collected immediately before inducing anesthesia (Preop), on arrival in the PACU (Post 1 h), and 24 h postoperatively (Post 24 h). Blood samples were obtained without or with minimal stasis (within 30 s) and centrifuged immediately at 3000 rpm for 15 min at 4°C. Plasma samples were frozen within 1 h of sampling and stored at −80°C until the analysis.

Breast cancer cell culture

The Michigan Cancer Foundation-7 (MCF-7) human breast cancer cell line (AcceGen Biotech, USA) was cultured in Roswell Park Memorial Institute medium 1640 (RPMI 1640) supplemented with 10% fetal bovine serum and 1% penicillin. The medium was replaced every 3–5 days. Cells were subcultured using the trypsin-ethylenediaminetetraacetic acid method.

C/EBP homologous protein (CHOP) in MCF-7 cell line cultured with the plasma from patients with breast cancer

To culture the MCF-7 cell line with plasma of breast cancer patients, 15,000 cells were counted and mixed with 4 µl of breast cancer patient plasma in a total volume of 100 µl. Then they were transferred into the wells of 96-well cell culture plates. After 24 h of incubation, the cells in each well were transferred to fluores-
cence-activated cell sorting (FACS) tubes. Then, the cells were washed twice with FACS buffer (0.1% bovine serum albumin and 0.05% sodium azide in 1 × phosphate-buffered saline [PBS]) for 5 min. After washing, the cells were fixed with fixation buffer (BD Biosciences, USA) for 15 min and washed with FACS buffer for a further 5 min. The cells were stained with DNA Damage Inducible Transcript 3/CHOP rabbit anti-human polyclonal antibody (Cat No. LS-C16732; LSbio, USA) for 30 min, and washed with FACS buffer for 5 min. Then, they were stained with goat anti-Rabbit IgG (H + L) secondary antibody (Cat No. A-11034; Invitrogen, USA) and incubated for 30 min. Finally, they were washed with FACS buffer again.

**CHOP on lymphocytes from blood**

Peripheral blood mononuclear cells (PBMCs) were isolated using density-gradient centrifugation for 20 min over Biocoll separating solution (Biochrom, Germany). The PBMCs were washed with 1 × PBS (pH 7.4, no calcium, no magnesium), 155.1 mM sodium chloride (NaCl), 2.9 mM sodium phosphate dibasic (Na₂HPO₄·7H₂O), and 1.0 mM potassium phosphate monobasic (KH₂PO₄) solution. After isolating the lymphocytes, the cells were stained with fluorescein isothiocyanate, an anti-human cluster of differentiation 4 antibody (BD Biosciences, USA) at room temperature for 30 min in the dark. After fixation, the cells were permeabilized with FACSperm2 (BD Biosciences, USA) buffer according to the manufacturer’s instructions. After permeabilization, the cells were stained and incubated with the same CHOP antibodies used in the MCF-7 cell line culture, using the same methods.

**Flow cytometric analysis**

All data were collected using the BD Accuri C6 flow cytometer (BD Biosciences, USA), and then analyzed with FlowJo™ software (Tree Star, USA).

**Determination of the leukocyte differential count**

The differential leukocyte count was determined preoperatively, and at 24 h postoperatively. To calculate the neutrophil to lymphocyte ratio, the ratio of neutrophils to leukocytes was divided by the ratio of lymphocytes to leukocytes.

**Clinical measurements**

The maximal and minimal effect-site concentrations of propofol and the maximal and minimal end-expiratory concentrations of sevoflurane were recorded during anesthesia. Postoperative pain was assessed using a visual analogue scale (VAS) ranging from 0 mm (no pain) to 100 mm (worst pain imaginable). Intravenous ketorolac 0.5 mg/kg was administered on demand as an additional rescue analgesic. The perioperative opioid doses were recorded.

**Statistics**

The primary outcome measure was the frequency of CHOP on MCF-7 cell lines over time in the Propofol and Sevoflurane groups. In a pilot study of 10 patients, we calculated a standardized effect size of 0.482 for the group difference in CHOP frequency on MCF-7 cell lines. For 80% power to detect intergroup differences using two-way repeated-measured analysis of variance (ANOVA) at the 5% significance level (α), a sample size of 22 per group was needed. Ultimately, 53 patients were enrolled, assuming a drop rate of 15%.

The differences in the frequency of CHOP on MCF-7 cell lines over time, and on circulating lymphocytes of patients with breast cancer, between the Propofol and Sevoflurane groups was analyzed by two-way repeated-measured ANOVA. For continuous variables, the distribution of the data was evaluated for normality using the Shapiro–Wilk test. The independent two-tailed t-test was used to compare means for continuous, normally distributed data between the Propofol and Sevoflurane groups. When the data were not normally distributed, the Mann–Whitney U test was used. Normally distributed continuous data are presented as the mean ± standard deviation; data that were not normally distributed are presented as the median (Q1, Q3). The chi-square test was used to compare the means of categorical variables between the two groups. For categorical variables, the number of patients (n) and proportion (%) were calculated. All calculations were performed using SPSS software (ver. 20.0; SPSS Inc., USA). A P value < 0.05 was taken to indicate statistical significance.

**Results**

Eighty-four patients were eligible for the study, of whom 31 were excluded: 14 refused to participate, nine had abnormal preoperative laboratory results, four previously had cancer, one had a propofol allergy, and three underwent other types of concurrent surgery. Therefore, 53 patients were included in the final analysis.
The patient demographics were similar between the Propofol and Sevoflurane groups (Table 1). The total amount of propofol was significantly higher in the Propofol than Sevoflurane group, and thiopental sodium was significantly higher in the Sevoflurane than Propofol group. The lowest and highest BIS values did not differ significantly between the two groups (Table 1). The amounts of medications, such as vasopressors, inotropics, opioids, and ketorolac, administered perioperatively were similar between the two groups (Table 2). The VAS and postoperative nausea and vomiting scores did not differ between the two groups during the study (Table 2).

The CHOP expression on MCF-7 cell lines did not differ between the Propofol and Sevoflurane groups (0.20% [0.14, 0.23%] vs. 0.13% [0.07, 0.21%], 0.22% [0.06, 0.24%] vs. 0.09% [0.05, 0.17%], and 0.14 ± 0.07 vs. 0.12 ± 0.07% preoperatively, 1 h postoperatively, and 24 h postoperatively, respectively; overall group difference (95% CI, 0.03 [–0.01, 0.07]; P = 0.108) (Fig. 2). The CHOP expression on MCF-7 cell lines in both groups decreased significantly over time (P = 0.027) (Fig. 2).

The CHOP expression on lymphocytes did not differ between the Propofol and Sevoflurane groups (0.16% [0.05, 0.41%] vs. 0.07% [0.03, 0.19%], 0.13% [0.07, 0.39%] vs. 0.04% [0.02, 0.13%], and 0.19% [0.08, 0.52%] vs. 0.05% [0.02, 0.38%] preoperatively, 1 h postoperatively, and 24 h postoperatively, respectively) (P = 0.485) (Fig. 3). In addition, the changes of CHOP expressions on lymphocytes in both groups showed no specific pattern over time (P = 0.836) (Fig. 3).

The ratios of neutrophils to leukocyte in the Propofol vs. Sevoflurane groups (55.3 ± 8.0% vs. 57.6 ± 6.7% and 57.5 ± 11.5% vs. 58.4 ± 11.0% preoperatively and 24 h postoperatively, respectively) and lymphocyte to leukocyte (36.2 ± 8.6% vs. 33.8 ± 6.1% and 34.1 ± 8.9% vs. 33.4 ± 9.6% preoperatively and 24 h postoperatively, respectively) did not differ significantly between the Propofol and Sevoflurane groups (P = 0.441 and P = 0.361, respectively) (Table 3). The ratios of neutrophils to lymphocytes (1.53 [1.16, 1.94] vs. 1.80 [1.48, 2.05], 1.63 [1.35, 2.20] vs. 1.62 [1.31, 2.31] preoperatively and 24 h postoperatively, respectively) also were not significantly different between the Propofol and Sevoflurane groups (overall difference [95% CI], –0.118 [–0.469, 0.232], P = 0.501) (Table 3).

**Discussion**

In this study, propofol did not induce greater ER stress in cancer cells than sevoflurane during breast cancer surgery. The anesthetics reduced the ER stress of cancer cells over time, but did not influence the ER stress of lymphocytes. The ratios of neutrophils

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**CONSORT flow diagram.** CHOP: C/EBP homologous protein.

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**Table 1.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Eligible</th>
<th>Assessed</th>
<th>Excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propofol</td>
<td>28</td>
<td>28</td>
<td>14</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>25</td>
<td>25</td>
<td>9</td>
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</table>

**Table 2.**

<table>
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<td>14</td>
</tr>
<tr>
<td>Sevoflurane</td>
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<td>9</td>
</tr>
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**Table 3.**

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<td>14</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>25</td>
<td>25</td>
<td>9</td>
</tr>
</tbody>
</table>

**Fig. 1.** CONSORT flow diagram. CHOP: C/EBP homologous protein.
Table 1. Demographic Characteristics of the Propofol- and Sevoflurane-based Anesthesia during Breast Cancer Surgery

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Propofol group (n = 28)</th>
<th>Sevoflurane group (n = 25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>48 (42, 55)</td>
<td>50 (44, 60)</td>
<td>0.412</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>57.5 (51.0, 62.5)</td>
<td>59.0 (51.0, 65.0)</td>
<td>0.748</td>
</tr>
<tr>
<td>ASA-PS classification</td>
<td>1.000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>27 (96.4)</td>
<td>24 (96.0)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1 (3.6)</td>
<td>1 (4.0)</td>
<td></td>
</tr>
<tr>
<td>Anesthesia duration (min)</td>
<td>153 ± 27</td>
<td>140 ± 34</td>
<td>0.126</td>
</tr>
<tr>
<td>Anesthetics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol total (mg)</td>
<td>876 (712, 1142)</td>
<td>NA</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Propofol minimal (μg/ml)</td>
<td>2.0 (2.0, 3.0)</td>
<td>NA</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Propofol maximal (μg/ml)</td>
<td>3.6 ± 1.0</td>
<td>NA</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Thiopental sodium (mg)</td>
<td>NA</td>
<td>300 (250, 325)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sevoflurane minimal (vol%)</td>
<td>NA</td>
<td>1.0 (1.0, 1.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sevoflurane maximal (vol%)</td>
<td>NA</td>
<td>2.0 (2.0, 2.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Remifentanil (μg)</td>
<td>1594 (1265, 1822)</td>
<td>1382 (1238, 1650)</td>
<td>0.276</td>
</tr>
<tr>
<td>Rocuronium (mg)</td>
<td>50 (50, 60)</td>
<td>50 (50, 60)</td>
<td>0.488</td>
</tr>
<tr>
<td>BIS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowest value</td>
<td>45 (41, 50)</td>
<td>46 (42, 53)</td>
<td>0.655</td>
</tr>
<tr>
<td>Highest value</td>
<td>55 ± 11</td>
<td>53 ± 10</td>
<td>0.580</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3), incidence (percentage), or mean ± SD. ASA-PS: American Society of Anesthesiologists physical status, BIS: bispectral index, NA: not-applicable.

Table 2. Amount of Medications Administered and Postoperative Pain and Nausea/vomiting

<table>
<thead>
<tr>
<th></th>
<th>Propofol group (n = 28)</th>
<th>Sevoflurane group (n = 25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenylephrine (μg)</td>
<td>0 (0, 80)</td>
<td>0 (0, 50)</td>
<td>0.787</td>
</tr>
<tr>
<td>Ephedrine (mg)</td>
<td>0 (0, 2)</td>
<td>4 (0, 4)</td>
<td>0.105</td>
</tr>
<tr>
<td>Fentanyl (μg)</td>
<td>159 (120, 205)</td>
<td>153 (120, 203)</td>
<td>0.914</td>
</tr>
<tr>
<td>Ketorolac use</td>
<td>11 (39.3)</td>
<td>14 (56.0)</td>
<td>0.347</td>
</tr>
<tr>
<td>VAS score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>25 (20, 30)</td>
<td>30 (20, 40)</td>
<td>0.169</td>
</tr>
<tr>
<td>Post 1 h</td>
<td>25 ± 12</td>
<td>30 ± 12</td>
<td>0.153</td>
</tr>
<tr>
<td>Post 24 h</td>
<td>15 (8, 25)</td>
<td>20 (10, 30)</td>
<td>0.059</td>
</tr>
<tr>
<td>PONV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>3 (10.7)</td>
<td>6 (24.0)</td>
<td>0.358</td>
</tr>
<tr>
<td>Post 1 h</td>
<td>2 (7.1)</td>
<td>6 (24.0)</td>
<td>0.185</td>
</tr>
<tr>
<td>Post 24 h</td>
<td>12 (42.9)</td>
<td>8 (32.0)</td>
<td>0.596</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3), incidence (percentage), or mean ± SD. VAS: visual analogue scale, PONV: postoperative nausea and vomiting.

to lymphocytes among leukocytes did not differ between the two groups.

Numerous studies have shown that propofol is superior to volatile anesthetics in terms of reducing cancer progression [12–14]. The anti-inflammatory effects of propofol might help reduce cancer progression [15]. However, in other studies the type of anesthetic did not influence cancer cell progression [16,17]. In our study, the anti-inflammatory effect of propofol has not been reproduced in a clinical situation, although it has been demonstrated in animal studies. The cancer environment is complex and
non-homogenous, such that the effects of anesthetics on cancer may not be dramatic. Several studies have evaluated the effects of various anesthetics on ER stress in different diseases. Propofol exerts an organ protective effect by modulating ER stress, although patterns of ER stress changes vary. Chen et al. [18] revealed that propofol enhanced ER stress and ultimately induced cell apoptosis of unnecessary muscle tissue to protect muscle. By contrast, Wang et al. [19] observed a neuroprotective effect of propofol through a reduction of ER stress and amelioration of neuronal cell apoptosis. Su et al. [20] showed an organ protective effect of propofol against ischemic reperfusion injury through a reduction of ER stress in normal cells. The up and down regulation of ER stress by propofol commonly induces ER stress related apoptosis of abnormal cells, which protect organs. Cui et al. [21] showed that propofol exerted anti-cancer effects by enhancing ER stress-related cancer cell apoptosis in a lung cancer model. However, in the present study, the ER stress of breast cancer cells was not higher under propofol-based anesthesia than volatile anesthetics-based anesthesia. In fact, independent of the anesthetic type, the ER stress of cancer cells decreased following anesthesia. We assume that this might be attributable to differences in the cell microenvironment among diseases and types of cancer. Li et al. [22] showed that regional anesthesia with bupivacaine reduced ER stress in colorectal cancer, but not in melanoma. In addition, our previous in vitro study showed that propofol reduced ER stress in normal tissues, but not cancer cells [23]. The cancer environment of breast cancer

Table 3. The Changes in Neutrophil and Lymphocyte during Breast Surgery

<table>
<thead>
<tr>
<th></th>
<th>Propofol group (n = 28)</th>
<th>Sevoflurane group (n = 25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ratio of neutrophils to leukocytes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>55.3 ± 8.0</td>
<td>57.6 ± 6.7</td>
<td>0.249</td>
</tr>
<tr>
<td>Post 24 h</td>
<td>57.5 ± 11.5</td>
<td>58.4 ± 11.0</td>
<td>0.781</td>
</tr>
<tr>
<td><strong>Ratio of lymphocytes to leukocytes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>36.2 ± 8.6</td>
<td>33.8 ± 6.1</td>
<td>0.247</td>
</tr>
<tr>
<td>Post 24 h</td>
<td>34.1 ± 8.9</td>
<td>33.4 ± 9.6</td>
<td>0.769</td>
</tr>
<tr>
<td><strong>NLR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preop</td>
<td>1.53 (1.16, 1.94)</td>
<td>1.80 (1.48, 2.05)</td>
<td>0.157</td>
</tr>
<tr>
<td>Post 24 h</td>
<td>1.63 (1.35, 2.20)</td>
<td>1.62 (1.31, 2.31)</td>
<td>0.873</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, or median (Q1, Q3). NLR: neutrophil to lymphocyte ratio.
may differ from that of other malignancies in which changes in ER stress as a result of propofol have been reported.

This study showed that propofol and sevoflurane inhibit ER stress in cancer cell over time. The decrement in CHOP expression on cancer cells after anesthesia reflected reduced ER stress of cancer cells due to propofol- and sevoflurane-based anesthesia. Chevet et al. [24] found that, when the immune status was inadequate, ER stress contributed to cancer progression. Moreover, cancer-related hypoxia modulated ER stress, leading to cancer cell progression [25]. In most breast cancers, high levels of ER stress suppress cancer cell apoptosis [26, 27]. However, we did not investigate the mechanism of decrement in ER stress after anesthesia. We assume that some cytokines and transcription factors can reduce ER stress after anesthesia [28].

There were several limitations to this study. First, the equipotent doses of propofol- and sevoflurane-based anesthesia were designed to achieve equivalent BIS value. However, whether these anesthetics have equivalent potency in terms of their effects on cancer cell ER stress is not clear. In clinical practice, the BIS provides a basis for clinical comparison between propofol and volatile anesthetics [29]. In several clinical studies, BIS values were maintained in the same range for propofol and volatile anesthetics, and equipotency was thus achieved [30–32]. However, we were unable to determine equivalent concentrations of these anesthetics in vitro. Nonetheless, we performed this study because the majority of anesthesiologists that use anesthetics ensure adequate BIS; anesthetics are always guided by the BIS or other kinds of processed electroencephalogram index during cancer surgery. We believe that referring to the BIS is the best option to ensure equipotency among diverse anesthetics. Second, we did not directly investigate the apoptosis of cancer cell lines. Moreover, we did not examine ER receptors such as inositol requiring enzyme-1α (IRE1α), double-strand RNA-dependent protein kinase (PERK), and activating transcription factor 6 (ATF6) [25], which sense ER stress. However, CHOP is a good marker of ER stress of cells [33]. Zheng et al. [34] showed that the CHOP level predicts disease free survival in breast cancer patients. Third, although the pro- and anti-apoptotic activities could differ among cancer cell lines, only one breast cancer cell line was cultured in this study [35]. Fourth, the mechanism underlying the decrement in ER stress seen in the cancer cell lines in this study after anesthesia was not identified. Possible mechanism related to ER stress of cancer cell after anesthesia should be evaluated in further studies. Finally, the effect of thiopental sodium on ER stress in the Sevoflurane group was not considered. Few studies have evaluated the effect of thiopental sodium on ER stress during cancer surgery [36]. However, a single dose of thiopental sodium during the early anesthesia period would have negligible effect on ER stress during cancer surgery.

In conclusion, propofol-based anesthesia did not induce greater ER stress of cancer cells than sevoflurane-based anesthesia in vitro setting. However, the ER stress of the cancer cells declined after anesthesia. These findings need to be validated in detailed studies explicitly investigating the effect of anesthesia on ER stress after cancer surgery.

Funding

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Conflicts of Interest

Seong-Hyop Kim has been an editor for the Korean Journal of Anesthesiology since 2019. However, he was not involved in any process of review for this article, including peer reviewer selection, evaluation, or decision-making. There were no other potential conflicts of interest relevant to this article.

Author Contributions

Chung-Sik Oh (Conceptualization; Investigation; Writing – original draft; Writing – review & editing)
Seung Wan Hong (Formal analysis; Methodology)
Sarah Park (Data curation; Investigation)
Yubi Kwon (Data curation; Investigation)
Seong-Hyop Kim (Conceptualization; Supervision)

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References


Introduction

Suprascapular nerve entrapment syndrome (SNES) is a peripheral neuropathy caused by compression of the suprascapular nerve. SNES is uncommon in patients with shoulder dysfunction. However, SNES has clinical implications because it innervates approximately 60–70% of the shoulder joint and often leads to pain over the lateral and posterior aspects of the shoulder as well as weakness of the infraspinatus or supraspinatus muscles due to suprascapular nerve innervation [1–6]. Trauma or traction injury due to repetitive overhead activities or massive rotator cuff tears occurs in SNES [7–10]. SNES should be differentiated from disorders of the cervical part of the spinal cord, damage to the brachial...
plexus, cervical discopathy, or diseases of the shoulder joint, such as damage to the rotator cuff or degeneration of the shoulder [11–13]. Thus, an exact diagnosis is important for managing SNES.

The diagnosis of SNES is typically based on physical examinations and interview [14,15]. Other additional examinations for the diagnosis of SNES include imaging modalities (ultrasonography, X-ray, and computed tomography), electromyography (EMG), and assessment of conduction velocity from the neck nerve point to the supraspinatus muscles [10,16–19]. Although EMG is the gold standard for the diagnosis of SNES, shoulder magnetic resonance imaging (S-MRI) is also useful for the analysis of pathologic abnormalities of the suprascapular notch [2]. Podgórski et al. [20] reported that there are many anatomical variations in the suprascapular notch region, and the shapes of the suprascapular notch are highly diverse. In addition, the suprascapular nerve is most commonly compressed at the suprascapular notch [2]. However, few studies have investigated how morphological changes in the suprascapular notch affect the SNES. Moreover, no studies have examined the clinical optimal cut-off point of the suprascapular notch cross-sectional area (SSNCSA to diagnose SNES).

To assess the relationship between SNES and the suprascapular notch, we developed a new morphological diagnostic parameter called SSNCSA. The SSNCSA has not yet been analyzed for its correlation with SNES. We hypothesized that the SSNCSA is an important morphological parameter in the diagnosis of SNES.

Materials and Methods

Participants

This original research protocol was approved by The Catholic Kwandong University Institutional Review Board (IRB no. IS-21RISI0021). We reviewed electronic medical records of patients who had visited the shoulder orthopedic clinic with SNES from November 2015 to December 2020 and who had taken S-MRI within six months of the visit.

The SNES group included patients diagnosed with SNES by attending physicians according to their history, physical examination, and imaging modality. In addition, the final diagnosis was confirmed using EMG. Exclusion criteria were as follows: (1) history of scapular fracture, (2) history of shoulder surgery, and (3) no available S-MRI. Patients who underwent S-MRI and had no structural abnormalities were included in the control group.

The SNES group comprised 10 patients. There were 8 (80.0%) men and 2 (20.0%) women, with an average age of 43.90 ± 15.57 years (range, 18–60 years) (Table 1). To compare SSNCSA between individuals with and without SNES, we enrolled a control group consisting of individuals who wanted to undergo S-MRI for accurate diagnosis. The control group included patients with shoulder pain who wanted to undergo S-MRI. Moreover, patients in the control group did not show any abnormal findings on S-MRI. The control group comprised 10 individuals (6 men and 4 women) with a mean age of 42.70 ± 13.28 years (range, 20–73 years).

Imaging parameters

S-MRI was performed on a 3.0T MR unit (MAGNETOM Skyra; Siemens Medical Solutions, Germany) and 3T Ingina (Philips Medical Systems, The Netherlands) scanners, and T2-weighted coronal plane turbo spin-echo images were acquired from all enrolled patients. The following S-MRI sequences were used: slice plane axial, field of view of 160 × 160 cm, repetition time of 619.0 milliseconds, echo time 13.0 milliseconds, flip angle 35 degrees, slice thickness 3.00 mm, matrix size 512 × 307 pixels, number of signals averaged = 2, scan time 4 min 32 s, and 3 > echo train length.

Image analysis

SSNCSA measurements were done by a board-certified pain specialist with 15 years of experience who was blinded to the shoulder state. We obtained coronal T2-weighted turbo spin echo S-MRI images that presented the best visualization of the suprascapular nerve. We measured SSNCSA on S-MRI using our image-analysis program (INFINITT PACS, ver. 3.0; INFINITT

Table 1. Comparison of the Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control group (n = 10)</th>
<th>SNES group (n = 10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (M/F)</td>
<td>6/4</td>
<td>8/2</td>
<td>0.355</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>42.70 ± 13.28</td>
<td>43.90 ± 15.57</td>
<td>0.855</td>
</tr>
<tr>
<td>SSNCSA (mm$^2$)</td>
<td>64.50 ± 8.93</td>
<td>44.94 ± 10.40</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Values are presented as number of patients or mean ± SD. SNES: suprascapular nerve entrapment syndrome, SSNCSA: suprascapular notch cross-sectional area.
Healthcare, Seoul, Korea) (Fig. 1).

**Statistical analysis**

We compared the SSNCSA between the SNES and normal individuals using independent t-tests. Statistical significance was set at P < 0.05. Receiver operating curve (ROC) curve analysis was used to present the diagnostic values of SSNCSA in the diagnosis of SNES, and the diagnostic values included the cut-off points, area under the curve (AUC), specificity, and sensitivity. SPSS (version 22.0; IBM Inc., USA) was used to analyze the collected data.

**Results**

Demographic characteristics were not significantly different between the groups. The average SSNCSA was $64.50 \pm 8.93 \text{ mm}^2$ in the control group and $44.94 \pm 10.40 \text{ mm}^2$ in the SNES group (Table 1). Patients with SNES had significantly lower SSNCSA scores (P < 0.01) than those in the control group (Table 1). The ROC analysis showed that the best cut-off value of the SSNCSA was $57.49 \text{ mm}^2$, with 80.0% sensitivity, 80.0% specificity, and the AUC of SSNCSA was 0.92 (95% CI [0.79, 1.00]) (Table 2, Fig. 2).

**Discussion**

This pilot study aimed to determine the clinical implications of SSNCSA in SNES. The present study showed that SSNCSA of $57.49 \text{ mm}^2$ had 80.0% sensitivity and 80.0% specificity for predicting SNES. This result demonstrates that the SSNCSA could be a meaningful predictor of SNES.

SNES is a neuropathic condition in which the suprascapular nerve is compressed along the pathway. Traumatic injuries, such as clavicular fractures, scapular fractures, proximal humerus fractures, and dislocation of the acromioclavicular joint or shoulder, are common causes of suprascapular nerve damage [4,12,13,21]. Most importantly, suprascapular nerve compression most commonly occurs at the suprascapular notch, and its symptoms and signs are caused by nerve compression based on morphological

**Table 2. Sensitivity and Specificity of Each Cut-off Point of the SSNCSA**

<table>
<thead>
<tr>
<th>SSNCSA (mm$^2$)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>29.49</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>45.79</td>
<td>50.0</td>
<td>100</td>
</tr>
<tr>
<td>48.51</td>
<td>70.0</td>
<td>100</td>
</tr>
<tr>
<td>57.49*</td>
<td>80.0</td>
<td>80.0</td>
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<tr>
<td>60.63</td>
<td>90.0</td>
<td>60.0</td>
</tr>
<tr>
<td>75.88</td>
<td>100</td>
<td>10.0</td>
</tr>
</tbody>
</table>

*Best cut-off point on the receiver operating curve. SSNCSA: suprascapular notch cross-sectional area.

**Fig. 1.** Measurement of the SSNCSA (white arrow) was acquired via magnetic resonance T2 weighted images. SSNCSA: suprascapular notch cross-sectional area.

**Fig. 2.** The ROC analysis shows that the best cut-off score for SSNCSA was $57.49 \text{ mm}^2$, with a sensitivity of 80.0% and specificity of 80.0%. The SSNCSA AUC (95% CI) = 0.92 (0.79, 1.00). ROC: receiver operating curve, SSNCSA: suprascapular notch cross-sectional area, AUC: area under the curve.
changes in the suprascapular notch [2,22,23]. Structures around the suprascapular nerve can be compressed and injured by various mechanical factors. Direct compression in the suprascapular notch region (e.g., labral cyst, ganglion cyst, tumor) [11], continuous nerve irritation after rotator cuff injuries, or inflammation of the shoulder can all lead to SNES [3,24].

SNES diagnosis is based on patient history and physical examinations while ruling out other similar pathologies, including cervical radiculopathy, cervical discopathy, and various rotator cuff injuries. Imaging studies can also be used for diagnosis [14,15]. Ultrasound, X-ray, computed tomography, and MRI provide information on the suprascapular nerve and surrounding structures, helping diagnose SNES [15,25,26]. Nerve conduction velocity and EMG are the gold standards for SNES diagnosis [14]. However, nerve conduction velocity and EMG cannot be performed in all patients and the efficacy of EMG is low. Although EMG can confirm nerve conduction problems or muscle weakness, it is not useful for the differential diagnosis of various shoulder diseases. Moreover, negative EMG results cannot rule out SNES when clinical signs and symptoms are highly suspicious of SNES [14]. Therefore, MRI is more commonly performed in shoulder injury patients than EMG, and the diagnostic criteria of MRI can be a useful tool to diagnose SNES.

Even though it has been reported that SNES is more likely to occur in patients with a V-shaped or narrow suprascapular notch, a significant correlation between the suprascapular notch type and SNES has not been confirmed. Ürgüden et al. [9] reported that Rangachery types 4 and 5 of the SSN may increase the risk of suprascapular nerve injury during rotator cuff tear operations. However, no clinical studies have been conducted to prove this theory. Polgúj et al. [17] reported that the size of the suprascapular notch is a major risk factor for SNES [22]; however, there is no study to analyze suprascapular notch objectively. In other words, the narrowed suprascapular notch is considered a major morphological parameter of SNES. Therefore, we believe that analyzing the cross-sectional area of the suprascapular notch is the most important factor in the diagnosis of SNES, and we designed the present study to prove the correlation between SSNCSA and SNES.

As the bone margin of the suprascapular notch has a wavy or curved contour and multiple signal intensities within the narrowed site, it is difficult to measure. Thus, the length or thickness of the suprascapular notch is not an appropriate measurement for diagnosing SNES. Instead, the cross-sectional area of the suprascapular notch may predict SNES effectively because the SSNCSA, which measures the whole cross-sectional area of the suprascapular notch represents the space of the SSN limited by surrounding structures. This study demonstrated that SSNCSA is a good morphological measurement diagnostic tool for SNES.

This study has some limitations. First, SNES has multiple causes such as rotator cuff tears, trauma, and repetitive overhead activities. Additionally, the structures around the suprascapular nerve, such as the supraspinatus muscle, infraspinatus muscles, suprascapular ligament, suprascapular notch, and spinoglenoid notches, were not considered. However, we focused only on the suprascapular notch, where the suprascapular nerve is most commonly compressed. In future studies, we will investigate other anatomical structures that affect SNES, especially the spinoglenoid notch, where the suprascapular nerve is also commonly compressed. Second, there might be some errors in the measurements of SSNCSA on S-MRI. Although we attempted to analyze this morphologic measurement method in the best plane that presents the suprascapular notch in the coronal image section, the coronal images we measured in the section image could be inhomogeneous because of differences in the cutting level or angle in the S-MRI as a result of individual anatomical differences and technical errors. Third, there are several alternative imaging diagnostic tools to evaluate SNES, such as ultrasound examination or computed tomography; however, this study analyzed only the measurement of the SSNCSA on S-MRI. Fourth, functional instability was not analyzed because it is a subjective finding that may vary from one interpretation to another. The goal of this study was to provide objective morphological indicators. Fifth, only a small number of patients were enrolled in the study. We enrolled all patients diagnosed with SNES at our hospital; there were only 10 SNES patients. Although this pilot study investigated a small number of patients, it is valuable because it provides diagnostic criteria using S-MRI, especially SSNCSA. Sixth, since this was a retrospective study, patients who underwent S-MRI and had no structural abnormalities were enrolled in the control group. The control group might have experienced shoulder pain and may not represent the normal population. In a future study, healthy individuals should be recruited in the control group and scanned for S-MRI prospectively, and a more accurate SSNCSA of normal people can be obtained.

Despite several limitations, we present the diagnostic criteria for SNES using S-MRI for the first time, especially using SSNCSA. In addition, the present study showed that the SSNCSA can be an objective and useful diagnostic tool for SNES.

We concluded that these data strengthen the finding that SSNCSA plays a significant role in determining SNES.

Acknowledgements

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None.

**Conflicts of Interest**

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

**Author Contributions**

Jiyeon Park (Formal analysis; Investigation; Resources; Writing - review & editing)
Min-Ying Su (Writing – review & editing)
Young Uk Kim (Conceptualization; Data curation; Formal analysis; Investigation; Project administration; Supervision; Writing – original draft)

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**References**


Feasibility and efficacy of erector spinae plane block versus transversus abdominis plane block in laparoscopic bariatric surgery: a randomized comparative trial

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Background: Overweight and obesity are growing public health concerns worldwide. Bariatric surgery is a modality of weight reduction; however, postoperative pain can increase the length of hospital stay, with all the associated consequences. While regional anesthesia is an available option, the feasibility of performing abdominal wall blocks on patients with obesity is questionable.

Methods: Sixty adult patients with a body mass index of 40–50 kg/m² undergoing laparoscopic bariatric surgery were randomly assigned to receive either an ultrasound-guided transversus abdominis plane (TAP) or erector spinae plane (ESP) block. The primary outcome was the analgesic effect in the first 24 h postoperatively, assessed using the mean visual analog scale (VAS) score. Secondary outcomes were the time required for a successful block, incidence of complications, time to first rescue analgesia, time to flatus or stool passage, and total opioid consumption.

Results: The mean VAS score during the first 24 h was higher with the TAP block than with the ESP block (2.78 ± 0.34 vs. 2.32 ± 0.12, P < 0.001). Additionally, the time to first rescue analgesia was greater with the ESP block (P = 0.001) and the time required for a successful block was higher with the TAP block (P = 0.001). However, the incidence of complications, total opioid consumption, and other secondary outcomes was similar between the groups.

Conclusions: Compared with the TAP block, the bilateral ESP block is a more feasible and effective method for intra- and postoperative analgesia in patients undergoing laparoscopic bariatric surgery.

Keywords: Analgesia; Anesthesia; Bariatric surgery; Nerve block; Opioid analgesics; Pain clinics.

Introduction

Obesity and overweight are growing public health concerns worldwide [1]. Since bariatric surgery can be an efficient method for managing obesity, the number of bariatric surgeries performed worldwide is increasing, resulting in an increase in number of patients suffering from the accompanying postoperative consequences [2].

Postoperative analgesia presents various challenges in vulnerable patient groups suffer-
ing from obesity. With the high potential risk of respiratory depression and postoperative pulmonary complications associated with opioid use, such as atelectasis and pneumonia, the availability of other pain management modalities is essential [3].

Transversus abdominis plane (TAP) blocks could provide a modality for postoperative pain management as part of a multimodal pain control regimen. The subcostal approach targets the innervation of the upper abdominal wall and provides analgesia for trocar site insertion in laparoscopic surgeries [4]. However, studies on the TAP block with a range of surgical procedures have demonstrated that it may not always reliably capture the T7 and T8 dermatomes. Sensory blocks at these dermatomes are necessary to achieve analgesic satisfaction in cases of laparoscopic abdominal surgery. Therefore, the feasibility of the TAP block in patients with obesity and a lack of visceral pain control may be low [5].

The ultrasound-guided erector spinae plane (ESP) block is a novel interfascial block that provides postoperative analgesia to the abdominal wall [6]. The ESP block could offer wider abdominal wall analgesic coverage along with visceral pain control [7], which would be an advantage over the TAP block. However, the main concern with the ESP block is feasibility together with the potency of the block in challenging populations, such as patients suffering from obesity.

Both blocks could provide effective postoperative analgesia. In this study, we aimed to compare the postoperative analgesic effect and feasibility of both the TAP and ESP blocks in patients with obesity undergoing bariatric surgery.

Materials and Methods

Methods

This was a prospective, double-blind, randomized clinical trial. The institutional Research Ethics Committee of Cairo University El-Kasr Alainy Hospital approved this study (IRB no. MD-250-2020). The trial was registered on clinicaltrials.gov (Ref no. NCT 04417179) and was conducted from January 2021 to February 2022 in accordance with the Helsinki Declaration-2013. All patients who were screened and met the eligibility criteria were invited to participate in the trial, and all enrolled patients provided written informed consent. Consent was requested from patients upon arrival to the operating suite for surgery or on the ward if they were admitted the night before surgery.

The inclusion criteria were as follows: patients of any gender aged 18–60 years with American Society of Anesthesiologists physical status classifications II–III and a body mass index (BMI) of 40–50 kg/m² who did not exhibit any of the following: contraindications to peripheral regional anesthesia blocks, existing infection at the block site, contraindication to regional anesthesia, history of opiate abuse, pre-existing chronic pain or cognitive dysfunction (which would impede accurate engagement with postoperative quality of recovery and analgesia assessment), refusal of the regional block, any neurological or psychological disorders, inability to cooperate, patients scheduled for concomitant laparoscopic cholecystectomy or paraumbilical hernia repair, those with a history of previous bariatric surgery or obstructive sleep apnea, patients with anatomic abnormalities at the site of injection, and those with skin lesions or a wound at the site of proposed needle insertion.

The individual indications for surgery were laparoscopic bariatric surgery, that is, sleeve gastrectomy and/or Roux-en-Y gastric bypass (RYGB) surgery.

The patients were assigned to one of the trial groups using a computer-generated random number table. Patients with even numbers were allocated into the ESP block group and those with odd numbers were allocated into the TAP block group. The patient study code number and group allocation were typed on separate pages, folded, and concealed in sequentially numbered, sealed envelopes. Block randomization in groups of six individuals was applied to ensure an even number in each group as the study progressed. The groups were named “ESP” and “TAP”. An independent third party held the randomization key. Both patients and anesthetists involved in postoperative data collection were blinded to the group to which the patients were allocated.

Upon arrival in the operating room, perioperative monitoring, which included continuous electrocardiogram (GE-Datex Ohmeda 5-lead ECG cable, USA), pulse oximetry (GE-Datex Ohmeda finger SpO₂ sensor), and non-invasive arterial blood pressure (GE-Datex Ohmeda NIBP cuff), were initiated. Baseline vital signs were recorded, including non-invasive measurements of systolic, mean, and diastolic arterial pressures, and HR and oxygen saturation. After intravenous (IV) access, the patient was premedicated with metoclopramide at 0.1–0.2 mg/kg. The patient was randomly assigned to one of two groups according to the intervention used: Group A (30 patients), which received the TAP block, and Group B (30 patients), which received the ESP block.

Both blocks were performed by the primary investigator and supervised by consultant anesthesiologists who had experience in regional anesthesia and were familiar with the ESP and TAP blocks. Additionally, prior to the administration of either block, 1 mg of IV midazolam and 5 ml of lidocaine 1% infiltration were administered on both sides at the site of the block needle injection.
Ultrasound-guided blocks were performed under full aseptic conditions according to randomization before the surgery. All patients received bupivacaine 0.25% at a total volume of 40 ml regardless of the block they received. All blocks were performed with a blunted tip, 20-gauge, short bevel needle (Pajunk Sonoplex, Germany) using the same ultrasound machine (high-frequency linear ultrasound transducer, Siemens Acuson x300 3–5 MHz ultrasound), which was placed in a sterile cover.

The patients randomized to the ESP group were first placed in the prone position. The ESP block was then performed using a high-frequency linear ultrasound transducer that was placed sagittally against the target vertebral level (T5 transverse process) in the prone position and moved approximately 3 cm laterally to the spinous process. The erector spinae muscle and transverse process were then identified, and a blunted tip, 20-gauge, short bevel needle (Pajunk Sonoplex, Germany) was advanced using the in-plane approach in a cephalad-to-caudal direction through the interfascial plane between the erector spinae and the underlying transverse process under strict aseptic precautions until the tip had been advanced deep into the erector spinae muscle, as evidenced by visible hydro-dissection below the muscle plane and a 5-ml injection of normal saline to confirm the correct needle position. The block was performed bilaterally by injecting 40 ml of 0.25% bupivacaine (20 ml on each side) into the fascial plane between the deep surface of the erector spinae muscle and transverse processes of the lumbar vertebrae laterally (at the most lateral part of the transverse process).

Patients randomized to the TAP group were placed in the supine position. The TAP block was then administered using a high-frequency linear ultrasound transducer. After skin preparation and isolation, the transducer was placed 2 cm subxiphoidian and moved along the subcostal edge to identify the rectus abdominis muscle and transversus abdominis. Once these structures were identified, a blunted-tip, 20-gauge, short bevel needle (Pajunk Sonoplex, Germany) was introduced using the in-plane approach 2–3 cm laterally to the transducer under direct ultrasound visualization, and 1–2 ml of saline was injected between the rectus abdominis and transversus abdominis muscles. After confirming the correct placement of the needle and negative aspiration probe, the rest of the anesthetic was injected along the subcostal line in the TAP (20 ml 0.25% bupivacaine), and dissection of the plane was observed. The block was performed bilaterally. A total of 20 ml of 0.25% bupivacaine was injected on each side after aspiration to avoid intravascular placement.

Thirty minutes after performing each block, all patients received general anesthesia induced with fentanyl (1.5 g/kg) based on lean body weight (maximum dose of 200 g), and propofol (2 mg/kg) was administered based on total body weight. Tracheal intubation was facilitated with 0.5 mg/kg of atracurium based on the ideal body weight. Anesthesia was maintained using isoflurane in oxygen and air. Additional doses of 0.1 mg/kg atracurium were administered every 30 min. A urinary catheter was placed to control diuresis. Surgical intervention was permitted 20 min after completion of the block procedure. Volume-controlled ventilation was adjusted to maintain normocapnia. Anesthesia was maintained using 1–1.5% isoflurane in a mixture of oxygen and air (50/50) and atracurium top-ups at a dose of 0.1 mg/kg every 30 min. All participants were then administered 1 g of IV paracetamol (maximum dose of 4 g/24 h) together with 4 mg of ondansetron 10 min prior to the end of surgery for postoperative nausea and vomiting prophylaxis.

After skin closure, the inhaled anesthesia was discontinued and muscle relaxation was reversed with IV atropine (0.02 mg/kg) and neostigmine (0.05 mg/kg) after the return of spontaneous breathing. Patients were transferred to the post-anesthesia care unit (PACU) for 60 min for complete recovery and monitoring.

If at any point hypotension occurred (defined as a decrease in mean arterial pressure > 25% from the baseline value or systolic arterial pressure of 100 mmHg), it was treated with 5 mg of IV bolus ephedrine, which was repeated every 3 min until the hypotension resolved. Bradycardia (defined as an HR of 40 beats/min) was treated with intravenous atropine (0.5 mg).

In the PACU, the visual analog scale (VAS) score was assessed 15 min after extubation by the attending anesthetist. When the score was ≥ 4/10, rescue analgesia in the form of naltubuphine 0.1 mg/kg (individual dose not to exceed 20 mg and a maximum dose of 50 mg/24 h) was administered. Another dose of naltubuphine 0.1 mg/kg was given in the PACU to patients with a VAS score > 4 30 min after the first dose.

After discharge from the PACU, the analgesia plan was intravenous paracetamol (1 g/8 h), naltubuphine (0.1 mg/kg/8 h) if the VAS score was ≥ 4, and ketorolac as a second rescue analgesia (0.5 mg/kg/6 h) as long as the pain score remained ≥ 4 (reassessment was done by the nurses in the ward 30 min after administration of the first rescue analgesia).

The primary outcome was the analgesic efficacy of the ESP block versus the TAP block, as assessed by the mean VAS score in the first 24 h postoperatively.

Secondary outcomes were as follows: the time required for a successful block (measured as the time from initiation of ultrasound scanning to completion of the block on both sides), incidence of complications, time to first rescue analgesia, time to first flatus or stool passage, and total opioid consumption.
Statistical analysis

In a previous study [9], the mean VAS in the TAP block group in the first 24 h was 3.34 ± 0.66 at rest and 4.46 ± 0.85 for dynamic postoperative pain. We calculated the sample size that could detect a mean difference of 20% between the study groups. MedCalc software (version 14; MedCalc Software Bvba, Belgium) was used to calculate the sample size. Fifty patients (25 patients per group) were estimated to have a study power of 80% and an alpha error of 0.05. This number was increased to 60 patients (30 per group) to account for possible dropouts. Data were coded and entered using the Statistical Package for the Social Sciences (SPSS) (version 26; IBM Corp., USA). Data were summarized using the mean ± SD for quantitative variables and frequencies (number of cases) and relative frequencies (percentages) for categorical variables. The Shapiro-Wilk test was used to assess data normality. Comparisons between groups were performed using the unpaired t-test. To compare categorical data, the chi-squared test was used. Statistical significance was set at P < 0.05.

Results

The Consolidated Standards of Reporting Trials (CONSORT) flow diagram for this trial is shown in Fig. 1. Seventy patients were initially screened for eligibility, 60 of which met the inclusion criteria and were randomly assigned to receive either the ESP block or TAP block. All enrolled patients were followed up successfully, and no patients were lost to follow-up.

Patient and surgical baseline data

Baseline patient data and the type of bariatric surgery were comparable between the groups apart from the STOP BANG score, which was higher in ESP compared TAP (P = 0.035) (Table 1).

Profile of monitoring and adverse events

Patient hemodynamics for each group are shown in Tables 2 and 3. There were no statistically significant differences in the patients' hemodynamics between the groups. In addition, patients who received the TAP block at 10 min after induction showed a significantly higher heart rate than those who received ESP at the same time point (P = 0.008). Adverse events were reported as incidents over the 24-h observation period of the study. There were no adverse events related to the regional anesthesia techniques used in either group.

Pain assessment based on the VAS score (primary outcome)

The patients' assessment of pain according to VAS scores after extubation is shown in Table 4. A statistically significant difference was found between the two groups, with a higher VAS score in the TAP than in the ESP block group in the period between 5 min to 30 min after extubation and at 18 and 24 h post-extubation, with a higher mean VAS score in the TAP block group in the first 24 h postoperatively compared to the ESP block group (P < 0.001).

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Fig. 1. CONSORT flow diagram for this study.

https://doi.org/10.4097/kja.22169
Secondary outcomes, such as the time to first rescue analgesia, total opioid consumption, and time of peristalsis between the two groups are shown in Table 5. The results were statistically significant for intestinal peristalsis, which was delayed more with the TAP than with the ESP block (P < 0.001). Additionally, the time to first rescue analgesia was longer with the ESP than with the TAP block (P = 0.001), the total nalbuphine consumption was lower with the ESP than with the TAP block (P < 0.001), and the time required for a successful block was higher with the TAP than with the ESP block (P = 0.001).

Discussion

This is the first randomized controlled study comparing the ESP and the TAP blocks in patients with obesity undergoing laparoscopic bariatric surgery. The main finding of our study was that the ESP block showed a better analgesic effect, with lower postoperative opioid consumption than the TAP block. Moreover, those in the ESP block group regained intestinal function earlier than those in the TAP block group, as indicated by the time to flatus or stool passage; however, the results regarding intraoperative hemodynamics were similar between the groups.

Consistent with our findings, Altıparmak et al. [8] found that an ultrasound-guided ESP block reduced postoperative tramadol...
Table 3. Comparison of Heart Rate

<table>
<thead>
<tr>
<th>Variable</th>
<th>ESP group</th>
<th>TAP group</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0 HR</td>
<td>85.30 ± 13.90</td>
<td>86.90 ± 11.10</td>
<td>-8.10, 4.90</td>
<td>0.624</td>
</tr>
<tr>
<td>T1 HR</td>
<td>85.93 ± 12.13</td>
<td>88.07 ± 8.67</td>
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<td>0.437</td>
</tr>
<tr>
<td>T5 HR</td>
<td>79.87 ± 10.22</td>
<td>84.37 ± 10.40</td>
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<td>0.096</td>
</tr>
<tr>
<td>T10 HR</td>
<td>76.17 ± 8.61</td>
<td>82.03 ± 7.97</td>
<td>-10.16, -1.58</td>
<td>0.008*</td>
</tr>
<tr>
<td>T20 HR</td>
<td>78.30 ± 10.52</td>
<td>80.70 ± 7.97</td>
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<td>0.323</td>
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<tr>
<td>T30 HR</td>
<td>78.97 ± 9.95</td>
<td>81.00 ± 8.00</td>
<td>-6.70, 2.63</td>
<td>0.387</td>
</tr>
<tr>
<td>T40 HR</td>
<td>79.87 ± 10.22</td>
<td>84.37 ± 10.40</td>
<td>-9.83, 0.83</td>
<td>0.096</td>
</tr>
<tr>
<td>T50 HR</td>
<td>78.40 ± 10.25</td>
<td>80.87 ± 7.97</td>
<td>-7.13, 2.20</td>
<td>0.294</td>
</tr>
<tr>
<td>T60 HR</td>
<td>79.23 ± 8.63</td>
<td>80.80 ± 8.52</td>
<td>-6.00, 2.87</td>
<td>0.482</td>
</tr>
<tr>
<td>Te0 HR</td>
<td>86.33 ± 8.70</td>
<td>88.53 ± 6.37</td>
<td>-6.14, 1.74</td>
<td>0.268</td>
</tr>
<tr>
<td>Te5 HR</td>
<td>84.40 ± 8.17</td>
<td>85.73 ± 7.47</td>
<td>-5.38, 2.71</td>
<td>0.512</td>
</tr>
<tr>
<td>Te10 HR</td>
<td>80.37 ± 7.50</td>
<td>84.37 ± 8.46</td>
<td>-8.13, 0.13</td>
<td>0.058</td>
</tr>
<tr>
<td>Te15 HR</td>
<td>79.83 ± 9.34</td>
<td>83.10 ± 7.82</td>
<td>-7.72, 1.18</td>
<td>0.147</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. T0–60 HR: heart rate from the time of induction of anesthesia to 60 min after induction (beats/min), Te0–15 HR: heart rate at the time of extubation to 15 min after extubation (beats/min), ESP: erector spinae plane block, TAP: transversus abdominis plane block. *represents statistical significance.

Table 4. Comparison of VAS Scores

<table>
<thead>
<tr>
<th>Variable</th>
<th>ESP group</th>
<th>TAP group</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS 5 min</td>
<td>2.37 ± 0.67</td>
<td>3.00 ± 1.11</td>
<td>-1.11, -0.16</td>
<td>0.010*</td>
</tr>
<tr>
<td>VAS 10 min</td>
<td>2.40 ± 0.77</td>
<td>3.20 ± 1.24</td>
<td>-1.33, -0.27</td>
<td>0.004*</td>
</tr>
<tr>
<td>VAS 15 min</td>
<td>2.50 ± 0.73</td>
<td>3.30 ± 1.37</td>
<td>-1.37, -0.23</td>
<td>0.007*</td>
</tr>
<tr>
<td>VAS 20 min</td>
<td>2.53 ± 0.73</td>
<td>3.37 ± 1.50</td>
<td>-1.44, -0.22</td>
<td>0.009*</td>
</tr>
<tr>
<td>VAS 25 min</td>
<td>2.37 ± 0.56</td>
<td>2.97 ± 1.16</td>
<td>-1.07, -0.13</td>
<td>0.014*</td>
</tr>
<tr>
<td>VAS 30 min</td>
<td>2.37 ± 0.56</td>
<td>2.73 ± 0.69</td>
<td>-0.69, -0.04</td>
<td>0.028*</td>
</tr>
<tr>
<td>VAS 2 h</td>
<td>2.30 ± 0.47</td>
<td>2.47 ± 0.57</td>
<td>-0.44, 0.10</td>
<td>0.221</td>
</tr>
<tr>
<td>VAS 4 h</td>
<td>2.30 ± 0.65</td>
<td>2.57 ± 0.73</td>
<td>-0.62, 0.09</td>
<td>0.140</td>
</tr>
<tr>
<td>VAS 8 h</td>
<td>2.27 ± 0.69</td>
<td>2.50 ± 0.63</td>
<td>-0.58, 0.11</td>
<td>0.177</td>
</tr>
<tr>
<td>VAS 12 h</td>
<td>2.30 ± 0.79</td>
<td>2.40 ± 0.62</td>
<td>-0.47, 0.27</td>
<td>0.589</td>
</tr>
<tr>
<td>VAS 18 h</td>
<td>2.10 ± 0.48</td>
<td>2.47 ± 0.63</td>
<td>-0.66, -0.08</td>
<td>0.014*</td>
</tr>
<tr>
<td>VAS 24 h</td>
<td>2.10 ± 0.48</td>
<td>2.43 ± 0.63</td>
<td>-0.62, -0.04</td>
<td>0.025*</td>
</tr>
<tr>
<td>Mean</td>
<td>2.32 ± 0.12</td>
<td>2.78 ± 0.34</td>
<td>0.32, 0.59</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. VAS 5–30: visual analog scale score from 5 min after extubation to 30 min after extubation, VAS 2–24 h: visual analog scale score from 2 h after extubation to 24 h after extubation, ESP: erector spinae plane block, TAP: transversus abdominis plane block. *represents statistical significance.

Table 5. Comparison of Secondary Outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>ESP group</th>
<th>TAP group</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to first rescue analgesia (h)</td>
<td>7.2 ± 1.56</td>
<td>5.3 ± 2.8</td>
<td>-3.07, -0.72</td>
<td>0.001</td>
</tr>
<tr>
<td>Total nalbuphine consumption (mg)</td>
<td>12.34 ± 2.16</td>
<td>16.87 ± 3.21</td>
<td>3.11, 5.94</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Time to first flatus or stool passage (h)</td>
<td>15.33 ± 1.03</td>
<td>17.33 ± 1.58</td>
<td>1.31, 2.68</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Time for a successful block (min)</td>
<td>9.50 ± 4.64</td>
<td>13.60 ± 4.66</td>
<td>1.69, 6.5</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. ESP: erector spinae plane block, TAP: transversus abdominis plane block.

Consumption and pain scores more effectively than did the oblique subcostal TAP block after laparoscopic cholecystectomy. In addition, the results of a study comparing the ESP and the TAP blocks in patients with obesity undergoing sleeve gastrectomy were consistent with our results regarding the superior analgesic effect of the ESP block [9]. The most striking difference between these studies and ours was that in these studies, the feasibility of each block (especially in

https://doi.org/10.4097/kja.22169
challenging populations such as patients with obesity) was not investigated. Additionally, the authors used tramadol and pethidine as postoperative pain control modalities rather than nalbuphine, which is considered to have a potent analgesic effect with a low incidence of adverse events [10].

According to another study [11], the TAP block and trocar site infiltration provide comparable pain relief in patients undergoing laparoscopic bariatric surgery. Because of its faster application and fewer side effects, we believe that the ESP block could be a potent, time-saving, and highly successful pain control method in patients undergoing laparoscopic bariatric surgery. This could result in a faster application, similar to trocar site infiltration, with a better analgesic effect.

On the other hand, Mittal et al. [12] found that the ultrasound-guided TAP block is a feasible, minimally invasive technique and can be part of effective multimodal analgesia in morbidly obese patients undergoing bariatric surgery. However, in that study, TAP blocks were compared with a control group with only systemic analgesia. In contrast, our study compared the TAP block to the ESP block and found that both were effective, but the ESP block showed a more potent analgesic effect. Our study also showed that less time was needed to perform the ESP block than the TAP block, and this time difference was clearly notable in our study due to the higher mean BMI in such a challenging population.

Additionally, Keller et al. [13] conducted a pilot study on the feasibility and learning curve associated with TAP blocks in patients with obesity and showed that novices reach appropriate time to perform a successful block with progressively less coaching to place TAP blocks safely and efficiently. However, the duration of the procedure can be prolonged in patients with extreme BMIs and prior abdominal surgery, potentially resulting in the need for additional coaching to facilitate placement. When we compared the time required for a successful TAP block in Keller et al.'s study with the time required to perform a successful ESP block in our study, it was clear that the ESP required less time than the TAP block, not to mention the patients' BMIs were clearly higher in our study.

Our study also showed, for the first time, a difference in the time to flatus or stool passage between the two groups, which could be explained by the sympathetic blockage associated with the ESP block. While the ESP block has been used to treat paralytic ileus [14], to the best of our knowledge, no previous studies have investigated whether the time to regain proper intestinal function is shorter with this block, which could result in a shorter hospital stay.

Our study also had some limitations. First, the results of intraoperative hemodynamics may be affected by other variables, such as duration of surgery, surgeons' skills, and manipulations during surgery such as bougie insertion. Furthermore, there were no data available to compare preoperative baseline pain and anxiety scores with postoperative scores; however, the VAS score was applied equally to both randomized groups. In addition, there was heterogeneity in the type of surgery between the two groups, with a higher percentage of patients undergoing RYGB compared to sleeve gastrectomy surgery in the ESP group than in the TAP group; however, we believe that it did not have an impact on the results, as the difference was not statistically significant, and the resemblance to the trocar site insertion in RYGB and sleeve gastrectomy surgeries would cause similar degrees of postoperative pain.

In conclusion, the bilateral ESP block is a more feasible and effective method for intra- and postoperative analgesia in patients undergoing laparoscopic bariatric surgery than the bilateral TAP block.

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**Conflicts of Interest**

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

**Author Contributions**

Mohamed Elshazly (Data curation; Formal analysis; Investigation; Methodology; Supervision; Writing – original draft; Writing – review & editing) Yasser Mohamed EL-Halafawy (Methodology) Dina Zakaria Mohamed (Methodology) Khaled Abd El Wahab (Investigation; Writing – original draft; Writing – review & editing) Tamer Mohamed Kheir Mohamed (Data curation)

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References

Determination of the 95% effective dose of remimazolam to achieve loss of consciousness during anesthesia induction in different age groups

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**Background:** Remimazolam is a new ultra short-acting benzodiazepine originally developed as an improved version of midazolam. Recent studies have demonstrated non-inferiority of remimazolam to propofol in general anesthesia. However, to date, few studies have investigated the induction bolus dose of remimazolam required to achieve general anesthesia. We aimed to determine the 95% effective dose ($ED_{95}$) of remimazolam bolus required to achieve loss of consciousness (LOC) and the appropriate doses for different age groups.

**Methods:** Patients aged 20–79 years with the American Society of Anesthesiologists physical status of I or II were enrolled in this study. A total of 120 patients were included representing young, middle-aged, and elderly groups. Loss of eyelash reflex and verbal response after the administration of remimazolam was considered successful LOC. The $ED_{95}$ of remimazolam was determined using a biased coin up-and-down design with sequential allocation and the isotonic regression method.

**Results:** The $ED_{95}$ of remimazolam for induction of general anesthesia was 0.367 mg/kg (95% CI [0.277, 0.392]) in the young group, 0.369 mg/kg (95% CI [0.266, 0.394]) in the middle-aged group, and 0.249 mg/kg (95% CI [0.199, 0.288]) in the elderly group. During the study period, none of the patients required rescue medications for hypotension or bradycardia.

**Conclusions:** This study investigated the $ED_{95}$ of remimazolam bolus for anesthesia induction. The precise dosing of the $ED_{95}$ can help maintain hemodynamic stability during the induction of anesthesia.

**Keywords:** General anesthesia; Hypnotics and sedatives; Intravenous anesthesia; Remimazolam; Unconsciousness; Vital signs.

**Introduction**

Intravenous anesthetics are some of the most commonly used sedative induction agents because of their ease of delivery and swift onset as they rapidly diffuse from the blood to the brain without concerns regarding airborne contamination that may be associated with inhalation anesthetics [1,2]. Propofol is currently the most popular intravenous anesthetic, but it has been reported to produce adverse effects such as hemodynamic instability, respiratory depression, and injection pain [3–6]. Compared to propofol, midazolam causes less hemodynamic depression and produces anterograde amnesia; however, its slow, variable induction time and accumulation of active metabolites make it...
inferior for general anesthesia [7–9].

Remimazolam was designed considering these shortcomings of midazolam. It is an ultra-short-acting benzodiazepine that produces equivalent sedative effects but is rapidly hydrolyzed in the body to an inactive metabolite. Consequently, remimazolam exhibits a shorter and more predictable duration of action than the current benzodiazepines [10–13]. In recent studies, the non-inferiority of remimazolam to propofol has been demonstrated in general anesthesia [14,15]. Several studies have reported the remimazolam dose for loss of consciousness (LOC) that was calculated from the continuous infusion of remimazolam (6 and 12 mg/kg/h) [15,16]. However, in clinical practice, anesthesia is commonly induced by a single bolus injection of intravenous sedatives. To date, few studies have explored the required induction bolus dose of remimazolam for general anesthesia [17]. This study aimed to investigate the 95% effective dose (ED$_{95}$) of remimazolam bolus for LOC and determine the appropriate doses for different age groups.

**Materials and Methods**

This study was approved by the Institutional Review Board of Ajou University Hospital (IRB no. AJIRB-MED-INT-21-521) and was registered at Clinical Research Information Service (CRIS no. KCT0006866). The study was conducted at a tertiary medical center, between December 2021 and March 2022. All patients were provided with adequate information regarding the study, and written informed consent was obtained from all patients. This study was conducted in accordance with the Helsinki Declaration-2013.

**Patients**

Patients aged 20–79 years with an American Society of Anesthesiologists physical status (ASA-PS) I or II, who were scheduled to receive general anesthesia were enrolled in this study. Patients were stratified into different age groups: young (20–39 years), middle-aged (40–59 years), and elderly (60–79 years) groups, with 40 patients enrolled in each group. The exclusion criteria were as follows: 1) body mass index > 30 kg/m$^2$ or < 20 kg/m$^2$, 2) allergy to benzodiazepines, 3) use of opioids, alcohol, benzodiazepines, and over-the-counter sleep aids, 4) communication difficulties (e.g., history of hearing disability, mental disorder, or cognitive impairment), and 5) pregnancy.

**Anesthesia**

No premedication was administered prior to induction, and as the patients were transferred to the operating room, standard monitors were applied. To monitor vital signs, non-invasive blood pressure, electrocardiography, and pulse oximetry were performed. In addition, a bispectral index (BIS) monitor (A-2000$^{TM}$, Aspect Medical Systems, USA) was used to assess the depth of anesthesia. Before induction of anesthesia, each patient performed spontaneous breathing with 100% oxygen for pre-oxygenation. Remimazolam was prepared at 1 mg/ml, and its predetermined dose was administered as a bolus intravenous injection using a syringe pump by an anesthesiologist who calculated its induction dose. The other anesthesiologist, who was blinded to the dose of remimazolam, checked for LOC in the patient over 3 min. No additional agents were administered during this period. If the patient’s mean arterial blood pressure (MAP) was < 65 mmHg during induction, 4 mg of ephedrine was administered. If a heart rate (HR) of < 50 beats per min was observed, atropine (0.5 mg) was used. Loss of eyelash reflex and verbal response after bolus administration of remimazolam was considered successful LOC. After the end of the 3-min study period, we used an inhalation agent, an opioid analgesic, and a neuromuscular blocking agent to obtain deeper analgesia and muscle relaxation for endotracheal intubation. The baseline MAP, HR, oxygen saturation, and BIS of all patients were recorded prior to remimazolam administration (T0), and these parameters were also recorded at 1 min (T1) and 3 min after administration (T2).

We used a biased coin up-and-down method to determine the ED$_{95}$ of remimazolam [18,19]. According to a previous study, patients who received continuous intravenous remimazolam at 6 and 12 mg/kg/h, successfully achieved LOC, and the accumulated mean dose ± SD was 0.17 ± 0.04 mg/kg and 0.29 ± 0.08 mg/kg, respectively [15]. With reference to this study, an initial dose of 0.2 mg/kg was used for all groups. The next dose of remimazolam was determined according to the success or failure of induction in the previous patient. The increase or decrease in the next dose was set at 0.05 mg/kg. If the first patient failed to achieve LOC, the dose of remimazolam for the next patient was increased by 0.05 mg/kg. If the induction was successful, the next patient’s dose was determined by a randomly selected card. In total, 19 cards were prepared, and the same dose was administered with a probability of 18/19 (= 0.95), and with a probability of 1/19 (= 0.05), the dose for the next patient was decreased by 0.05 mg/kg.

**Statistical analysis**

In the biased coin up-and-down method, the behavior of the estimated parameters can be stabilized with 40 participants using
the Monte Carlo simulation [20]. Therefore, we enrolled 40 patients in each group.

Data are presented as mean ± SD or number of patients. Continuous variables were analyzed using one-way analysis of variance (ANOVA) or the Kruskal–Wallis test, depending on the normality test results. The normality of all continuous variables, except for the ED95, was assessed using the Shapiro–Wilk test. Categorical variables were analyzed using the chi-square test. Hemodynamic and BIS variables were analyzed using one-way repeated-measures ANOVA. Subsequently, post-hoc analysis using a paired sample t-test was performed to determine whether there was a within-group difference in the hemodynamic and BIS variables from the baseline.

The ED95 was determined using isotonic regression with a pooled adjacent violators algorithm (PAVA) to adhere to prediction in a monotonically increasing dose–effect relationship, and a bootstrapping approach was used to produce 95% CIs for estimation [19]. Statistical analyses were performed using R Statistical Software (version 4.05; R Foundation for Statistical Computing, Austria) and analyses of the hemodynamic results were only performed for patients that were successful in achieving LOC. Statistical significance was set at P < 0.05.

Results

The young, middle-aged, and elderly groups included 40 patients each. Hence, a total of 120 patients were analyzed (Fig. 1). The demographic characteristics of the patients are shown in Table 1. The characteristics were generally similar among the three groups, except for the mean age and ASA-PS score. The elderly group had a significantly higher percentage of patients with ASA-PS II, than the young and middle-aged groups. ASA-PS II comprised of 5, 40, and 70%, in the young, middle-aged, and elderly groups, respectively.

![Fig. 1. CONSORT flow diagram of this study.](https://doi.org/10.4097/kja.22331)

### Table 1. Demographic Data

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Young group (n = 40)</th>
<th>Middle-aged group (n = 40)</th>
<th>Elderly group (n = 40)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>29.5 ± 5.8</td>
<td>49.7 ± 5.4</td>
<td>66.6 ± 5.3</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>19/21</td>
<td>24/16</td>
<td>18/22</td>
<td>0.356</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.1 ± 11.6</td>
<td>66.2 ± 11.6</td>
<td>64.7 ± 10.7</td>
<td>0.405</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.8 ± 9.2</td>
<td>166.2 ± 8.3</td>
<td>161.8 ± 8.8</td>
<td>0.024</td>
</tr>
<tr>
<td>BMI</td>
<td>24.3 ± 2.5</td>
<td>23.8 ± 2.6</td>
<td>24.6 ± 2.8</td>
<td>0.376</td>
</tr>
<tr>
<td>ASA-PS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>38 (95.0)</td>
<td>24 (60.0)</td>
<td>12 (30.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>II</td>
<td>2 (5.0)</td>
<td>16 (40.0)</td>
<td>28 (70.0)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number (%). BMI: body mass index, ASA-PS: American Society of Anesthesiologists physical status.
The sequences for success and failure of LOC during anesthesia induction by predetermined bolus dose of remimazolam are shown in Fig. 2 for each group according to the biased coin up-and-down method. The adjusted success rates from the PAVA are depicted in Fig. 3. The ED_{95} of remimazolam required for LOC using isotonic regression was 0.367 mg/kg (95% CI [0.277, 0.392]) in the young group, 0.369 mg/kg (95% CI [0.266, 0.394]) in the middle-aged group, and 0.249 mg/kg (95% CI [0.199, 0.288]) in the elderly group (Table 2). The ED_{95} values overlapped at the 95% CI level, resulting in no significant difference between the groups.

Intra-group analysis involved comparing each MAP at 1 and 3 min after administration with that at baseline. MAP decreased significantly compared to baseline throughout the 3-min study period in each group (Fig. 4A). HR in all three groups increased at 1 min and 3 min after administration, compared to baseline values (Fig. 4B). During the 3-min of this study, none of the patients experienced hypotension or bradycardia that required rescue medications. Compared to baseline, BIS values at 1 and 3 min after administration were significantly reduced in all three groups, indicating adequate depth of anesthesia (Fig. 4C). BIS values at 3 min were 59.14 (± 7.25), 58.8 (± 7.91), and 59.92 (± 9.05) in the young, middle-aged, and elderly groups, respectively. No adverse events including injection pain were reported during the study period.

**Discussion**

Using the biased coin up-and-down method, we observed that
Table 2. The ED₉₅ with 95% CI of Remimazolam for LOC Using Isotonic Regression in Each Group

<table>
<thead>
<tr>
<th>Group</th>
<th>Young (n = 40)</th>
<th>Middle-aged (n = 40)</th>
<th>Elderly (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ED₉₅ (mg/kg)</td>
<td>0.367</td>
<td>0.369</td>
<td>0.249</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.277, 0.432</td>
<td>0.266, 0.394</td>
<td>0.199, 0.288</td>
</tr>
</tbody>
</table>

The ED₉₅ values overlapped at 95% CI. No significant differences were observed between the groups. ED₉₅: 95% effective dose, LOC: loss of consciousness.

The ED₉₅ of remimazolam required to achieve LOC was 0.367 mg/kg in the young group, 0.369 mg/kg in the middle-aged group and 0.249 mg/kg in the elderly group, demonstrating that the required dose of remimazolam was reduced in the old age group compared to the younger groups. However, the ED₉₅ values overlapped at the 95% CI, and the null hypothesis of equal effective doses was not rejected at an α value of 0.05. Remimazolam induction showed a trend of gradual decline in MAP and an increase in HR. However, MAP and HR were within the clinically normal range, and no patients required vasoactive medications. Consequently, the remimazolam used for induction did not cause significant hemodynamic depression.

In previous studies, continuous infusion of remimazolam for general anesthesia induction resulted in a statistically longer time to achieve LOC compared to single dose propofol induction. For example, a multicenter phase IIb/III trial revealed that the mean time to LOC in the continuous remimazolam 6 and 12 mg/kg/h groups were 102 and 88.7 s, respectively, whereas the propofol bolus group achieved LOC at 78.7 s, indicating that the propofol group had a shorter time to LOC [15]. This difference in onset time is thought to be caused by different methods of drug application. In practice, in the field of anesthesia, intravenous sedatives are usually administered as a single bolus dose to rapidly achieve high drug concentrations and then maintain adequate drug concentrations with subsequent continuous infusions [21]. That is why we sought to determine a single bolus dose of remimazolam to deliver the drug in a more practical, simple, and fast way. In this study, the time to achieve LOC when remimazolam was administered as a bolus was not measured, but it is likely to be faster than the time taken by the continuous infusion method in previous studies.

This study also evaluated the hemodynamic stability after single-bolus dose remimazolam induction in different age groups. In previous studies, the incidence of adverse events, such as hypotension, bradycardia, and low oxygen saturation, was significantly lower in the continuous remimazolam infusion group than in the propofol group [14,22,23]. Our study findings are consistent with those of previous studies as bolus administration of remimazolam did not induce hypotension or bradycardia across various age groups. As described above, although remimazolam induces less hypotension than propofol, a recent study reports that the incidence of hypotension increases as the dose of remimazolam increases [17]. This result justifies our study findings as selecting an appropriate dose considering other requirements, such as age, can reduce the possibility of hypotension. Therefore, we conclude that a single dose of remimazolam after precise dosing of the ED₉₅ value can help maintain hemodynamic stability, even in elderly patients. Regarding the effect of remimazolam on HR, although previous studies have consistently shown that remimazolam is much less likely to cause bradycardia than propofol, the pattern of HR changes over time with remimazolam has not been clearly documented [14,17,22,23]. In this 3-min study conducted after remimazolam bolus without other anesthetics, remimazolam did not cause severe tachycardia, but HR significantly increased compared to that at baseline in all groups. Therefore, sufficient attention is required for the increase in HR caused by remimazolam.

In general, the estimation of the dose for new agents is aimed at the minimum dose, which provides a 50% probability of response (effective dose 50, ED₅₀). The Dixon and Mood up-and-down method that targets the ED₅₀ is commonly used for dose-finding studies of fast response drugs such as anesthetics [19,24]. In a previous study, the estimation of the remimazolam dose to achieve LOC was a mean dose [15]. However, it is important to identify the ED₉₅ to determine the dose of drugs for anesthesia [24], as...
50% efficacy is an inappropriately low threshold for anesthesia. The biased coin up-and-down method generalized the Dixon and Mood up-and-down method as it finds ED values for other quantiles using modifications to the dose assignment rule and is commonly utilized for calculating the ED_{95} of anesthetics. To determine a dose such as the ED_{95}, the biased coin uses a probability of 1/19 (≈ 0.05). In this method, the doses are allocated sequentially based on the responses of the previous patient. In detail, doses are increased after an identification of negative response (failure of LOC), indicating that the current dose is not sufficient. However, following a positive response (success of LOC), the next patient is randomized with a probability of 0.05 to the next lower dose and with a probability of 0.95 to the same dose. Examples of the biased coin up-and-down method in anesthesia to find an ED_{95} dose can be found in numerous studies [25–29]. Therefore, we used this method to investigate the ED_{95} of remimazolam.

As life expectancy is increasing globally, the proportion of elderly individuals requiring surgery is also increasing. Elderly patients scheduled for surgery pose a challenge as anesthesiologists frequently need to titrate anesthetic drug doses to account for the physiology of older individuals. These concerns are valid for all anesthetic drugs, and a phase I study, ONO-2745-01, conducted in Japan evaluated the pharmacokinetics and pharmacodynamics of an intravenous bolus of remimazolam in young adults (aged 20–45 years) and elderly individuals (aged 65–74 years) [30]. No difference in pharmacokinetics was observed between the young and elderly groups, but a small pharmacodynamic effect related to increased age was identified (i.e., shorter onset of LOC and longer...
duration of sedation in the elderly group). In this study, we used elderly patients to determine the ED$_{95}$ of remimazolam for induction and found that the results showed a decreasing trend in elderly patients.

This study had several limitations. First, the study was designed to evaluate the success and failure of LOC for only 3 min after remimazolam administration without any additional anesthetics, such as opioids or neuromuscular blocking agents. Therefore, the interaction of remimazolam with other anesthetic agents, as well as the hemodynamic stability after 3 min, was not evaluated. Second, we enrolled relatively healthy patients (ASA-PS I and II). Patients with severe comorbidities may exhibit different sensitivities to remimazolam; therefore, subsequent studies are required to confirm the safety and efficacy of remimazolam in such patients. Third, we used the biased coin up-and-down method to select the sample size, and 40 patients was the minimum number required. Although our results were consistent with those of previous studies, we suggest that studies involving larger cohorts will help to determine a more accurate dose of the ED$_{95}$.

In conclusion, the ED$_{95}$ of remimazolam bolus for LOC in general anesthesia was 0.367 mg/kg in the young group, 0.369 mg/kg in the middle-aged group and 0.249 mg/kg in the elderly group. In all patients in this study, hemodynamic stability was maintained with a bolus administration of remimazolam, and no injection site pain was observed. Therefore, in clinical practice, titration of remimazolam bolus according to age is recommended, and further studies are needed on the interaction of remimazolam with other anesthetics.

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Conflicts of Interest

Sung Yong Park has been an editor for the Korean Journal of Anesthesiology since 2016. However, he was not involved in any process of review for this article, including peer reviewer selection, evaluation, or decision-making. There were no other potential conflicts of interest relevant to this article.

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References


Dexmedetomidine attenuates subarachnoid hemorrhage-induced acute lung injury through regulating autophagy and TLR/NFκB signaling pathway

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Background: Acute lung injury (ALI) is the most serious complication of subarachnoid hemorrhage (SAH). We investigated role of autophagy and inflammatory signaling pathways in lung damage and therapeutic effects of dexmedetomidine (DEX).

Methods: Fifty male Wistar rats were randomly divided into five groups: sham, SAH, SAH+DEX5, SAH+DEX25, and SAH+DEX50. SAH was induced using endovascular perforation technique. All rats received mechanical ventilation for 60 min. At 2 and 24 h of SAH induction, SAH+DEX groups were treated with 5, 25, and 50 µg/kg of DEX, respectively. Histological ALI score and pulmonary edema were assessed after 48 h. Lung expression of LC3B, ATG3, p62, TLR4, TLR9, and NFκB was assessed using western blotting and quantitative PCR. Blood levels of IL-6, IL-1β, IFN-γ, and TNFα were also assessed.

Results: SAH induced ALI and pulmonary edema, which were attenuated in SAH+DEX5 (\(P < 0.001\) for both) and SAH+DEX25 groups (\(P = 0.001\) and \(P < 0.001\) for ALI and edema, respectively). Histological ALI score and pulmonary edema were assessed after 48 h. Lung expression of LC3B and ATG3 were upregulated in SAH group, which was attenuated in SAH+DEX5 and SAH+DEX25 groups. Lung expressions of TLR4, TLR9, and NFκB were increased in SAH group, which was attenuated in SAH+DEX5 group. Blood IL-6 level was increased in SAH group and attenuated in SAH+DEX5 and SAH+DEX25 groups. Blood IFN-γ level was lower in SAH group than in sham group, and it was increased in SAH+DEX25 group.

Conclusions: Low-dose DEX treatment after SAH may protect against ALI by disrupting pathological brain-lung crosstalk and alleviating autophagy flux and TLR-dependent inflammatory pathways.

Keywords: Acute lung injury; Autophagy; Dexmedetomidine; Inflammation; Subarachnoid hemorrhage; Toll-like receptors.

Introduction

Subarachnoid hemorrhage (SAH), a leading cause of death and neurological devastation, mostly induces extracerebral organ dysfunction. The lungs are most commonly affected as they are particularly vulnerable to harmful signals, such as massive sympathetic stimulation and systemic inflammatory responses, which are activated during SAH [1]. Once attacked, the lungs become highly sensitive to mechanical ventilation, surgery, and
infection that follow after severe brain injury and get irreversibly damaged [2]. Pulmonary complications are largely responsible for the mortality and healthcare burden of SAH [1]. The current therapeutic approach is mainly supportive, since the exact molecular mechanism of SAH-induced acute lung injury (ALI) has not been fully elucidated.

Autophagy maintains cellular homeostasis by recycling damaged materials and regulating cellular bioenergetics [3]. Accordingly, coping with various cellular stresses depends on its activity [4]. As autophagy balances the beneficial and detrimental actions of immunity, the pathogenesis and prognosis of inflammatory diseases are strongly affected by its involvement [5]. The implication of autophagy in lung injury is complex because its function is multifaceted according to the cell types and environment [6], which complicates autophagy-based diagnostic and therapeutic approaches. Likewise, a number of previous experimental studies on ALI models support autophagy activation as a mechanism of action for several therapeutic agents, while a few have reported that attenuating autophagic activity facilitates protection against damage [7]. To date, molecular switches between the injurious or protective activity of autophagy in the lungs after SAH have not been explored. The association of autophagy with pro-inflammatory signaling pathways involved in brain-lung crosstalk remains elusive.

Dexmedetomidine (DEX), a highly selective Alpha 2-adrenergic receptor agonist, is a widely used sedative and analgesic agent. A large body of evidence supports its organ-protective effects, including anti-inflammatory, antioxidative, and sympatholytic properties [8]. Regarding its impact on the lungs, a number of experimental studies have revealed that DEX attenuates various types of ALI [8], which is consistent with promising clinical results in patients with pulmonary dysfunction and those undergoing lung surgery [9,10]. Recently, autophagy suppression has been suggested as a mechanism of lung protection by DEX in ALI induced by ischemia-reperfusion, lipopolysaccharide instilation, and toxic shock [11–13]. However, there are reports that autophagy activation induced by DEX plays a central role in protection against neuronal and myocardial damage [14,15].

In this study, we investigated whether autophagy promotes or protects against ALI induced by SAH in a rat model of endovascular perforation undergoing mechanical ventilation. We also evaluated the protective effects of DEX against SAH-induced ALI with the mechanistic insights.

Materials and Methods

Ethical statement and animal preparation

The experimental protocol was approved by our institutional animal care and use committee (No. 2015-0217). All experimental animals were handled in accordance with the National Institute of Health (NIH) guidelines and the Guide for the Care and Use of Laboratory Animals. Fifty male Wistar rats aged 20–22 weeks were housed in temperature- and humidity-controlled animal quarters with a 12 h light/dark cycle and free access to food and water before the experiments.

SAH model

SAH was induced using the endovascular perforation technique, as previously described [16]. Briefly, after rats were anesthetized with 3% isoflurane in 50/50% medical air/oxygen, the left common carotid artery (CCA) and its branches were exposed. Two small loose ligatures were placed on the left external carotid artery (ECA) and a small distal incision was made. A 3–0 monofilament nylon suture was inserted through this incision, and the loose ligatures were fastened over the filament when advanced to the internal carotid artery (ICA). The filament was continuously fed into the vessel until resistance was encountered, indicating that the filament had reached the intracranial bifurcation of the ICA. The filament was advanced further by approximately 3 mm to perforate the artery, and was then immediately withdrawn. In the sham group, sutures were inserted into the ECA, but arterial perforation was not performed. The incision was closed after surgery.

Experiments continued only on the rats that developed a considerable amount of hemorrhage; the severity of SAH was assessed after perfusion by a blinded observer based on a previously described grading system [17]. Briefly, the brain base was divided into six parts, each of which was scored from 0 to 3 points according to the amount of blood extravasated into the subarachnoid space. The total score was defined as the sum of six segments, ranging from 0 (no hemorrhage) to 18 (most severe hemorrhage). SAH rats with a score ≤ 7 were excluded from the study. No hemorrhaging was observed in the sham-operated rats and thus received a score of 0.

Mechanical ventilation and drug administration

Rats were randomly assigned to the following five groups: sham, SAH, SAH+DEX5, SAH+DEX25, and SAH+DEX50 (n =
10 each). Immediately after SAH or sham surgery, all rats were intubated and mechanically ventilated for 60 min in a volume-controlled mode with a tidal volume of 6 ml/kg, at a fractional inhaled oxygen concentration of 0.5, inspiration to expiration ratio of 1 : 1, and respiratory rate of 80 breaths/min. A 1.5% isoflurane anesthesia was continued during mechanical ventilation. Two and 24 h after surgery, the sham and SAH groups were intraperitoneally injected with 2 ml of normal saline, while the SAH+DEX5, SAH+DEX25, and SAH+DEX50 groups received the same volumes of 5, 25, and 50 μg/kg of DEX (Precedex®, Hospira Inc., USA) intraperitoneally.

**Neurobehavioral assessment**

The neurobehavior of the rats was evaluated (n = 7–10 per group) 48 h after surgery using the previously described modified limb-placing test (MLPT) [18]. Ambulation was assessed by walking with the lower limbs, which was graded as follows: 0 points (normal walking), 1 point (mildly ataxic gait with flat toes under the body), 2 points (ataxia with knuckle walking), 3 points (presence of lower limb movement but unable to walk), and 4 points (absence of lower limb movement, dragging legs). Second, the placing/stepping reflex was assessed by dragging the dorsum of the hind limb over the edge of the table, which induced lifting and placing responses such as stepping, and graded as follows: 0 points (well-coordinated lifting and placing response), 1 point (mildly uncoordinated and weakened response), 2 points (severely impaired response or knuckle walking), and 3 points (no response). The sum of the scores in the two tests (ranges 0–7) was defined as the motor deficit index (MDI). Rats with an MDI ≥ 3 were considered paraplegic.

**Lung histopathology and immunohistochemistry**

The rats (n = 7–10 per group) were anesthetized with isoflurane 48 h after SAH or sham surgery and intracardially perfused with 1% phosphate-buffered saline (PBS) immediately after blood collection. The lower lobe of the left lung was harvested, fixed in 4% paraformaldehyde for 24 h, and then immersed in 30% sucrose overnight. The tissue was embedded in paraffin and cut into 4 μm sections. For histopathological scoring and immunohistochemistry, tissue sections were deparaffinized, rehydrated using 10 mM citrate buffer (pH 6.0) in a microwave at 750 W for 20 min, and subsequently cooled. Half of the sections were stained with hematoxylin and eosin (H&E) and scanned under light microscopy by two experienced pathologists who were blinded to the group assignment. Alveolar congestion, hemorrhage, alveolar wall thickness, and inflammatory cell aggregation were evaluated according to previously described criteria [4], with some modifications: 0, normal tissue; 1, minimal inflammatory change; 2, slightly thickened alveolar septa by mild infiltration of inflammatory cells, but without obvious architectural distortion; 3, formation of nodules and/or severe inflammatory changes that distort the architecture; and 4, total fibrous obliteration of the field.

The other half of the sections was incubated in 3% H₂O₂ in PBS at room temperature for 10 min and then washed with 1X PBS. The samples were blocked with REAL Peroxidase-Blocking Solution (S2023, DAKO, Denmark) for 20 min, incubated with LC3B (1 : 1000, Novus Biologicals, USA) primary antibody overnight at 4°C, and then washed with 1X PBS. The samples were subjected to the REAL EnVision Detection System (DAKO K5007), washed thoroughly under tap water, and mounted on slides. Mayer's hematoxylin was used for counterstaining. Images of the colonies were captured using a light microscope OLYMPUS BX40 (40× magnification).

**Lung wet/dry weight ratio**

To assess the development of pulmonary edema, the lung wet/dry weight ratio was measured in the fresh right lung (n = 7–10 each), as described previously [19]. Briefly, lung samples were extracted immediately after perfusion, and excess fluid was blotted. The samples were then placed in pre-weighed glass vials and weighed (wet weight). The samples then were wrapped in tinfoil and placed in an oven at 80°C for 48 h. The wet/dry weight ratio was calculated as [(wet weight − dry weight) / wet weight] × 100.

Since lung histology and the degree of pulmonary edema in the SAH+DEX50 group did not show any beneficial effects of the agent, this group was excluded from further experiments for mechanistic analysis.

**Quantitative real-time polymerase chain reaction (PCR)**

Immediately after intracardiac perfusion, tissue samples from the left upper lobe were freeze-clamped in liquid nitrogen and stored at −80°C. Total RNA was isolated using an RNaseqy Mini Kit (Qiagen, USA). Complementary DNA (cDNA) was synthesized from 1 μg of total RNA using AccuPower RT premix kits (BIONEER, Korea). Real-time PCR analysis was performed using the TB GreenTM Premix Ex Taq II kit (TAKARA, Japan) and QuantStudio3 (Applied Biosystems, USA) according to the manufacturer's instructions. Each sample was analyzed in quadruplicate, and target genes were normalized to the reference house-
keeping gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Fold differences were calculated for each group using the normalized CT values for the sham groups. The primer sequences for real-time PCR are as follows: LC3B: Forward 5’-AGAGCGATACAAAGGTTGA-3’, Reverse 5’-ACTTCAGAGATGGGTGTGAT CT-3’; Reverse 5’-TACAATTCGACCTGCTGCT-3’; TLR 4: Forward 5’-CCAGAGCCGTTGGTGTAT CT-3’, Reverse 5’-TACAATTCGACCTGCTGCT-3’; TLR 9: Forward 5’-ACATGGTTGAGGCTATCCC-3’; GAPDH: Forward 5’-CTGAGAATGGGAAGCTGGTC-3’; Reverse 5’-CTCCACGACATACTCCGAC-3’.

Western blotting

Immediately after intracardiac perfusion, tissue samples from the left upper lobe were freeze-clamped in liquid nitrogen and stored at −80°C. Frozen tissues were homogenized in western lysis buffer (4°C) containing 20 mM Tris, 150 mM NaCl, 1 mM ethylenediaminetetraacetic acid, 1 mM ethylene glycol tetra acetic acid, 1% Triton X-100, complete protease inhibitor cocktail (one tablet per 10 ml; Roche Diagnostics Corporation, Indianapolis, IN), and phosphate inhibitor cocktail set II (EMD Biosciences, Germany). Thereafter, the homogenates were centrifuged at 12,000 rpm for 30 min at 4°C. The total protein concentration was determined using the Quick Start Bradford reagent (Bio-Rad, USA), with bovine serum albumin as a standard. Whole-cell protein extracts (50 µg) were denatured by heating to 100°C for 5 min, separated on 10–15% sodium dodecyl sulfate-polyacrylamide electrophoresis (SDS-PAGE) gels, and transferred onto Immobilon-P transfer membranes (Millipore, USA). The membranes were incubated successively with ATG3 (1 : 1000, Cell Signaling Technologies, USA), p62 (1 : 1000, Abnova, Taiwan), LC3B (1 : 2000, Novus Biologicals, USA), Toll-like receptor (TLR) 4 (1 : 200, Santa Cruz Biotechnology, USA), TLR 9 (1 : 200, Santa Cruz Biotechnology), phospho-nuclear factor-kappaB (NF-κB) (1 : 200, Santa Cruz Biotechnology), NF-κB (1 : 1000, Cell Signaling Technologies), or GAPDH (1 : 1000, Cell Signaling Technologies) overnight at 4°C. The signal was detected using WestGlow FEMTO chemiluminescent substrate (BIOMAX, Korea). GAPDH was used as the protein-loading control.

Enzyme-linked immunosorbent assay (ELISA)

Levels of IL-1β (R&D Systems, USA), TNF-α (Abcam, UK), IL6 (BioLegend, USA), and IFN-γ (MyBioSource, USA) in the serum were determined using ELISA commercial kits according to the manufacturer’s instructions.

Statistical analysis

Statistical analyses were performed using GraphPad Prism 9 software (GraphPad Software, Inc., USA) and SPSS version 23 (IBM Corp., USA). Statistical significance of comparisons among the groups was analyzed using one-way analysis of variance (ANOVA) followed by Bonferroni post-hoc analysis for multiple comparisons. All data are presented as mean ± SD or standard error of the mean (SEM). Statistical significance was defined as 2-sided P < 0.05.

Results

Effects of DEX on SAH grade and neurological deficit

Mortality before completion of the experimental protocol was 30% and 50% in the SAH group and the SAH+DEX50 group, respectively. Two rats in the SAH+DEX5 group and three in the SAH+DEX25 group (out of 10 rats in both groups) showed SAH grading scores of ≤ 7 and were excluded from the study. The scores in the remaining rats with SAH induction were similar among the groups. In the neurobehavior assessment (Table 1), the SAH group showed severe neurological deficit, contrary to the sham group with normal neurobehavior (3.7 ± 0.9 vs. 0.1 ± 0.4, P < 0.001). However, the SAH+DEX50 group (5.4 ± 0.7) had significantly higher deficit scores than the other groups (P

Table 1. Neurobehavior Outcomes Assessed by MLPT

<table>
<thead>
<tr>
<th></th>
<th>Sham (n = 10)</th>
<th>SAH (n = 10)</th>
<th>SAH+DEX5 (n = 8)</th>
<th>SAH+DEX25 (n = 7)</th>
<th>SAH+DEX50 (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor deficit index</td>
<td>0.1 ± 0.4</td>
<td>3.7 ± 0.9</td>
<td>1.2 ± 0.8</td>
<td>0.7 ± 0.8</td>
<td>5.4 ± 0.7</td>
</tr>
<tr>
<td>Ambulation</td>
<td>0</td>
<td>1.8 ± 1.1</td>
<td>0.6 ± 0.7</td>
<td>0.3 ± 0.9</td>
<td>2.5 ± 0.9</td>
</tr>
<tr>
<td>Placing/stepping reflex</td>
<td>0.1 ± 0.4</td>
<td>1.9 ± 0.7</td>
<td>0.5 ± 0.5</td>
<td>0.4 ± 0.5</td>
<td>2.9 ± 0.6</td>
</tr>
<tr>
<td>Paraplegic</td>
<td>0</td>
<td>9 (90)</td>
<td>0</td>
<td>0</td>
<td>8 (100)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number (%). Motor deficit index was defined as a sum of the scores in the ambulation and reflex tests. Paraplegia was defined as a motor deficit index > 3. MLPT: modified limb-placing test, SAH: subarachnoid hemorrhage, DEXS, 25: dexametomidine 5, 25 µg/kg administered at 2 and 24 h after surgery.

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< 0.001 vs. sham group, SAH+DEX5 group, and SAH+DEX25 group and P < 0.001 vs. SAH group). Nine out of ten rats in the SAH were paraplegic (MDI ≥ 3), whereas none of the sham group, SAH+DEX5, and SAH+DEX25 groups developed paraplegia. All eight rats in the SAH+DEX50 group developed paraplegia.

Effects of DEX on severity of ALI and pulmonary edema

As shown in Fig. 1A, H&E staining of lung tissue in the SAH group revealed thickened and broken alveolar wall, inflammatory cells infiltration in alveoli, and patchy hemorrhage with fibrinous exudate in the alveola and interstitium, in contrast with that in the sham group showing normal lung architecture and no or minimal inflammation, which was probably induced by mechanical ventilation. Pathological changes were ameliorated by treatment with 5 µg/kg (SAH+DEX5 group) and 25 µg/kg (SAH+DEX25 group) DEX. However, histology of the SAH+DEX50 group showed severe injury, diffuse inflammatory cell infiltration in the alveoli and interstitium, and thickened or disrupted alveolar walls. Quantification of the injury demonstrated a significant attenuation of the ALI by treatment with 5 µg/kg and 25 µg/kg DEX (1.5 ± 0.5 vs. 3.2 ± 0.9 in SAH+DEX5 group and SAH group, P < 0.001; and 1.7 ± 0.5 vs. 3.2 ± 0.9 in SAH+DEX25 and SAH groups, P = 0.001; Fig. 1B). The ALI score in the SAH+DEX50 group was higher than those in the SAH+DEX5 and SAH+DEX 25 groups, but the difference was not statistically significant.

The lung water content, assessed by wet/dry weight ratio, was significantly increased in the SAH group compared with the sham group (6.4 ± 0.6 vs. 3.1 ± 0.3, P < 0.001; Fig. 1C). The SAH+DEX5 group and the SAH+DEX25 group showed lower lung wet/dry ratio compared with the SAH group (4.5 ± 0.5 and 4.1 ± 0.4 vs. 6.4 ± 0.6, P < 0.001, respectively). The wet/dry ratio in the SAH+DEX50 group was comparable to that in the SAH group.

Fig. 1. Effects of DEX on severity of lung injury and pulmonary edema. (A) Representative histology images of lung tissue assessed by hematoxylin–eosin staining at 48 h after SAH induction. (B) A quantification of severity of lung injury assessed by modified ALI score that ranges from 0 to 4. (C) A quantification of pulmonary edema assessed by ratio of lung wet/dry weight. n = 7–10 per group and three technical replicates per each rat. Values are presented as means and SD. *P < 0.05 vs. sham group, †P < 0.05 vs. SAH group. ALI: acute lung injury; SAH: subarachnoid hemorrhage, DEX5, 25, 50: dexmedetomidine 5, 25, 50 µg/kg administered at 2 and 24 h after surgery.
group (6.9 ± 0.9 vs. 6.4 ± 0.6, P = 0.794) and was significantly higher than that in the SAH+DEX5 and SAH+DEX25 groups (both P < 0.001).

**Effects of DEX on expression of autophagy-regulatory factors in lung tissue**

To determine the role of autophagic activation in SAH-induced ALI and the effects of DEX, we evaluated the gene and protein expressions of essential regulatory factors for autophagy (Fig. 2).

The protein expression levels of LC3B and p62 between the sham and SAH groups were not significantly different (P = 0.096 and 0.065, respectively) compared to the sham group, while the level of ATG3 was significantly higher in the SAH group than in the sham group (Fig. 2A). The levels of LC3B and ATG3 in the SAH+DEX5 and SAH+DEX25 groups were significantly lower than those in the SAH group. The mRNA expression of LC3B was significantly increased in the SAH group compared with the sham group, while the expression was significantly decreased in the SAH+DEX5 group compared with the SAH group (data not shown). As shown in Fig. 2B, there were a greater number of LC3B positive cells in the tissue sections of the SAH group than in those of the sham group. The SAH+DEX5 and SAH+DEX25 groups showed lower expression of LC3B positive cells than the SAH group.

**Effects of DEX on expression of TLRs and NFκB in lung tissue**

To evaluate whether TLR signaling pathways are responsible for lung inflammation induced by SAH and the effects of DEX, we assessed the lung expression levels of TLR4, TLR9, and downstream molecules (Fig. 3). The protein and mRNA expression levels of TLR4 and TLR9 were significantly higher in the SAH group than those in the sham group. The mRNA expression of TLR4 was significantly lower in the SAH+DEX5 and SAH+DEX25 groups than in the SAH group, but the decrease in protein expression levels was not statistically significant. The protein and mRNA expression levels of TLR9 were lower in the SAH+DEX5 group compared with the SAH group. The protein expression level of

Fig. 2. Effects of DEX on expression of autophagy-regulatory factors in lung tissue. (A) Representative western blots and a quantification of protein levels of LC3B, ATG3, and p62 normalized to GAPDH. n = 7–10 per group and three technical replicates per each tissue sample. (B) Representative LC3B immunohistochemistry images. Black arrows indicate LC3B-positive cells (brown color). Values are presented as means and SD. *P < 0.05 vs. sham group, †P < 0.05 vs. SAH group. SAH: subarachnoid hemorrhage, DEX5, 25: dexmedetomidine 5, 25 µg/kg administered at 2 and 24 h after surgery.
phosphorylated NFκB was significantly higher in the SAH group than in the sham group, while the levels were significantly decreased in the SAH+DEX5 group. In the additional qPCR analysis, mRNA levels of IL-6 and IL-18 were significantly higher in the SAH group than in the sham group, while the levels in the SAH+DEX5 and SAH+DEX25 groups were significantly lower than those in the SAH group (data not shown).

**Effects of DEX on systemic levels of inflammatory cytokines**

In the ELISA to determine the role of systemic inflammation in mediating the brain-lung crosstalk (Fig. 4), the blood level of IL-6 was significantly higher in the SAH group than in the sham group, and the level was significantly decreased in the SAH+DEX5 group and in the SAH+DEX25 group, compared with the SAH group. The blood level of IFN-γ was significantly lower in the SAH group than in the sham group, and the level was significantly higher in the SAH+DEX25 group than in the SAH group. Blood levels of IL-1β and TNF-α did not differ among the groups.

**Discussion**

Autophagy has recently emerged as an adaptive response to pulmonary insults induced by various stresses that manifest as chronic obstructive pulmonary disease, asthma, pulmonary fibrosis, and acute respiratory distress syndrome (ARDS) [7].

One of the most important autophagic activities in this regard is the regulation of inflammation [20]. Considering that SAH frequently causes ALI, which is characterized by an inflammatory process in lung tissue, autophagy might play an important role in the development of SAH-induced lung damage, which has not yet been revealed. In this study on the SAH rat model, we found that the crucial regulators of autophagy were significantly altered towards the activation of autophagy, which was linked to pulmonary edema, alveolar infiltration of inflammatory cells, and architectural distortion. This finding suggests that autophagic flux may be responsible for pulmonary complications in patients with SAH.
Furthermore, we observed that DEX treatment after SAH reversed lung injury and pulmonary edema with attenuation of increases in the tissue expression of autophagy regulators, which confirms that autophagy might serve as a potential therapeutic target in SAH-induced ALI.

Pattern-recognition receptors (PRRs) that are activated by danger-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns were demonstrated to promote activation of autophagy in diverse inflammatory states [5]. TLR4, one of the best-characterized PRRs, is known to specifically recognize bacterial lipopolysaccharides (LPS) as well as several DAMPs, especially high-mobility group box (HMGB)-1, and activates NFκB and mitogen-activated protein kinases (MAPK), thereby leading to lung inflammation either by various direct or indirect insults [21,22]. Our study is the first to reveal that activation of TLR4 and NFκB in lung tissues after SAH could be induced by the massive release of HMGB-1 from neuronal cells [23]. TLR4 has been demonstrated to trigger the activation of autophagy via a number of downstream signaling pathways, including TNF receptor-associated factor (TRAF)6, Toll/IL-1 receptor domain-containing adaptor interferon-β (TRIF), phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway, and the MyD88/NFκB pathway [24]. A previous in vitro study on macrophages identified TLR4 as a major trigger for LPS-induced proinflammatory cytokine release and autophagic activation [25]. In contrast, mediators of autophagy have also been demonstrated to stimulate TLR4 and NF-κB, thereby exaggerating inflammation in various diseases [26]. In terms of lung injury, a previous study on a minipig model of lung ischemia-reperfusion (IR) demonstrated that autophagy amplifies lung inflammation by activating TRAF6, MAPK, and NF-κB [27]. The role of autophagy in aggravating the inflammatory response and lung damage via mTOR signaling has also been demonstrated in LPS-induced ALI [28]. Autophagic activation in the lung tissues of SAH rats along with the severe inflammatory changes and upregulated genes encoding IL-6 and IL-18 in our study may support the interactive role of autophagy and inflammatory pathways initiated by TLR4 in pathological brain-lung crosstalk.

**Fig. 4.** Effects of DEX on circulating levels of inflammatory cytokines. (A–D) A quantification of blood serum levels of IL-1β, IL-6, IFN-γ, and TNF-α. n = 7–10 per group and three technical replicates per each tissue sample. Values are presented as means and SD. *P < 0.05 vs. sham group, †P < 0.05 vs. SAH group. SAH: subarachnoid hemorrhage, DEX, 25: dexmedetomidine 5, 25 µg/kg administered at 2 and 24 h after surgery.

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In contrast, a number of reports have suggested a protective role of autophagic activation against ALI. A study on an LPS-induced ALI mouse model revealed the cytoprotective effects of autophagy mediated by endoplasmic reticulum stress and exacerbation of cytotoxicity by administering an autophagy inhibitor [29]. A study on a traumatic brain injury (TBI) rat model showed that TBI promoted autophagy flux in lung tissues, which was consistent with our findings; however, enhanced autophagy flux attenuated lung inflammation and apoptosis, while inhibition of autophagy flux exacerbated lung damage [30]. The two-edged sword of autophagy modulation in cell survival, inflammation, and immunity, due to highly variable autophagy function according to cell type and causative stimuli, has been widely recognized [26]. Although SAH-induced ALI may share some pathophysiology of brain-lung crosstalk with TBI-induced ALI, a difference may also exist, which can be inferred by distinct proteins in cerebrospinal fluid (CSF) between TBI patients and those with non-TBI, including SAH [31]. In addition, superimposed ventilation-induced lung injury (VILI) in the current study, but not in the TBI model [30], could have contributed to the discrepancy in the role of autophagy. VILI is characterized by increased pulmonary vascular permeability, infiltration of immune cells, and robust activation of pro-inflammatory signaling and is widely recognized to aggravate lung damage in patients with ALI/ARDS [32]. Autophagy has been implicated in inflammatory injury during mechanical ventilation via inflammasome activation and stimulation of the NF-κB pathway [33,34]. Increased lung expression of TLR9 in SAH rats in the current study may support a recent report on the role of TLR9 in mechanical ventilation-induced inflammatory injury through the MyD88/NFκB pathway [35]. Synergistic interactions between autophagy and the TLR9/NFκB signaling pathway may potentially contribute to double-hit lung injury, which requires further investigation.

Given the safety and efficacy profile and widely recognized lung-protective properties of DEX [8], we investigated its therapeutic effects on SAH-induced ALI. Although autophagic function in the role of DEX in protecting organs has been controversial, recent evidence from experimental studies on ALI supports that DEX may inhibit activation of autophagy in injured lung tissues, which is consistent with our findings. In a rat model of toxic shock-induced ALI, a single dose of 50 µg/kg DEX downregulated lung expression of LC3B and Beclin-1, as well as inflammatory proteins, with attenuation of pulmonary edema and apoptosis [13]. A study on a rat model of lung IR injury also revealed that pre-treatment with 1–10 µg/kg DEX prevented ALI along with the downregulation of BCL2 Interacting Protein3 (BNIP3), a potent inducer of mitochondrial autophagy, as well as LC3B [11]. The mechanisms for the inhibition of autophagy may include the potent anti-inflammatory property of DEX. In a TBI-induced ALI mouse model, a single dose of 50 µg/kg DEX exerted protective effects via suppression of HMGB-1 signal transduction in the lung tissue [36]. A study in a rat model of sepsis-induced ALI revealed that treatment with 10–20 µg/kg DEX inhibited lung inflammation by suppressing the TLR4/MyD88/NFκB [37]. These results are consistent with our finding of attenuated upregulation of TLRs, NF-κB, and ILs by DEX along with autophagy inhibition, which may indicate an interrupted vicious cycle of autophagic damage and inflammation in SAH-induced ALI.

A dosing protocol used in our experiment was based on previous studies that showed protective effects described above. We also selected repeating dose to reflect the clinical situation of SAH management better. In contrast to the single dose of 50 µg/kg that showed protective effects against the secondary ALI previously [13,36], a double administration of 50 µg/kg at 2 h and 24 h after brain damage in the current study did not bring any benefits. Considering the poor neurobehavioral scores in this group, we could assume that repeated high dose could have led to exaggerated pathological activation of brain-lung crosstalk and consequent severe lung damage. Indeed, there is a report on neurotoxicity of 100 µg/kg DEX, although the toxic dose of this agent is still controversial [38,39]. The timing of drug administration in the current study, which occurred after brain insults could also be responsible for neurotoxicity because the brain may become more vulnerable to toxicity compared to pre-treatment or preconditioning. The second-hit damage by mechanical ventilation in our study compared with those studies without it could be another reason of the different result. A high dose of DEX may also be ineffective or harmful to the lung itself, although there is scarce data to support this hypothesis. One previous study that evaluated the effects of 100 µg/kg on ALI and reported no benefit, while the lower doses, 10 µg/kg and 50 µg/kg, exerted significant protection [40]. Notably, the protective effects observed in our SAH+DEX5 and SAH+DEX25 groups were comparable and not dose-dependent. Moreover, tissue expression of TLR9 and NF-κB was only attenuated in the SAH+DEX5 group, and the level of LC3B in the SAH+DEX5 group was significantly lower than that in the SAH+DEX25 group. These findings suggest that the dosing protocol of DEX post-SAH should be very cautious, and a more sophisticated evaluation needs to be performed. Although inflammation is a widely accepted mechanism of brain-lung crosstalk, data on the circulating levels of inflammatory mediators are scarce. Remarkable changes in blood IL-6 levels according to the occurrence of SAH and treatment with DEX, which were associated with ALI severity in the current study may

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indicate systemic inflammation as a connecting link between the brain and lungs. We previously observed in our rat model of SAH-induced vasospasm that blood and CSF levels of IL-6 were strongly correlated with the severity of vasospasm and the therapeutic effects of DEX [41], which may explain the different neurobehavioral changes among the groups in the present study. Circulating IL-6 has also been reported to mediate inflammatory damage in the lungs after acute kidney injury in mice [42], supporting its role in triggering secondary ALI induced by distant organ damage. Additionally, we found that the blood level of IFN-γ was inversely related to SAH-induced ALI and the therapeutic effects of DEX. Despite the widely recognized role of IFN-γ in the stimulation of inflammatory responses to pathogens, its activity in sterile inflammation remains controversial [43]. Indeed, its blood level has shown to decrease in some pathological states, such as trauma and hepatitis [44,45], which is consistent with the current results. Decreased IFN-γ levels may contribute to a high incidence of pneumonia in patients with brain injury by creating an environment in which infectious pathogens thrive [46]. The expression of IFN-γ by immune cells in patients with viral respiratory infection and interstitial lung disease was lower in severe cases than in those with a moderate form of the disease [47]. In addition, a decrease in the blood IFN-γ level was shown to be a risk factor for lung fibrosis in this disease [48]. More sophisticated exploration of the role of circulating IFN-γ in the pathophysiology of ALI induced by SAH is needed.

The current study has several limitations. First, we did not proceed into molecular studies on the SAH+DEX50 group, since the high dose DEX was not protective against the ALI. Information on the autophagy and inflammatory signaling pathway could have helped in the understanding of no benefit and confirming the potential toxicity of the high dose, which needs future investigation. Second, although the role of autophagy in SAH-induced ALI was assessed using the lung expression of essential regulators of autophagy, we did not confirm this role by applying inhibitors or activators, which may not permit a definite conclusion. Nevertheless, the severity of lung damage and pulmonary edema was well correlated with autophagy activity, which may support the current assertion. Third, we did not assess alterations in lung mechanics and oxygenation function, which are important in defining ALI from a clinical perspective on SAH management. Fourth, mechanical ventilation was performed in all animals in our study in light of actual clinical situations, in which the majority of SAH patients needed ventilatory support. This could have contributed to the comparable protein expression levels of LC3B in the sham and SAH groups, although the severity of ALI was significantly different between the two groups. The presence of additional groups of sham and SAH without mechanical ventilation in the experimental protocol might have better clarified the molecular mechanisms underlying each of the SAH-induced ALI and VILI, as well as the impact of their combination, which could have provided superior information to improve the management of SAH patients regardless of ventilatory support. Fifth, the association of autophagy with the other specified pathophysiology of brain-lung crosstalk, such as oxidative stress or sympathetic overdrive, was not assessed in the current study, for which further evaluation is needed.

Overall, we demonstrated in this study that autophagic flux and the TLR-dependent inflammatory signaling pathway participate in ALI induced by SAH. We also proved that systemic inflammation, one of the theoretical mechanisms of brain-lung crosstalk, mediates SAH-induced ALI. These molecular findings might be potential therapeutic targets, as each of them was attenuated by the administration of DEX within 24 h after SAH. Prompt clinical research in patients with SAH to define the effects of DEX is warranted to support the current results.

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**Conflicts of Interest**

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

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Anti-N-methyl-D-aspartate (NMDA) receptor encephalitis is an autoimmune disease. Antibodies against the GluN1 subunit of the NMDA receptor are detected in the patient’s serum or cerebrospinal fluid (CSF), resulting in characteristic symptoms [1]. Clinical manifestations range from prodromal symptoms such as fever, headache, nausea, vomiting, and upper respiratory symptoms, to psychosis and seizures. Autonomic dysfunction (hyperthermia, tachycardia, bradycardia, hypotension, and hypertension) and central hypoventilation requiring mechanical ventilation support can occur in severe cases [2]. The estimated incidence is approximately 1.5 per million people annually. The majority of the patients are young women with a median age of 21 years. Tumors are detected in many of these patients, most of which are ovarian teratomas [3].

The first-line treatment for anti-NMDA receptor encephalitis includes immunotherapy and resection of the tumor, if present [2]. Therefore, anesthesiologists occasionally encounter these patients in the operating room for tumor resection. Since the NMDA receptor is an important target of general anesthetic agents [4], we cannot exclude the pos-
rituximab and tocilizumab were administered as second-line therapies. The abdominal CT revealed a 7.4 cm-sized benign ovarian cystic tumor lesion of the right adnexa and laparoscopic right salpingo-oophorectomy under general anesthesia was considered. Written informed consent for publication was obtained from the patient’s guardian.

Antiepileptic drugs were continued on the day of the surgery. Continuous infusions of intravenous midazolam (2 mg/h), propofol (40 mg/h), norepinephrine (0.25 µg/kg/min), and morphine (1.5 mg/h) that were being administered in the ICU were maintained during the intraoperative period. Remimazolam and remifentanil were selected as the main anesthetic drugs. The preanesthetic baseline values were as follows: the bispectral index (BIS): 96, SpO₂ at room air: 94%, body temperature: 38.1°C, heart rate: 102 beats/min, and non-invasive blood pressure (NIBP): 102/65 mmHg. Preoperative mental status assessment in the operating room before induction revealed that the Richmond Agitation-Sedation Scale (RASS) was -4 and the Glasgow Coma Scale (GCS) was E:4/V:T/M:1. Concurrently the patient presented with myoclonus on both feet. Due to her unstable respiratory ability, manual positive pressure ventilation was performed through a tracheostomy tube to support the patient’s ventilation during transfer to the operating room. The ventilator was connected to the patient’s tracheostomy tube through a breathing circuit. General anesthesia was induced with a continuous infusion of remimazolam (3 mg/kg/h) and remifentanil (0.2 µg/kg/min) for 3 min until the patient’s eyes were closed. Rocuronium (40 mg) was also administered to achieve appropriate neuromuscular blockade. Anesthesia was maintained with a continuous infusion of remimazolam (1 mg/kg/h) and remifentanil (0.3–0.4 µg/kg/min). During surgery, the BIS values remained between 70 and 78 and did not fall below 70 despite intermittent intravenous bolus administration of 2 mg of remimazolam. The vital signs remained stable between mean arterial pressure (MAP) of 90–110 mmHg and heart rate of 70–100 beats/min until the end of surgery. The resection was completed without any problems. Continuous infusion of remimazolam and remifentanil was stopped at the time of skin closure. To reverse the neuromuscular blockade, we administered intravenous pyridostigmine (10 mg) and glycopyrrolate (0.4 mg) and the train-of-four ratio soon reached 100%. Approximately 15 min after the discontinuation of remimazolam and remifentanil, the patient opened her eyes and the BIS value increased to 95. Immediately before leaving the operating room, the patient’s vital signs were stable, with a body temperature of 37.6°C, NIBP of 121/80 mmHg, and heart rate of 80 beats/min. The duration of the operation and anesthesia were 50 min and 90 min, respectively.

No myoclonic movement was observed during ICU transfer. The biopsy result of the resected ovarian mass confirmed it to be...
a mature cystic teratoma containing 15% neural tissue and mild lymphocytic infiltrates. During the postoperative period, the patient continuously experienced intermittent seizures and the EEG results did not improve. Her mental status was assessed daily but did not return to the patient's preoperative status. The continuous infusion of propofol and midazolam used to control the patient's seizures gradually tapered as the incidence of seizures slightly decreased and enabled the patient's consciousness to improve. One week after surgery, propofol was completely stopped and the continuous infusion of midazolam was stopped on postoperative day 13. Instead, an intravenous bolus of lorazepam or midazolam was administered intermittently when seizure activity recurred. On postoperative day 15, the patient's spontaneous breathing partially recovered. On postoperative day 20, IVIG 400 mg/kg/day was re-administered for 5 days to remove the remaining antibodies because of persistent seizure activities. Her spontaneous breathing ability completely recovered and mechanical ventilation was discontinued two weeks later. The patient's blood pressure was also well maintained, so norepinephrine infusion was stopped. The MAP was maintained well above 60 mmHg, so additional cardiovascular drugs for hemodynamic support were not initiated. However, the patient's mental status did not improve, and she continuously experienced intermittent seizure activities. Eventually, on postoperative day 40, the patient died of brain injury from status epilepticus.

Case 2

In March 2022, a 21-year-old woman (height: 155 cm, weight: 75 kg, ASA II), visited the emergency room of our hospital with headaches lasting 10 days, memory disturbance, and confusion that occurred 7 days before. There were no known underlying diseases other than being diagnosed with COVID-19 nine days before admission.

Brain CT and MRI did not reveal any significant abnormalities. EEG showed rare ill-defined sharp waves in the bitemporal region. Initially, meningoencephalitis due to viral, tuberculosis, or autoimmune causes was suspected, and acyclovir (600 mg every 8 h), anti-tuberculosis medication, and steroid pulse therapy (glucocorticoid 1 g/day) were promptly started. However, no virus or Mycobacterium tuberculosis was detected in the subsequent CSF analysis. The abdominal CT revealed a mature cystic teratoma, measuring 4 cm in diameter, in the right ovary. An additional CSF study for antibody analysis was conducted. Surgical resection of the teratoma was scheduled with anti-NMDA receptor encephalitis suspected. Two days later, on hospital day 7, laparoscopic right salpingo-oophorectomy was performed under general anesthesia.

Written informed consent for publication was obtained from the patient's guardian.

On arrival to the operating room, the preanesthetic baseline vital signs indicated a SpO₂ of 99% at room air, body temperature of 37.0°C, heart rate of 60 beats/min, and NIBP of 140/85 mmHg. The initial BIS value was 96 and the GCS score was E:4/V:4/M:6 indicating irritability and confusion. General anesthesia was induced with a continuous infusion of remifentanil (6 mg/kg/h) and remifentanil (0.2 µg/kg/min) for 5 min. Rocuronium (50 mg) for the neuromuscular blockade was administered. Anesthesia was maintained with a continuous infusion of remifentanil (1–2 mg/kg/h) and remifentanil (0.1–0.3 µg/kg/min). The BIS values remained between 60 and 65 during surgery. The patient's vital signs were stable during the surgery and the teratoma was successfully resected without any complication. Remimazolam and remifentanil infusions were discontinued after the resection. Muscle relaxation was successfully reversed with intravenous pyridostigmine (15 mg) and glycopyrrolate (0.4 mg). The train-of-four ratio was 100%. Flumazenil (250 µg) was administered to fully awaken the patient. After the patient regained consciousness, successful tracheal extubation was performed, and she was transferred to ICU for postoperative care. The duration of the operation and anesthesia were 30 min and 85 min, respectively.

The biopsy result of the resected ovarian mass confirmed a mature cystic teratoma with neural elements. The result of the CSF analysis performed before surgery was available 2 days after surgery, which confirmed the presence of anti-NMDA receptor antibodies. The patient was diagnosed with anti-NMDA receptor encephalitis. The next day, IVIG was administered at a dose of 400 mg/kg/day for 5 days. The patient's condition gradually improved and she was discharged 12 days after the surgery for further management at another hospital.

Discussion

Anti-NMDA receptor encephalitis is a type of autoimmune encephalitis, a disease in which patients’ antibodies to the GluN1 subunit of the NMDA receptor reduce NMDA receptor density through antibody-mediated capping and internalization, resulting in characteristic neuropsychiatric symptoms [5].

Brain MRI sometimes presents FLAIR or T2 signal hyperintensity in some brain regions. However, this is not observed in all patients. EEG results typically show nonspecific, generalized slow rhythmic delta or theta activity. A definitive diagnosis can be made by detection of IgG GluN1 antibodies in CSF analysis and at the same time accompanied by the rapid onset (< 3 months) of one or more typical symptoms including psychiatric behavior,

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speech dysfunction, seizure, movement disorders, decreased level of consciousness, autonomic dysfunction, and central hypoventilation [6].

The primary treatment strategies include immunotherapy such as steroids, IVIG, and plasma exchange, and tumor resection if there is a tumor present. Patients with a diagnosed tumor and treated with surgical removal within four months of the onset of neurological symptoms showed better outcomes compared to patients with an untreated tumor or one that was treated four months after the onset of neurological symptoms. Earlier interventions generally lead to a higher incidence of complete recovery and fewer or more minor deficits. Furthermore, the reported median time from the onset of symptoms to early signs of improvement is approximately eight weeks (range, 2–24 weeks) for the early tumor resection group versus 11 weeks (range, 4–40 weeks) for the late or untreated group [1]. Second-line immunotherapy may include rituximab or cyclophosphamide and 80% of patients with tumors and 48% of patients without tumors show significant improvement with first-line immunotherapy [2].

The NMDA receptor is a complex that is comprised of four subunits derived from three major subtypes (GluN1, GluN2A-B, and GluN3A-B) [7]. NMDA receptors mediate excitatory neurotransmission in the central nervous system (CNS) and are important targets of general anesthetic agents. In addition to nitrous oxide (N₂O) and ketamine which have a major inhibitory effect on NMDA receptors, propofol and volatile anesthetics (isoflurane, sevoflurane, and desflurane) are also known to have inhibitory effect on NMDA receptors to some extent [4].

Considering this, it can be hypothesized that the use of these anesthetic agents in patients with anti-NMDA receptor encephalitis who present with various clinical symptoms may produce unexpected effects or even worsen their clinical status. However, only a few studies have been conducted on which anesthetic method is the most appropriate for these patients. Few case reports have described the use of a combination of propofol and volatile anesthetics [8,9], or total intravenous anesthesia (TIVA) with propofol and remifentanil [10,11] for general anesthesia. Moreover, the effects of TIVA or inhalational agents in patients with anti-NMDA receptor encephalitis are controversial.

Some patients who underwent general anesthesia with TIVA did not develop major complications and their symptoms improved [10,11]. In one case report, propofol 80 mg and sufentanil 15 µg were used for induction and then propofol and remifentanil were continuously administered at a rate of 270 mg/h and 0.1 µg/kg/min respectively for 1 h and 5 min of the total surgical duration. After the surgery, the patient’s condition improved, and she was discharged 20 days after surgery [10]. However, in other studies that used propofol for induction and volatile anesthetic agents for maintenance, patient outcomes did not improve and for some, patient outcomes worsened [8,9]. In one case report, 50–150 mg/h of propofol was continuously administered to the patient before surgery for several days, and 100 mg of propofol was used as the induction dose for general anesthesia. Sevoflurane was used to maintain anesthesia. After surgery, propofol was continuously administered at a rate of 50–80 mg/h for sedation, and the patient’s symptoms worsened, resulting in dyskinesia and generalized tonic-clonic seizures. These symptoms improved after discontinuation of the propofol infusion. Therefore, the authors of this case report concluded that propofol and sevoflurane aggravated NMDA receptor inhibition and exacerbated disease symptoms. Based on this, they recommended anesthetic management using benzodiazepines, opioids, and curare to minimize the potential effects on NMDA receptors in their conclusion [9].

Based on these previous studies, we decided to use remimazolam and remifentanil for general anesthesia induction and maintenance in both cases. Remimazolam is a novel sedative-hypnotic agent, classified as a benzodiazepine, which enhances the effects of the GABA receptor, a major target of general anesthesia [12]. Some of the benefits of remimazolam anesthesia include a lower incidence of hypotension and rapid reversal of the sedative effect by flumazenil when the patient’s awakening is delayed, compared to propofol anesthesia [13]. In addition, remifentanil is an ultra-short acting opioid that acts on the μ-opioid receptor and effectively controls intraoperative hemodynamic responses [14].

In our first case, the patient was sedated with continuous low-dose infusions of midazolam, propofol, and morphine for several weeks before surgery due to status epilepticus. Nevertheless, intermittent seizure events were present and the preanesthetic baseline BIS value in the operating room was as high as 96. Therefore, we judged that although her mental status was affected by the disease, the sedative effect of these low-dose infusions was only modest, and sudden cessation of the sedatives could trigger adverse events such as generalized seizures. Therefore, we decided to add remimazolam and remifentanil for general anesthesia while maintaining the preoperative drug infusion status during the entire intraoperative period.

However, the remimazolam induction dosage was arbitrarily reduced by half to prevent unexpected oversedation from interacting with other sedatives administered concurrently. In addition, in both cases, a much higher maintenance dose was administered because the BIS values did not fall within the appropriate ranges for general anesthesia during the intraoperative period. Based on this, we hypothesized that the depth of anesthesia was not shallow, but the abnormal electrical activities due to the dam-

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aged brain may not have correctly corresponded to the patients’ consciousness level [15], thereby resulting in incorrect and high BIS values. In both cases, the operations were completed without any patient movement or excessive change in the vital signs.

We predicted better outcome in our two patients compared to previous studies in which the patient underwent anesthesia with propofol and sevoflurane [9] because remimazolam and remifentanil did not have any inhibitory effects on NMDA receptor function, and the amount of propofol used in our first case was smaller (40 mg/h). In our first case, the patient’s incidence of seizures decreased, and she recovered normal spontaneous breathing ability over time after surgery. However, her mental status remained stuporous and she died 40 days after surgery. We suspected that the delay in teratoma resection, which was performed 83 days after hospitalization could be one of the reasons why the patient’s clinical condition did not improve dramatically. During this long period, the patient’s brain was likely already irreversibly damaged by persistent seizure activities from NMDA receptor antagonism. In addition, the continued use of propofol in the ICU during the postoperative period may have contributed in part to the undesired outcome. If sedation is required after surgery in other patients with this disease, benzodiazepine such as midazolam and remimazolam, or dexmedetomidine may be preferable to propofol. As dexmedetomidine is a Alpha-2 agonist that is widely used for sedation, and at the same time does not have NMDA receptor inhibitory potential. In our second case, propofol was not used perioperatively; the diagnosis and treatment were earlier, which may have contributed to more favorable outcomes.

Anti-NMDA receptor encephalitis was first identified about 15 years ago [2]. However, there are currently few studies on the most appropriate anesthetic management for patients with the disease. Furthermore, most of the general anesthetic agents currently used have antagonistic effects on the NMDA receptor function. General anesthesia using these agents can worsen the patient’s disease course or produce unanticipated effects. We recommend the use of remimazolam, a novel general anesthetic agent that does not have any effect on NMDA receptors, and has a rapid onset and offset after prolonged continuous infusion, an appropriate drug for general anesthesia and sedation in patients with anti-NMDA receptor encephalitis. Furthermore, remimazolam is associated with fewer hypotensive events compared to propofol [13], which can assist anesthesiologists in managing intraoperative blood pressure and can be another potential advantage in patients with advanced anti-NMDA receptor encephalitis who present severe hemodynamic instability due to autonomic dysfunctions. Although our patient in the first case died, the patient in the second case who underwent general anesthesia only with remimazolam and remifentanil had a positive outcome. To date, there are no reported studies on the use of remimazolam in patients with anti-NMDA receptor encephalitis. This is the first case report. Future studies on the use of remimazolam in patients with anti-NMDA receptor encephalitis will help establish an appropriate anesthetic plan for the management of general anesthesia for these patients.

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We read with interest the recently published original article by Park et al. [1] presenting the claim that the suprascapular notch (SSN) cross-sectional area is a highly accurate candidate magnetic resonance imaging (MRI) diagnostic indicator for suprascapular nerve (SN) entrapment. We appreciate the authors’ attempt to explore additional parameters using different MRI methods. However, this study contained vital anatomical errors that need to be addressed and clarified. In addition, the claim that their analysis of the SSN space and correlation to SN entrapment is novel and has not previously been reported is inaccurate. We would like to direct the authors’ attention to the original article published by Al-Redouan et al. [2] and the articles cited in that study. Additionally, the authors’ claims regarding the accuracy of their method, or rather, the efficacy of their approach, were not driven by a supporting power study but rather a qualitative descriptive study with a sample size of 10. Park et al. [1] also did not compare their MRI method with other explored modalities. We kindly refer the authors to the article by Jezierski et al. [3] that elaborated on ultrasound as an imaging modality revealing the influence that the different morphological types of SSN have on visualization.

The study by Park et al. [1] also presented an MRI figure demonstrating the SSN cross-sectional area that included anatomical errors in the localization and bordering of the SSN. This section is in fact more dorsal to the SSN and is within the suprascapular canal (SSC), which resides within the spinoglenoid fossa (SGF) [4]. In Fig. 1, we present a serial frontal section of the shoulder on an MRI of the SSC to clarify the anatomy. Localization of the SSN is achieved by identifying its bordering anatomical landmarks. The base of the coracoid process borders the SSN laterally and can be easily navigated on cross-section (Fig. 1A). The authors mentioned that MRI frontal sections cut through the SSN in rather oblique planes, which we do agree with. Therefore, the medial border forming the second anatomical landmark, which is the medial peak of the SSN where the omohyoid muscle attaches, is poorly visualized on MRI and is not usually accurately seen. The space delineated in the figure presented by Park et al. [1] is a site in the middle of the SSC [4], which corresponds to our Fig. 1D. It is an anatomically visible groove that contains the traveling suprascapular neurovascular bundle that resides within the SGF and is roofed by the supraspinatus muscle. The SGF is identified by its laterally bordering gneoid and medially bordering spinoacromial arch proximal to the spinoglenoid notch (SGN). The spinoacromial arch may not be visible on the same plane as the MRI owing to the obliquity of its trajectory. However, because the SGF connects SSN and SGN [4], this connection can be confirmed by navigating the proceeding sections where the SGN is detected by observing the base of the spine of the scapula between the supraspinatus...
Fig. 1. Retrospective MRI frontal section series illustrating the suprascapular notch and suprascapular canal anatomy. SSN: suprascapular notch, Snv: suprascapular neurovascular bundle traveling within the suprascapular canal, SGF: spinoglenoid fossa housing the suprascapular canal, SGN: spinoglenoid notch, CorP: coracoid process (the base of the coracoid process), Gln: glenoid, Spn: spine of scapula, SprS: supraspinatus muscle, InrS: infraspinatus muscle, SubS: subscapularis muscle.

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and infraspinatus muscles (Fig. 1E). In fact, this is a common imaging trap, as described by Podgórski et al. [5] in their ultrasound study, in which they explained that capturing a section behind the SSN yields a pseudo-notch image on ultrasound. This imaging concept is the same on MRI and computed tomography of the SSC.

Park et al. [1] claimed novelty in their study and asserted both that the SSN area had not previously been analyzed and that no morphological correlation between SSN typing and SN entrapment had previously been reported. However, a previous study by Al-Redouan et al. [2] demonstrated five morphological SSN stenosis patterns using previously established SSN typing systems and included five parameters from statistically driven correlation analyses of dry bones [2]. To accurately measure the cross-sectional area digitally, an observer must be able to delineate the margins of all bordering parameters. This is a major limitation of MRI and thus comparisons with other modalities such as ultrasound, which allows for plane manipulation, should be undertaken. With MRI, measuring the height or width of the SSN could potentially be more accurate than the cross-sectional area since the chance of having a single parameter fully appearing in the visualization plane is much higher. This is not the case when attempting to capture three collective parameters that are aligned in different spatial orientations. The parameters that govern the cross-sectional area have previously been analyzed, and the height versus upper and mid width were demonstrated to be candidate indicators of SSN stenosis in correlation with SN entrapment [2–4].

In conclusion, the SSN cross-sectional area proposed by Park et al. [1] does not appear to be an accurate approach for estimating SSN stenosis; hence, its reliability as an indicator to assess SN entrapment is questionable. Rather, examining the height and width of the SSN individually could be used to detect SSN stenosis more accurately [2]. MRI is a useful modality for screening the surrounding tissues of the SSC for pathologies [4], while ultrasound has a greater potential for navigating SSC intervals because an observer can manipulate the probe orientation and, thus, the projecting planes [3].

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**Conflicts of Interest**

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

**Author Contributions**

Azzat Al-Redouan (Conceptualization; Investigation; Project administration; Visualization; Writing – original draft)

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**References**

Thank you so much for your thoughtful recommendations [1]. We greatly appreciate your evaluation of our paper and the various anatomical suggestions you provided. As the authors have noted, we are aware that the study we conducted has some limitations. Your feedback is similar to that which the editor and reviewers provided during the previous revision. As a result, most of what you mentioned has been included in the limitations section of our paper. We strongly agree with your suggestion regarding the diagnostic usefulness of ultrasound. Therefore, we are working hard to analyze both MRI and ultrasound to establish a more accurate integrated diagnostic tool. As mentioned, ultrasound has many advantages; however, one disadvantage is that the test result can be influenced by the examiner. In our opinion, the ideal scenario would be if these limitations could be compensated for through MRI. Thanks again for your time and your thoughtful suggestions.

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In this case-based technical report, the novel and straightforward obturator fascia compartment (OFC) block will be described. This superficial fascial block targets the pudendal nerve (PN) at the level of Alcock’s canal and, ultimately, the nerve to the obturator internus (NOI). Owing to the cranial spread of the local anesthetic below the obturator fascia, the OFC block can potentially anesthetize the proximal rami of the PN (Fig. 1A–C). Written informed consent for publication was obtained from the patient.

Fig. 1A and 1B show a 66-year-old patient who underwent a vulvectomy in the context of oncologic disease and experienced intense pain in the post-anesthetic care unit despite receiving significant intravenous (IV) analgesia (8 mg IV morphine, 1 g IV paracetamol, 2 g IV metamizol, 30 mg IV ketorolac, 2 g IV magnesium sulfate, 15 mg IV ketamine, and 150 mg IV tramadol). After the block, immediate pain relief was achieved (the pre-block numeric pain rating scale score was 9 out of 10). Under conventional analgesia (1 g IV paracetamol every 8 h, 2 g IV metamizol every 12 h, 100 mg IV tramadol every 8 h, and IV ketorolac 30 mg every 8 h), the patient had a numeric pain rating scale score < 2 starting on postoperative day one. The patient reported numbness and thermally sensitive alterations in the perineal region for 12 h (8 ml of ropivacaine 0.5% were given per side).

For the OFC block, the patient is placed in the lateral decubitus position with the hips flexed at 90°. After observing the ischial tuberosity (IT) with the probe positioned transversally but oriented cranially (towards the patient’s head), the sacrotuberous ligament (STL) is visualized covering the IT medially at the inferior edge (thinner portion) of the gluteus maximus superficial to the ligament (the STL runs from the IT to its medial/upper insertion in the sacrum). Unlike with other approaches at the obturator foramen level, in this view, the gemelli muscles are not observed and are thus not a complicating factor (Fig. 1A–C).

The needle is then inserted from the lateral side in the vicinity of the IT and advanced in the caudal to cranial direction, targeting the medial/superior surface of the Obturator Internus Muscle (OIM). It is advanced tangentially to the superficial (distal) third of the STL. This maneuver facilitates local anesthetic spread beneath the obturator fascia, which can be seen running deeply and cranially (the OIM is visualized in the short axis view below the STL). On ultrasound, the local anesthetic can be seen dispersing easily within Alcock’s canal owing to the textile arrangement of its walls (a single layer of the obturator fascia) (Fig. 1A and 1B).

Owing to the proximal emergence of the inferior rectal nerve, a proximal PN block is necessary for proctologic procedures. While transperineal techniques reach the branches to the genitals, such as the dorsal penis/clitoris or dorsal labial nerves, they spare the inferior rectal nerves and several perineal nerve rami. The transvaginal techniques, on the other hand, only uses landmarks as guidance and may cause discomfort and ultimately fail [1].
The proximal ultrasound-guided technique at the level of the ischial spine relies on the accurate identification of the ischial spine and the sacrospinous ligament (SSL) (deep structures) immediately caudal to the piriform muscle and cranial to the OIM. Though the injection is performed only after the neurovascular structures are identified, intrapelvic organs can easily be inadvertently punctured given the lack of muscular layers beneath the SSL [1].

Bendtsen et al. [1] have previously described a PN block at the entrance of Alcock’s canal that can anesthetize all three branches...
of the PN before they ramify in the ischioanal fossa. The roadmap described by these authors suggests that the PN can be targeted at this level by following the margin of the hip bone sonographically (cranial to caudal direction) along the 1) greater sciatic notch, 2) ischial spine, and 3) lesser sciatic notch. However, this technique requires maneuvering in the deep, thick, and round gluteal region where minor probe adjustments can cause dramatic changes in the ultrasound image.

To the best of my knowledge, a PN block at the obturator foramen level has only been described in cadaveric specimens. For this block, the PN is approached from the lateral side (which eliminates the need to cross the ischiorectal fossa); however, this technique still requires a perineural injection around milimetric structures within Alcock's canal [2]. Some difficulties with this approach include identifying the OIM and obturator fascia beneath the thick gluteus maximus and the need to place the patient in the prone position [2].

The OIM belongs to the external hip rotator muscle group. It is the only component that posteriorly covers the obturator foramen (the superior and inferior gemelli muscles arise from the posterior surface of the superior ramus of the ischium and run laterally) [3].

The obturator fascia splits to form Alcock's canal, which encloses the pudendal vessels and the PN when they cross over the surface of the OIM. Of note, the obturator fascia attaches distally to the STL [4,5]. Fortunately, anesthesia of the PN can be achieved without the need to identify Alcock's canal, which can be visualized easier on ultrasound after an OFC block. However, the PN anatomy has considerable variability and thus the OFC block is a tool that increases the success of and democratizes the PN block [4,5] by reducing the prevalence of unsuccessful injections in the ischiorectal fossa in the vicinity of Alcock's canal (Fig. 1A–C).

However, the pudendal block is ineffective in the transobturator tape (TOT) procedure for female urinary incontinence, as the cranial portion of the vagina is innervated by the uterovaginal nerves from the hypogastric plexus; nevertheless, the afferences, through the NOI, from the obturator fascia and the OIM (both crossed by the TOT) are a source of postoperative pain that can be managed using the OFC block.

Therefore, the OFC block may be helpful in adult and pediatric patients undergoing urologic, proctologic, and gynecologic/obstetric surgeries.

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

References
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  ① Title and Running title
  ② Abstract
  All manuscripts should contain a structured abstract that is written only in English. Provide an abstract of no more than 250 words. It should contain 4 subsections: Background, Methods, Results, and Conclusions. Quotation of references is not available in the abstract. A list of keywords, with a minimum of 6 and maximum of 10 items, should be included at the end of the abstract. The selection of keywords should be from MeSH (http://www.ncbi.nlm.nih.gov/mesh) and should be written in small alphabetic letters with the first letter in capital letter. Separate each word by a semicolon (;), and mark a period (.) at the end of the last word.
  ③ Introduction
  The introduction should address the purpose of the article concisely and include background reports that are relevant to the purpose of the paper.
  ④ Materials and Methods
  · The materials and methods section should include sufficient details of the design, subjects, and methods of the article in order, as well as the data analysis methods and control of bias in the study. Sufficient details need to be addressed in the methodology section of an experimental study so that it can be further replicated by others.
  · When reporting experiments with human or animal subjects, the authors should indicate whether they received approval from the IRB for the study and the IRB approval number needs to be provided. When reporting experiments with animal subjects, the authors should indicate whether the handling of the animals was supervised by Institutional Board for the Care and Use of Laboratory Animals. “American Society of Anesthesiologists physical status classification” should not be abbreviated. As a rule, subsection titles are not recommended.
  · Clearly describe the selection of observational or experimental participants. 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). For additional information, please visit http://www.icmje.org/about-icmje/faqs/icmje-recommendations/.

- Reports of randomized trials must conform to the revised CONSORT guidelines and should be submitted with the CONSORT flow diagram. The CONSORT checklist should be submitted as a separate file along with the manuscript. The CONSORT statement, checklist, and flow diagram can be found at http://www.consort-statement.org or EQUATOR Network (https://www.equator-network.org/home/)
- Units
Laboratory information should be reported in International System of Units [SI]. Please refer to A Guide for Biological and Medical Editors and Authors, 6th Edn. Baron DN and Clarke HM, ed. (2008), CRC Press. or visit http://www.icmje.org/about-icmje/faqs/icmje-recommendations/
- Exceptions
  a. The unit for volume is "L", others in "dl, ml, μl".
  b. The units for pressure are mmHg or cmH₂O.
  c. Use Celsius for temperature
  d. Units for concentration are M, mM, μM.
  e. When more than 2 items are presented, diagonal slashes are acceptable for simple units. Negative exponents should not be used.
  f. Leave 1 space between number and units.
  Exception) 5%, 36°C
- Drug Names and Equipment
Use generic names. If a brand name must be used, insert it in parentheses after the generic name. Provide ® or TM as a superscript and manufacturer’s name, and country.
- Ions
Ex) Na⁺ [O], Mg²⁺ [O], Mg³⁺ [X], Mg²⁺ [X]
- Statistics
Statistical methods must be described with enough detail so that readers can reproduce the same results if the original data available. The KJA strongly encourages authors to show confidence intervals. It is not recommended to present the P value without showing the confidence interval. A sample size calculation should be described in detail. Sample size calculation must aim at preventing false negative results pertaining to the primary, instead of secondary, endpoint.
- Results
Results should be presented in logical sequence in the text, tables, and illustrations, giving the main or most important findings first. Do not repeat all of the data in the tables or illustrations in the text; emphasize or summarize only the most important observations. Results can be sectioned by subsection titles but should not be numbered. Citation of tables and figures should be provided as Table 1 and Fig. 1.
- Discussion
The discussion should be described to emphasize the new and important aspects of the study, including the conclusions. Do not repeat the results in detail or other information that is given 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.
- References
  a. References should be obviously related to documents and should not be exceed 50. For exceeding the number of references, it should be negotiated with the Editorial Board. References should be numbered consecutively in the order in which they are first mentioned in the text. Provide footnotes in the body text section. All of the references should be stated in English, including author, title, name of journal, etc.
  b. If necessary, the editorial board may request original documents of the references.
  d. Six authors can be listed. If more than 6 authors are listed, only list 6 names with ‘et al.’
  e. Provide the start and final page numbers of the cited reference.
  f. Abstracts of conferences are not allowed to be included in the references. The American Society of Anesthesiologists (ASA) refresher course lecture is not acceptable as a reference.
  g. Description format
A. Regular journal
Author name. Title of journal Name of journal published
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 Figure 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 Figures (line drawings) should be clearly printed in black and white.

⑧ Figures should be explained briefly in the footnotes. The format is the same as the table format.

⑨ An individual should not be recognizable in the photographs or X-ray films unless written consent of the subject has been obtained and is provided at the time of submission.

⑩ Pathological samples should be pictured with a measuring stick.

(4) Other submission elements (Video submission)
The KJA publishes supplemental video (movie) clip(s) that will be available online. Not only recording of the abstract, text, audio or video files, but also data files should be added here.

Each video clip should clearly illustrate the primary findings within an adequate amount of viewing time and 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 name and/or ID number, hospital name, and date of the procedure, should be removed.

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.

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

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

② The maximum number of video clips is 20.

③ The video clip(s) should be playable on both Windows and MAC computers. 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.

④ Individual video files should be a minimum of 480 x 320 pixels (smaller clips will not be accepted) and a maximum of 2 GB. Files of < 15 MB will be rejected outright unless special arrangements have been made with the editorial board prior to submission. Approval of files of > 2 GB will be made at the end of the review process.

⑤ 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).

2) Systematic review and meta-analysis
Systematic reviews are systematic, critical assessments of literature and data sources in order to answer a specific question, and/or includes a statistical technique leading to a quantitative summary of results and examining sources of differences in results among studies, if any. The subtitle should include the phrase "A systematic review" and/or "A Meta-analysis."

Organization of systematic review and meta-analysis: Same as clinical and experimental studies, except,

- All systematic reviews and meta-analyses should be registered at an appropriate online public registry (eg, PROSPERO; http://www.crd.york.ac.uk/PROSPERO/), and registration information should be included with the submission.

- Authors of reports of meta-analyses of clinical trials should submit the PRISMA flow diagram. The PRISMA checklist should be submitted as a separate file along with the manuscript. For information regarding PRISMA guidelines, please visit http://www.prisma-statement.org or EQUATOR Network (https://www.equator-network.org/home/).

- Systematic reviews and meta-analyses of observational studies in epidemiology should be reported according to MOOSE guidelines. For more information regarding MOOSE guidelines, please visit http://www.equator-network.org/reporting-guidelines/meta-analysis-of-observational-studies-in-epidemiology-a-proposal-for-reporting-meta-analysis-of-observational-studies-in-epidemiology-moose-group/.

- No limitation the number of the references.

3) 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. Authors should submit copies of written informed consents by using the online manuscript submission system. If it is unavailable, the IRB approval should be needed. Copy of IRB approval should be kept. If necessary, the editor or reviewers may request copies of these documents. Rarity of a disease condition is itself not an acceptable justification for a case report.

(1) Title page: Same as clinical and experimental studies.

(2) Manuscript
   ① Title and Running title.
   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 6 and maximum of 10 items, should be included at the end of the abstract. The selection of keywords should be from MeSH (http://www.ncbi.nlm.nih.gov/mesh) and should be written in small alphabetic letters with the first letter in capital letter. Separate each word by a semicolon (;), and mark a period (.) at the end of the last word.
   ③ Introduction: Should not be separately divided. Briefly describe the case and background without a title.
   ④ Case report: Describe only the clinical statement that is directly related to 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: Do not exceed 15 references. For exceeding the number of references, it should be negotiated with the Editorial Board.
   ⑦ Tables and figures: Proportional to clinical and experimental studies.

4) 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 equal to or less than 250 words in English. Figures and tables should be provided in English. References should be obviously related to documents and should not be exceed 100. For exceeding the number of references, it should be negotiated with the Editorial Board. Body text should not exceed 30 A4 pages, and the number of figures and tables should be equal to or less than 6.

5) Letters to the Editor
Letters to the Editor also should include brief constructive comments on the articles published in KJA and interesting cases. Book reviews as well as news of scientific societies and scientific meeting dates in Korea or abroad can be included. Letters to the editor of humans must state in the text that informed consent to publication was obtained from the patient or guardian. Authors should submit copies of written informed consents by using the online manuscript submission system. If it is unavailable, the IRB approval should be needed. Copy of IRB approval should be kept. If necessary, the editor or reviewers may request copies of these documents. Letters to the Editor cover individual articles not described by any of the above categories. The short manuscripts with a constructive note on the Journal or the anesthesiology at large are welcome.

Cover pages should be formatted as those of clinical research papers. The body text should not exceed 1,000 words and should have no more than 5 references. For exceeding the number of references, it should be negotiated with the Editorial Board. A figure or a table may be used. A maximum of five authors is allowable. Letter may be edited by the Editorial Board and if necessary, responses of the author of the subject paper may be provided.

6) Statistical Round
A Statistical Round is a narrative review of the application of contemporary quantitative sciences to issues of concern to anesthesiology researchers. A Statistical Round involves a focused discussion on one or more unique or interesting statistical analysis methods that has previously been published in this journal or expresses the general policies or opinions of the Statistical Round Board. They are solicited by the Statistical Round Board and reviewed by the Statistical Editor. There are no word limits to or rules regarding the structure of a Statistical Round. They should have an unstructured abstract of no more than 250 words in English. All articles in a Statistical Round will be published in English and translated into Korean for the convenience of Korean readers. The Korean version of the Statistical Round will be published only on the Web page of the Journal (https://ekja.org). The inclusion of sample datasets as Web (Supplemental) content is encouraged.

8. Recently revised instructions for authors are applied from February 2021 submissions.