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Emergence agitation: current knowledge and unresolved questions

Seok-Jin Lee, Tae-Yun Sung

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Emergence agitation (emergence delirium) is also known as emergence agitation (EA), which may lead to harmful outcomes. The mechanism of emergence agitation is still unclear. Risk factors for emergence agitation include age, male gender, type of surgery, emergency surgery, lower blood-gas exchange, use of volatile inhalation anaesthetic agents, longer surgery duration, anticholinergic drugs, benzodiazepines, propofol, midazolam, fentanyl, opioid, remifentanil, ketamine, and nitrous oxide. If objective monitoring of agitation in emergence is possible, it could help to decrease harmful outcomes. There are several tools available for the assessment of emergence agitation. However, there is no standardized clinical practice guideline, and the incidence rate can differ due to the tools or definitions used. Intravenous anaesthesia, propofol, μ-opioid agonist, N-methyl-D-aspartate receptor antagonist, remifentanil, α₂-adrenergic agonist, local anaesthesia, multimodal analgesia, and education about surgery before surgery can help to prevent emergence agitation. However, it is difficult to identify high-risk patients and apply preventive measures in various clinical settings. The efficacy of risk factors and preventive strategies can vary depending on the study methods and patients. This review discusses the important results of research on emergence agitation and future research directions.

Keywords: Anesthesia; Emergence agitation; Emergence delirium; Incidence; Practice guideline; Risk.
Anesthesia guidelines for COVID-19 patients: a narrative review and appraisal

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Keywords: Anesthesia; Coronavirus infections; COVID-19; Guidelines; Perioperative management; Perioperative medicine; Review.
Data transformation: a focus on the interpretation
통계 처리를 위한 변수 변환과 결과의 해석

Dong Kyu Lee

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의학 논문에서 자주 사용되는 모수적 통계방법들은 대부분 정규성 검정, 변수들 간의 직선형 관계, 동분산성과 같은 여러 가지 기본 가정을 요구한다. 임상이나 실험에서 얻어진 자료들은 이런 가정을 위반하는 경우가 종종 관찰된다. 변수 변환 방법은 이런 가정들에 부합하게 하여 모수적 통계검정을 오류 없이 시행하도록 한다. 변수 변환의 목적은 모수적 통계방법을 수행하는 것이지만, 궁극적인 목표는 변환된 변수들로 이루어진 통계 결과를 완벽하게 해석하는 것이다. 변수 변환은 측정된 자료의 단위나 성격을 바꾸게 되므로 원래의 변환을 통해 결과를 해석하는 과정이 필요하다. 이 글은 변수 변환에 대한 일반적인 개념에서 출발하여 의학 논문에서 자주 사용되는 로그변환에 대해 소개한다. 또한, 결과 해석을 위한 역변환에 대한 내용과 통계분석 전에 변수 변환과 함께 고려하여야 할 사항들에 대하여 기술하였다.

Keywords: Back-transformation; Box-Cox transformation; Homoscedasticity; Logarithmic; Normality; Power; Retransformation; Skewed distribution; Transformation.
Nebulized heparin and salbutamol versus salbutamol alone in acute exacerbations of chronic obstructive pulmonary disease requiring mechanical ventilation: a double-blind randomized controlled trial

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Background: Nebulized heparin is widely used for the management of many pulmonary diseases. However, to our knowledge, the effect of nebulized heparin in mechanically ventilated acute exacerbations of chronic obstructive pulmonary disease (AECOPD) patients has never been studied. The aim of this study was to compare the effects of nebulized heparin and salbutamol (HS) with salbutamol alone (S) on ventilator-free days (VFD) in ventilated AECOPD patients. In addition, we aimed to evaluate the effect of nebulized heparin on breathing and coagulation.

Methods: This was a double-blind randomized controlled trial, 60 adult patients with AECOPD who were on mechanical ventilation were randomized into two groups: HS group consisting of patients who received nebulized heparin (25,000 IU) and salbutamol (5 mg) every 6 hours for a maximum of 14 days. In the S group, patients received nebulized salbutamol (5 mg) only. The primary endpoint was VFDs at day 14. Secondary outcomes were arterial and oxygen and carbon dioxide tensions (PaCO2, PaO2), CRP, and activated partial thromboplastin time (APTT).

Results: The HS group had a significant higher mean VFDs compared to the S group (4.7 ± 3.3 vs 2.4 ± 2.6 day, P = 0.007). In both groups, there was a significant decrease in CRP and APTT compared to baseline. No significant difference was observed in PaCO2, PaO2, or FiO2.

Conclusion: In mechanically ventilated AECOPD patients, nebulized heparin and salbutamol vs salbutamol alone did not increase bleeding and significantly improved VFDs in comparison to salbutamol alone.

Keywords: Albuterol; Artificial respiration; Asthma chronic obstructive pulmonary disease overlap syndrome; C-reactive protein; Heparin.
Incidence of newly developed postoperative low back pain with median versus paramedian approach for spinal anesthesia

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Background: The adverse effect of postdural puncture backache (PDPB), such as low back pain, is known to be associated with factors such as patient characteristics, anesthesia factors, and surgical sites. The purpose of this study was to compare the incidence and intensity of postdural puncture backache (PDPB) between median (M) and paramedian (P) approaches.

Methods: Patients were randomly assigned to the M group (n = 50) or the P group (n = 50). The number of needle attempts, patient positioning, and duration of surgery were recorded. The incidence and intensity of pain were assessed at 1, 7, and 28 days after surgery.

Results: The overall incidence of PDPB was higher in the M group (16/50, 32%) than in the P group (8/50, 16%). At 24 hours postoperatively, 8 patients in the M group and 6 patients in the P group reported pain. The average pain intensity was similar between the two groups. At 7 days, 16 patients in the M group and 1 patient in the P group reported pain (P = 0.007). At 1 month, 5 patients in the M group and 1 patient in the P group reported pain. At 3 months, only 1 patient in each group reported pain.

Conclusion: This study suggests that the paramedian approach may reduce the incidence of PDPB compared to the median approach.

Keywords: Adverse effects; Anesthesia; Low back ache; Median-paramedian; Numeric rating scale; Spinal.
The immunosuppressive effects of volatile versus intravenous anesthesia combined with epidural analgesia on kidney cancer: a pilot randomized controlled trial

Sergey Mihailovich Efremov, Victoria Sergeevna Kozireva, Gleb Borisovich Moroz, Marat Nikolaevich Abubakirov, Olga Sergeevna Shkoda, Anna Nikolaevna Shilova, Sergey Valeryevich Yarmoshuk, Alexandr Alexandrovich Zheravin, Giovanni Landoni, Vladimir Vladimirovich Lomivorotov

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Keywords: Anesthesia; Cancer; Epidural analgesia; Immunity; Propofol; Sevoflurane.
일측폐환기 중 고탄산혈증이 동맥혈 산소화에 미치는 영향: 전향적 무작위 배정 교차 연구

Jun Ho Lee, Yesull Kim, Juhan Mun, Joseph Lee, Seonghoon Ko

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배경: 본 연구의 목적은 일측폐환기(one-lung ventilation, OLV) 중 고탄산혈증이 동맥혈 산소화에 미치는 영향을 평가하는 것이다.

방법: 비디오 보조 흉강경을 이용하여 폐엽절제술 또는 폐절제술을 받는 성인 환자 50명이 참여하였다. 제1군은(n = 25) 처음 30분 동안 정상 동맥혈탄산가스분압(PaCO₂: 38–42 mmHg)을 유지 후에는 고탄산혈증(45–50 mmHg)을 유지하였고, 2군은(n = 25), 반대로 고탄산혈증 유지 후 정상 동맥혈탄산가스분압을 유지하였다. 동맥혈산소분압, 헬륨 혈증과 혈액학적 변수에 유의한 차이를 보이지 않았다.

결과: 정상 탄산가스분압과 고탄산혈증 동안 동맥혈 산소분압은 각각 66.5 ± 10.6 mmHg와 79.7 ± 17.3 mmHg었다(평균 차이: 13.2 mmHg, 평균 차이에 대한 95% 신뢰구간: 17.0–9.3, P < 0.001). 동맥혈 산소포화도는 정상 탄산가스분압과 고탄산혈증에서 각각 92.5 ± 4.8% 및 94.3 ± 3.1%였다(P = 0.009). 폐의 정적탄성(33.0 ± 5.4 vs. 30.4 ± 5.3 ml/cmH₂O, P < 0.001), 동맥혈의 산소단량(15.4 ± 1.4 vs. 14.9 ± 1.5 ml/dl, P < 0.001) 및 산소전달량(69.9 ± 18.4 vs. 65.1 ± 18.1 ml/min, P < 0.001)은 고탄산혈증에서 정상 탄산가스분압 일 때에 비해 유의하게 높았다.

결론: 고탄산혈증은 일측폐환기 중 동맥혈 산소분압 및 산소 운반능력을 증가시키고 폐의 역할을 개선시킴으로써 동맥혈 산소화에 도움을 줄 것으로 생각된다. 그러므로 일측폐환기 중 동측 흉강경(permissive hypercarbia)이 동맥혈 산소화를 위한 간단하고 유용한 방법이 될 수 있다.

Keywords: Arterial oxygen partial pressure; Carbon dioxide; Hypercarbia; One-lung ventilation; Shunt; Thoracic surgery.
Retrospective analysis of risk factors of hypotensive bradycardic events during shoulder arthroscopic surgery under interscalene blockade in the sitting position

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Keywords: Brachial plexus block; Bradycardia; Hypotension; Logistic models; Risk factors; Shoulder arthroscopy; Syncope.
Rhomboid intercostal and subserratus plane block -a case series-

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Case Report

배경: 능형 늑간-거근하면(rhomboid intercostal-subserratus plane, RISS) 차단기법은 복부 및 흉부 수술에 유용한 결과를 보이는 새로운 근막차단 기법이다. 본 연구의 목적은 주요 복부 수술 후 양측 RISS 차단술을 받은 환자에서 진통 및 피부 적용부위를 기술하는 것이었다.

증례: 복부 수술을 받는 21명의 환자를 대상으로 T5–T6 수준에서 능형 늑간 차단을, T6–T9 수준에서 거근하면 차단을 실시하였다. RISS 차단을 통해 효과적인 수술 후 진통이 제공되었다. 피부 적용범위는 T3부터 T12까지 다양했다. 환자들은 통증 관리평가에서 높은 만족도를 보였다.

결론: 복부 수술에서 RISS의 차단은 수술기 통증 관리에 중요한 역할을 한다는 것으로 보이며, 여러 방식의 진통요법을 보완한다. 복부 수술에 대한 RISS 차단의 유효성을 확인하기 위해서는 추가적인 무작위 배정 대조 임상시험의 필요하다.

Keywords: Facial plane block; Interventional ultrasonography; Pain; Pain management; Postoperative pain; Regional anesthesia.
Perioperative considerations for COVID-19 patients: lessons learned from the pandemic -a case series-

COVID-19 환자를 위한 주술기 고려사항: 팬데믹으로부터 얻은 교훈

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증례: 최근 여행 과거력, 감염 증상, 흉부 X선 검사 결과 COVID-19 감염이 의심되는 66세 남성이 본원에 내원했다. 환자의 패혈증 상태를 고려하여 응급 수술을 실시하기로 결정했다. 환자는 안면 마스크를 통해 산소를 보충받으면서 플라스틱으로 덮은 트롤리를 통해 수술실로 이송되었다. 숙련된 마취통증의학과 전문의가 비디오 후두경을 이용하여 빠른 신속마취유도(rapid sequence intubation)를 실시하였고 바람, 접촉 및 공기매개 감염에 대한 예방조치가 시행되었다. 호흡곤란의 초기 증상이 있었으므로, 재삽관을 피하기 위해 환자는 수술 후에도 삽관이 유지되었다.

결론: 본 증례의 목적은 COVID-19가 진단되었거나 의심되는 환자의 외과적 관리를 용이하게 하고 의료 종사자 및 다른 환자들에 대한 원내 전파 위험도를 최소화하는 것이다.

Keywords: Communication; Coronavirus; COVID-19; Infection control; Pandemics; Perioperative care; Perioperative period; Personal protective equipment.
One-lung ventilation (OLV) is the gold standard for several thoracic surgeries, such as lung, esophageal, aortic, or mediastinal procedures [1]. With OLV, access to the surgical field could be improved, and the process of operation could also be expedited. During OLV, only one lung is ventilated, and both lungs are perfused; therefore, transpulmonary shunting and impairment of oxygenation inevitably occurs. This occasionally results in hypoxemia, and maintenance of adequate arterial oxygenation is a challenge for both anesthesiologists and surgeons.

Hypoxemia during OLV could be treated with either reinflation of the operated lung or increasing the inspiratory oxygen fraction of the ventilated lung. The alternative or supplemental approaches are either intermittent positive airway pressure [2] or differential lung ventilation [3] to the ventilated lung.

There are some reports about permissive hypercarbia during OLV in patients who have undergone thoracotomy. Permissive hypercarbia is defined as the acceptance of hypercarbia and continuation of the ventilation strategy, and permissive hypercarbia is usually achieved by slowly lowering the tidal volume and/or the respiratory rate. Sticher et al. [4] reported that cardiac index and pulmonary vascular resistance were increased, systemic vascular resistance decreased, and oxygenation remained unchanged with hypercarbic hypoventilation during OLV. In that study, minute ventilation was reduced from 8.8 ± 1.7 L/min to 4.2 ± 0.70 L/min, and arterial PaCO$_2$ increased from 41.3 ± 3.0 mmHg to 63.8 ± 7.5 mmHg.

In the current issue of the *Korean Journal of Anesthesiology*, Lee et al. [5] reported the relationship between hypercarbia and arterial oxygenation compared to normocarbia during OLV. In this report, the ventilatory rate was adjusted to maintain the preset target PaCO$_2$ (normocarbia, PaCO$_2$: 38–42 mmHg, hypercarbia, PaCO$_2$: 45–50 mmHg). The authors concluded that hypercarbia increased PaO$_2$ and O$_2$ carrying capacity and improved pulmonary mechanics without significant hemodynamic changes during OLV, and it may help manage hypoxemia during OLV. Therefore, permissive hypercarbia may be a simple and valuable modality for managing arterial oxygenation during OLV. In this study, permissive hypercarbia is considered as one of the treatment modes for hypoxemia during OLV, and the results support the theoretical basis for including permissive hypercarbia to manage hypoxemia during OLV.

More rigorously designed multicenter randomized clinical trials and large-scale observational studies are required to determine the effectiveness of permissive hypercarbia in managing arterial oxygenation during OLV.
Conflicts of Interest

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

References

Emergence agitation (EA), also referred to as emergence delirium, can have clinically significant consequences. The mechanism of EA remains unclear. The proposed risk factors of EA include age, male sex, type of surgery, emergency operation, use of inhalational anesthetics with low blood–gas partition coefficients, long duration of surgery, anticholinergics, premedication with benzodiazepines, voiding urgency, postoperative pain, and the presence of invasive devices. If preoperative or intraoperative objective monitoring could predict the occurrence of agitation during emergence, this would help to reduce its adverse consequences. Several tools are available for assessing EA. However, there are no standardized clinical research practice guidelines and its incidence varies considerably with the assessment tool or definition used. Total intravenous anesthesia, propofol, μ-opioid agonists, N-methyl-D-aspartate receptor antagonists, nefopam, α2-adrenoreceptor agonists, regional analgesia, multimodal analgesia, parent-present induction, and preoperative education for surgery may help in preventing EA. However, it is difficult to identify patients at high risk and apply preventive measures in various clinical situations. The risk factors and outcomes of preventive strategies vary with the methodologies of studies and patients assessed. This review discusses important outcomes of research on EA and directions for future research.

Keywords: Anesthesia; Emergence agitation; Emergence delirium; Incidence; Practice guideline; Risk.

Introduction

Emergence agitation (EA) involves restlessness, disorientation, excitation, non-purposeful movement, inconsolability, thrashing, and incoherence during early recovery from general anesthesia [1]. The incidence of EA varies, from approximately 0.25% to 90.5%, with age, assessment tool used, definitions, anesthetic techniques, type of surgery, and time of EA assessment during recovery [2–6]. The clinical consequences of EA are similarly varied. It is typically short lived and resolves spontaneously, and its clinical consequences are often considered minimal [7,8]. However, it may have clinically significant consequences, such as injury to the affected patient or their medical staff, falling out of bed, bleeding at the surgical site, accidental removal of drains or intravenous catheters, unintended extubation, respiratory depression, and increasing medical care costs [9–11].

Emergence delirium (ED) is an acute confusion state during recovery from anesthesia; patients with ED may present with disorientation, hallucination, restlessness, and purposeless hyperactive physical behavior [8,12]. ED is not fully equivalent to EA; ED can involve hypoactive signs or mixed forms and hyperactive signs similar to agitation [13–15]. Nevertheless, the terms EA and ED have been used interchangeably in several studies [16,17]. Moreover, the same assessment tools (e.g., Riker Sedation-Agitation Scale or
Richmond Agitation-Sedation Scale) have been used for both conditions [18–21]. EA and ED should be differentiated from postoperative delirium. Postoperative delirium involves ED; ED represents the early onset of postoperative delirium in the operating room or on arrival at the postanesthesia care unit (PACU) immediately after the anesthesia period [18,21,22]. EA and ED in the PACU are strong predictors of postoperative delirium, which is associated with prolonged hospital stay and increased morbidity (e.g., pulmonary complications), mortality, and the need for institutionalization of adult patients [2,23]. The terms EA and ED are used interchangeably in this review, as in previous studies [16,17,24,25].

This review discusses the important themes of EA research, issues that remain unresolved, and future research directions.

**Mechanism of emergence agitation**

The precise pathophysiological mechanism of EA after general anesthesia is unknown [19,20]. In children, proposed causes of EA include high levels of anxiety regarding surgery, new environments, separation from parents, and encounters with unfamiliar medical staff [9,26]. These may lead to increased sympathetic tone and prolongation of the excited state during anesthesia recovery [27].

The advent of volatile agents with low blood solubility, such as sevoflurane and desflurane, has increased the incidence of EA in children [11,12,28]. A proposed explanation for this is that sevoflurane and desflurane cause differential recovery rates in brain function, due to differences in clearance of inhalational anesthetics from the central nervous system [12,29]; whereas audition and locomotion recover first, cognitive function recovers later, resulting in EA. In addition, elevated lactate and glucose concentrations in the parietal cortex due to sevoflurane anesthesia, and the occurrence of clinically silent sevoflurane-induced epileptogenic activity have been proposed to induce EA [16,30,31].

Functional magnetic resonance imaging has been used to study the mechanisms underlying the alteration of consciousness during anesthesia [32,33]. Studies have reported that alterations of brain network connectivity vary with the level of sedation. During emergence from general anesthesia, thalamocortical connectivity in sensory networks, and activated midbrain reticular formation are preserved. However, delayed recovery of impaired functionality of subcortical thalamoregulatory systems could contribute to defects in cortical integration of information, which could lead to confusion or an agitated state [33].

**Proposed risk factors for emergence agitation**

The etiology of EA is multifactorial [3]. It is important to identify the causes and risk factors of EA, and modify them, when applicable, to reduce incidence and prevent adverse consequences. Results from previous studies have been inconsistent due to the application of different assessment tools, definitions, and study designs (e.g., prospective randomized controlled studies, prospective observational studies, or retrospective studies). In addition, proposed risk factors of EA have been different for children and adults. Potential risk factors for EA in children are as follows: preschool age (2–5 years), no previous surgery, hospitalization or high number of previous interventions, poor adaptability, attention-deficit hyperactivity disorder, patient pre-existing behavior, psychological immaturity, preoperative anxiety, parental anxiety, patient and parent interaction with healthcare providers, lack of premédication (with midazolam), paradoxical reaction to midazolam stated in child’s medical history, type of surgery, use of inhalational anesthetics with low blood–gas partition coefficients (e.g., sevoflurane and desflurane), excessively rapid awakening (in a hostile environment), and pain [6,12,17,29,34–36].

The proposed risk factors for EA in adults are age, sex, obesity (body mass index ≥ 30 kg/m²), African ethnicity, number of intubation attempts, type of surgery, emergency operation, method of anesthesia (inhalation anesthesia), duration of surgery or anesthesia, pre-existing mental health problems (e.g., psychiatric problems or cognitive impairment), chronic lung disease, recent smoking, history of social drinking, substance misuse, anticholinergics, doxapram, premédication with benzodiazepines, voiding urgency, postoperative pain, postoperative nausea and vomiting, and the presence of invasive devices (e.g., urine catheter, chest tube, or tracheal tube) [2,3,8,18,21,37–44] (Table 1). We review common risk factors and other related issues presented in literature.

**Age**

EA is more common in children than in adults [38,45,46]. In a study of children aged 2–12 years, the incidence of EA was inversely correlated with age [47]. In a prospective cohort study of children aged 3–10 years, younger age was associated with increased risk of preoperative anxiety [48]. The frequency of EA after surgery was higher in children with preoperative anxiety than those without [49].

In adults, the association between age and EA have varied among studies. Age was not associated with EA in a prospective observational study of 2000 patients, and in a case-controlled study [2,3]. Among studies that showed a relationship between
age and EA, a variety of age groups were reported as risk factors. Kim et al. [39] reported that young age was a risk factor for EA. Rim et al. [41] and Rose [50] reported that old age was a risk factor for EA. Radtke et al. [21] reported that EA more frequently affected younger (18–39 years) and older (≥ 65 years) patients compared to middle-aged (40–64 years) patients. In a recent study on EA after sevoflurane anesthesia, age ≥ 65 years was significantly associated with EA [40]. Age-related changes in physiology can increase drug sensitivity and toxicity in elderly patients compared to young adults [51,52]. Adverse events caused by EA can also have more serious consequences in elderly patients. Further studies in elderly patients will facilitate better prevention of EA.

Sex

The effect of sex on EA in children is not well known [53]. However, in a prospective observational study of children, sex was not associated with the occurrence of EA [54]. Conversely, several studies have shown that male sex is associated with EA in adults [3,8,38,41,55,56]. The higher rate of EA in men is explained by lower pain tolerance and a significant association between postoperative pain and the male sex [41,57]. In addition, male sex is a risk factor for catheter-related bladder discomfort, which is defined as voiding urgency. Voiding urgency is an independent risk factor for EA [42,58].

Surgery

In a prospective cohort study of 521 children aged 3–7 years, ophthalmological and otorhinolaryngological procedures were found to be associated with EA. In particular, otorhinolaryngological procedures were independent risk factors for EA [29]. Similarly, several studies have identified strabismus surgery and tonsillectomy as risk factors for EA in pediatric patients [54].

In a prospective observational cohort study of 1970 adult patients, the type of surgery was not a risk factor for EA [8]. However, the type of surgery was associated with EA in multiple other studies [3,18,21,42]. Spine surgery, musculoskeletal surgery, oral cavity surgery, otolaryngological surgery, breast surgery, and abdominal surgery have been associated with a high risk of EA in adult patients [3,18,21,41].

Conflicting results have been reported, depending on whether elective or emergency surgery was performed. In a 2006 study, Lepouse et al. [18] found that emergency surgery did not affect the incidence of EA. In a 2019 study, Ramroop et al. [40] found that emergency surgery increased the risk of postoperative EA.

| Table 1. Possible Risk Factors for Emergence Agitation |
|-----------------------------|-----------------------------|-----------------------------|
| **Risk factor**             | **Children**                | **Adult**                   |
| Patient related             | Preschool age (2–5 years)   | Age                        |
|                             | No previous surgery         | Sex                        |
|                             | Hospitalization or high number of previous interventions | Obesity (body mass index ≥ 30 kg/m²) |
|                             | Poor adaptability           | African ethnicity           |
|                             | Attention-deficit hyperactivity disorder | Pre-existing mental health problems (e.g., psychiatric problems or cognitive impairment) |
|                             | Patient preexisting behavior | Chronic lung disease       |
|                             | Psychological immaturity     | Recent smoking              |
|                             | Preoperative anxiety        | History of social drinking  |
|                             | Parental anxiety            | History of substance dependence |
|                             | Patient and parent interaction with healthcare providers | Number of intubation attempts |
| Anesthesia related          | Lack of premedication (with midazolam) | Method of anesthesia (inhalation anesthesia) |
|                             | Paradoxical reaction to midazolam stated in child’s medical history | Duration of surgery or anesthesia |
|                             | Use of inhalational anesthetics with low blood–gas partition coefficients (e.g., sevoflurane and desflurane) | Premedication with benzodiazepines |
|                             | Excessively rapid awakening (in a hostile environment) | Neuromuscular blocking agents and anticholinergics |
|                             | Pain                        | Doxapram                    |
| Surgery related             | Type of surgery             | Voiding urgency             |
|                             |                            | Postoperative pain          |
|                             |                            | Postoperative nausea and vomiting |
|                             |                            | Presence of invasive devices (e.g., urine catheter, chest tube, or tracheal tube) |
|                             |                            | Type of surgery             |
|                             |                            | Emergency operation         |
compared to elective surgery. The authors speculated that greater anxiety and uncorrected physiological derangements may have contributed to the increased incidence of EA in patients undergoing emergency surgery.

**Duration of surgery/anesthesia**

The duration of anesthesia changes with the duration of surgery. Caution is needed when interpreting studies that suggest a longer duration of surgery or anesthesia is a risk factor for EA; only one of these parameters (i.e., anesthesia time or surgery time) may have been measured and analyzed in the given study [18,40,41]. In a study that analyzed both surgery and anesthesia time, patients with EA had significantly longer surgery and anesthesia times than patients without EA [42]. Furthermore, in a prospective observational study of 1868 adult patients, a longer duration of surgery was identified as a risk factor for hypoactive ED [21].

**Inhalational anesthetics**

Halothane, isoflurane, desflurane, and sevoflurane can all serve as triggers of EA; however, EA is more common with inhalational anesthetics with low blood–gas solubility, such as sevoflurane and desflurane [8,9,28]. In a meta-analysis of pediatric patients performed in 2015, desflurane induced EA less frequently than sevoflurane [59]. Similarly, in a randomized controlled double-blind study of adult patients with orthognathic surgery, desflurane reduced the incidence of EA compared to sevoflurane (24% vs. 71%, respectively) [4].

Nitrous oxide is an inhalational anesthetic agent commonly used in general anesthesia as an adjunct to other inhalational anesthetics; its use is reportedly not associated with EA [21,40]. Nitrous oxide was shown to attenuate EA in pediatric patients [60,61], but few studies have investigated its effects in adult patients. Therefore, further studies are needed to determine the impact of nitrous oxide on EA in adult patients.

**Rapid awakening from anesthesia**

In studies of pediatric patients, rapid awakening by strange medical staff in unfamiliar environments has been identified as a potential risk factor for EA [29,62]. However, the rapid awakening process did not cause a higher incidence of EA after sevoflurane anesthesia in children [63]. Moreover, a study of adult patients revealed that desflurane was associated with a lower incidence of EA compared to sevoflurane, although desflurane was associated with a more rapid recovery time [4].

**Neuromuscular blocking agents and reversal agents**

Anticholinergics (e.g., atropine and scopolamine) are known risk factors for EA [51,64,65]. Neuromuscular blocking agents and reversal agents, such as anticholinergics (e.g., glycopyrrolate and atropine), cholinesterase inhibitors (e.g., pyridostigmine and neostigmine), and sugammadex, are commonly used for general anesthesia. However, only a few randomized controlled trials have been conducted to assess the effects of neuromuscular blocking agents and/or reversal agents on EA. In a prospective randomized controlled study, rocuronium-sugammadex reduced the incidence, severity, and duration of EA in patients undergoing closed reduction of nasal bone fracture compared to succinylcholine [5]. The authors speculated that elevated lactate and potassium concentrations, incomplete neuromuscular blockade during surgery, increased intraocular pressure, and histamine release due to administration of succinylcholine may have led to more negative effects on EA, relative to those caused by the use of rocuronium-sugammadex. Studies comparing the effects of sugammadex and cholinesterase inhibitors on EA have shown inconsistent results. In a retrospective study of children undergoing strabismus surgery, sugammadex showed no EA-preventive effect compared to pyridostigmine + glycopyrrolate [66]. In contrast, a prospective randomized controlled study of children undergoing adenotonsillectomy revealed that the use of sugammadex decreased the severity of EA resulted in less EA compared to the use of neostigmine + atropine [67]. Studies of EA-related drugs have mainly focused on sedatives and analgesics. Further studies are needed to investigate the effects of the depth of intraoperative neuromuscular blockade, sugammadex, and cholinesterase inhibitors on EA.

**Pain**

Pain is a major risk factor for EA in both children and adults, although EA has been reported in spite of pain-free procedures and may occur regardless of pain intensity [3,6,9,11,38,68]. These findings indicate that EA and postoperative pain are separate clinical phenomena; however, it is difficult to distinguish between EA and behavioral changes due to postoperative pain [69,70]. In adults, when postoperative pain was assessed with a numerical rating scale, a score ≥ 5 points was found to increase the risk of EA [21,38,39]. Nonetheless, EA may increase postoperative pain. Therefore, adequate perioperative pain control may influence onset of EA.
Presence of invasive devices

The presence of invasive devices (e.g., urine catheters, nasogastric tubes, chest tubes, and tracheal tubes) during emergence is a well-known risk factor for EA [2,3,8,39]. It can cause embarrassment, distress, discomfort, and pain in patients during emergence; it can also exacerbate delirium in the PACU by increasing the use of opioids and benzodiazepines [13,43].

Prediction of emergence agitation

Prevention is preferred over treatment, for EA; EA can have serious consequences for patients, and increase the patient care burden [16,71]. Recently, Hino et al. [54] developed and validated the EA risk scale (consisting of four domains—age, Pediatric Anesthesia Behavior score, operative procedure, and anesthesia time) for children receiving sevoflurane anesthesia in a single-center study. The EA risk scale showed excellent predictive performance. Therefore, the EA risk scale may be used to predict and prevent EA after sevoflurane anesthesia in pediatric patients. However, the EA risk scale is not validated for use in patients anesthetized with drugs other than sevoflurane. Further studies are needed to demonstrate external validity in other hospitals. In addition, for effective prevention of EA, it would be helpful to identify a biomarker that could predict the occurrence of EA, based on preoperative blood sample examination. In elderly patients undergoing gastrointestinal surgery, the plasma level of brain-derived neurotrophic factor (BDNF) collected at skin closure via blood sampling was significantly increased in patients with EA [72]. However, the study showed that the level of plasma BDNF collected before induction of anesthesia did not differ between patients who did and did not show EA. The study included only a limited number of well-selected patients. Thus, larger-scale clinical trials are needed to ensure the validity of BDNF as a predictive biomarker for EA. In addition, if the occurrence of postoperative EA can be predicted through objective monitoring during surgery, it may contribute to improved postoperative outcomes by preventing the occurrence of EA. In a prospective observational study published in 2019, the occurrence of specific electroencephalogram patterns (burst suppression and emergence trajectory) during anesthesia was associated with PACU delirium [73]. The authors could not provide information regarding agitation during emergence because all patients underwent assessment for PACU delirium after the return of consciousness. However, they suggested that EA could be predicted through intraoperative patient monitoring.

Assessment tools for emergence agitation

Although several scales and their variants have been proposed as tools for assessing EA in children, the most commonly used in pediatric EA studies is the Pediatric Anesthesia Emergence Delirium (PAED) scale developed in 2004 (Table 2). It provides a score from 0 to 20 and reportedly shows validity for assessment of EA in children [74]. However, the PAED scale has disadvantages of inherent subjectivity in assessing each behavior item and suboptimal interrater reliability [75]. In addition, the cutoff point for defining the presence of EA is controversial. Bong and Ng [76] suggested that PAED score ≥ 10 was the ideal cutoff for EA. In contrast, Bajwa et al. [69] reported that PAED score > 12 had greater sensitivity and specificity than PAED score ≥ 10 in the assessment of EA PAED. In another study, PAED score ≥ 16 was adopted as an indicator of EA without an obvious rationale [68].

In adults, the Riker Sedation-Agitation Scale (RSAS, 7-point scale with three levels of agitation) [71], Richmond Agitation-Sedation Scale (RASS, 10-point scale with four levels of agitation) [77], Aono’s 4-point scale [78], Nurses Delirium scale [79], and the 3-point scale (graded as mild, moderate, or severe) [3] have been introduced for assessment of EA (Table 2). Although the RSAS and RASS have been commonly used, and show high interrater reliability in adult intensive care unit patients [80,81], none of the scales have been validated in the operating room and/or the PACU. There have been few studies of EA in intensive care unit patients [37]; the majority of EA studies have been performed in PACUs or operating rooms [19,20,82]. Consequently, the reported incidence of EA differed with the evaluation site (e.g., operating room vs. PACU), assessment tool (e.g., RSAS vs. RASS), and definition of EA (e.g., RASS ≥ +1 vs. ≥ +2 vs. ≥ +3). The reported incidence of EA was higher in the operating room when emerging from general anesthesia than in the PACU (e.g., 3.7% vs. 1.3% and 54.3% vs. 28.6%, respectively) [8,38,83]. The RSAS tended to show an incidence of EA that was similar to or higher than the incidence indicated by the RASS for the same patient group (13.8% by the RSAS vs. 11.2% by the RASS, respectively) [83] or same

### Table 2. Assessment Tools for Emergence Agitation

<table>
<thead>
<tr>
<th>Children</th>
<th>Adults</th>
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<tr>
<td>Pediatric Anesthesia Emergence Delirium scale</td>
<td>Riker Sedation-Agitation Scale</td>
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<td>Richmond Agitation-Sedation Scale</td>
<td>Aono’s 4-point scale</td>
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<td>Nurses Delirium scale</td>
<td>Three-point scale (graded as mild, moderate, or severe)</td>
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type of surgery (50% by the RSAS vs. 22% by the RASS, respectively) [39,82]. Fields et al. [2] used RASS ≥ +3 as an indicator of EA, while Jee et al. [20] and Ham et al. [84] adopted RASS ≥ +2 as an indicator of EA; most other groups defined RASS ≥ +1 as an indicator of EA [38,39,83].

Standardized clinical research practice guidelines are needed to reduce the variations of EA incidence with assessment tools and definitions among researchers. Furthermore, there is a need to develop a tool that can objectively evaluate the degree of agitation, in a manner similar to the bispectral index, which is an objective tool for assessing the depth of sedation during general anesthesia.

Strategies to prevent emergence agitation

In this section, we review strategies to prevent EA, classified into pharmacological and non-pharmacological methods (Table 3). Caution is needed when interpreting the results of studies comparing the preventive effects of drugs or agents on EA; the same drugs may not have identical effects depending on the dose, method of administration (e.g., continuous infusion or single bolus), timing of administration, or patients (e.g., children, adults, or elderly patients) [20,85].

Pharmacological methods

Choice of anesthesia methods: Total intravenous anesthesia, inhalational anesthesia, balanced anesthesia

Several types of anesthesia methods may be used—total intravenous anesthesia (TIVA), inhalational anesthesia, or balanced anesthesia. In a randomized controlled trial, TIVA with propofol and remifentanil reduced EA compared to volatile induction and maintenance of anesthesia with sevoflurane, in children aged 2–6 years, after strabismus surgery [86]. However, conflicting results have been reported regarding the effects of balanced anesthesia vs. inhalation anesthesia on EA in pediatric patients [47,87–89]. This was presumably due to differences in the types of surgery (i.e., fiberoptic bronchoscopy, adenotonsillectomy, or minor surface surgery), adjuvant analgesics (i.e., ketorolac and dexmedetamine compared to none), regimens of balanced anesthesia (i.e., sevoflurane-remifentanil or sevoflurane-fentanyl), and tools for assessment of EA. In addition, the effects of balanced anesthesia on EA can differ with the doses of drugs that are administered, even with the same regimen [88,89]. Thus, further studies are needed to determine the optimal doses for effective EA prevention.

In adults, the effects of anesthetic techniques on EA showed diverse results; overall, TIVA showed no significant difference or lower incidence of EA compared to inhalational anesthesia [3,18,37,39,42,83]. In a prospective study of 1,359 patients, and a retrospective study of 488 patients, the incidence of EA did not differ with the anesthetic technique [18,42]. Conversely, EA was less frequent with TIVA than with inhalational anesthesia in both a prospective observational study of 2,000 patients, and a retrospective study of 792 patients [3,39]. Similarly, in a prospective cohort study, TIVA and a short duration (≤ 5.7 hours) of balanced anesthesia protected against EA [37]. In addition, a prospective randomized controlled clinical study showed that TIVA with propofol and remifentanil reduced the incidence of EA compared to volatile induction and maintenance of anesthesia with sevoflurane [83]. Therefore, TIVA may be appropriate for patients with a high risk of EA.

In a multicenter randomized controlled trial of adult patients undergoing elective craniotomy, the incidences of EA were similar in patients undergoing balanced anesthesia (sevoflurane-remifentanil and sevoflurane-fentanyl) and those undergoing TIVA (propofol-remifentanil) [90]. However, in that study, agitation was only evaluated as an adverse outcome; no specific definition of agitation was provided, and no tool for assessment of agitation was specified. Therefore, further well-designed prospective studies are needed to compare the effects of balanced anesthesia and TIVA on EA.

Propofol

Propofol is the preferred drug for the prevention and treatment

| Table 3. Strategies to Prevent Emergence Agitation |
| Pharmacological methods |
| Total intravenous anesthesia |
| Propofol |
| Opioids |
| Ketamine |
| Magnesium sulfate |
| Tramadol |
| Nefopam |
| Dexmedetomidine |
| Regional analgesia |
| Multimodal analgesia |
| Avoidance of premedication with benzodiazepine (especially in adults) |
| Non-pharmacological methods |
| Informing the patient of predictable pain or discomfort prior to anesthesia |
| Removing indwelling invasive devices as early as possible |
| Parental presence during induction of anesthesia and recovery (in pediatric patients) |
| Family-centered behavioral preparation for surgery |
of EA in pediatric patients [36,91]. In a meta-analysis of pediatric patients, propofol showed a prophylactic effect against EA, depending on the timing of administration [85]. An intravenous bolus of 2 mg/kg propofol, administered immediately after induction of anesthesia, did not reduce EA after desflurane anesthesia [92]. In contrast, continuous infusion of propofol during maintenance of anesthesia, or addition of a bolus of propofol at the end of surgery showed a preventive effect against EA in pediatric patients undergoing general anesthesia [93–95]. These effects can be explained mainly by the rapid pharmacokinetics of propofol [85]. As observed in pediatric patients, continuous infusion of propofol alone during maintenance of anesthesia reduced the incidence of EA in adult patients undergoing closed reduction of nasal bone fracture compared to sevoflurane anesthesia [96]. However, to the best of our knowledge, there are no studies on the effects of a single bolus injection of propofol at the end of surgery on EA in adult patients. Therefore, further research is needed on this aspect of propofol usage.

**Opioids**

In a meta-analysis of 19 randomized controlled trials with 1528 children, prophylactic administration of μ-opioid agonists (i.e., fentanyl, sufentanil, alfentanil, or remifentanil) was found to reduce the incidence of EA following sevoflurane anesthesia [97]. In addition, in a meta-analysis of 37 studies with 3,172 children, fentanyl had a prophylactic effect in the prevention of sevoflurane- and desflurane-related EA [85]. In contrast to children, only a few studies assessed the effects of opioids on EA in adult patients. In a prospective double-blind randomized trial of 60 adult patients, maintenance of low-dose remifentanil (range 0.01–0.05 μg/kg/min) infusion during the emergence phase reduced the incidence of non-purposeful movement [98]. In a randomized double-blind placebo-controlled study of 34 adult patients undergoing an oral surgical procedure, intravenous injection of alfentanil (15 μg/kg) during emergence suppressed EA after isoflurane anesthesia compared to placebo [99]. In a randomized controlled trial comparing pre-anesthesia use of fentanyl and oxycodone, an intravenous bolus of oxycodone (0.2 mg/kg) reduced the incidence of EA compared to a bolus of fentanyl (2 μg/kg); however, it resulted in delayed awakening in patients undergoing closed reduction of nasal bone fracture under desflurane anesthesia [100].

**Ketamine**

Ketamine is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, which has sedative, amnestic, and analgesic properties. Ketamine (0.25 mg/kg and 0.5 mg/kg) administered 10 minutes before the end of surgery contributed to EA prevention without delayed recovery in children after sevoflurane anesthesia [101,102]. At the dose of 0.5 mg/kg, ketamine did not show a significant difference in the incidence of EA compared to 0.25 mg/kg; however, patients’ pain scores decreased as the dose of ketamine increased [102]. In adult patients undergoing anesthesia with sevoflurane, 0.5 mg/kg of ketamine injected 20 minutes before the end of surgery contributed to EA prevention after rhinoplasty; however, it prolonged the anesthesia time due to delayed recovery [38].

**Magnesium sulfate**

Magnesium sulfate is a noncompetitive NMDA receptor antagonist, which has central sedative, neuroprotective, and analgesic-sparing effects [103,104]. In a study of pediatric patients (3–16 years old), magnesium sulfate (30 mg/kg) administered 10 minutes prior to the end of surgery did not reduce EA after sevoflurane anesthesia [105]. In contrast, a 30 mg/kg bolus with continuous infusion of 10 mg/kg/h (from the start of surgery to the end of surgery) reduced the incidence and severity of EA in pediatric patients (4–7 years) undergoing the same surgery (adenotonsillectomy) under sevoflurane anesthesia [53]. The authors speculated that the neuroprotective and anticonvulsant properties of magnesium sulfate may have reduced the incidence of EA. Similarly, in a randomized double-blind placebo-controlled trial in adult patients (20–60 years old) undergoing endoscopic sinus surgery, magnesium sulfate administered throughout the surgery was effective in preventing EA [104].

**Tramadol**

Tramadol is an atypical centrally acting opioid that inhibits M1 and M3 muscarinic acetylcholine and nicotinic acetylcholine as well as NMDA receptors [106–108]. In a retrospective cohort study, a single dose (2 mg/kg) of tramadol administered intravenously at the start of surgery was found to reduce the incidence of EA after sevoflurane anesthesia in adult patients undergoing nasal surgery [19]. The authors speculated that the analgesic, antitussive, and anti-shivering effects of tramadol, as well as its ability to reduce voiding urgency, may have resulted in the prevention of EA. In a prospective randomized controlled study of children undergoing adenotonsillectomy with sevoflurane anesthesia, 2 mg/kg of tramadol intravenous infusion after tracheal intubation for 10 minutes was found to show a similar protective effect against EA compared to 1 μg/kg of dexmedetomidine administered in the same manner [109].

**Nefopam**

Nefopam is a centrally acting nonnarcotic analgesic drug. Nefo-
pam modulates glutaminergic transmission via inhibition of postsynaptic NMDA receptors, while inhibiting serotonin and noradrenaline reuptake; thus, it has anticonvulsant, antidepressant, anti-shivering, and opioid-sparing effects [110,111]. In a prospective randomized controlled trial, 20 mg of nefopam infusion for 20 minutes immediately after induction of anesthesia was found to be effective in reducing the incidence and severity of EA after desflurane anesthesia in adult patients undergoing nasal surgery [20].

\(\alpha_2\)-adrenoreceptor agonists

\(\alpha_2\)-adrenoreceptor agonists (clonidine and dexmedetomidine) possess sympatholytic, analgesic, and sedative properties [112–114]. In a double-blind trial, 2 μg/kg of clonidine injected intravenously after induction of anesthesia was found to effectively reduce the incidence and severity of sevoflurane-induced EA in male children [115]. In addition, in a meta-analysis that examined clonidine as a premedication agent in children, premedication with clonidine was found to be superior to premedication with midazolam for attenuation of EA [112].

Dexmedetomidine is a highly selective \(\alpha_2\)-adrenoreceptor agonist with 7 to 8-fold greater affinity for the \(\alpha_2\)-adrenoreceptor compared to clonidine [116]. In a meta-analysis of the effects of dexmedetomidine on EA after sevoflurane anesthesia in children, dexmedetomidine was found to reduce the incidence of EA compared to placebo; however, it was associated with a delay in recovery [117]. Nonetheless, in a network meta-analysis study of the effects on EA, of anesthetic adjuvants for sevoflurane anesthesia in children, dexmedetomidine was found to be the most effective drug for prevention of EA compared to ketamine, propofol, clonidine, midazolam, fentanyl, and sufentanil [118]. Furthermore, in adult patients undergoing nasal surgery, an intraoperative dexmedetomidine infusion (0.4 μg/kg/h) provided hemodynamically stable emergence and an EA reduction effect, without a delay in extubation [82]. In contrast, in adult patients undergoing microvascular free flap surgery, preoperative and postoperative dexmedetomidine infusions did not affect the overall incidence of EA [119]. In addition, in adult patients undergoing orthognathic surgery, the addition of a single dose of dexmedetomidine (1 μg/kg) to postoperative remifentanil infusion (0.02 μg/kg/min) did not reduce the incidence of EA compared with remifentanil infusion alone [84]. In adult patients undergoing nasal surgery with desflurane anesthesia, dexmedetomidine infusion (0.04 μg/kg/h) from the induction of anesthesia to extubation showed a better EA preventive effect than placebo (saline) infusion; however, it was inferior to remifentanil infusion (0.05 μg/kg/min) [120].

Benzodiazepines

Benzodiazepines, especially midazolam, are commonly used as premedication agents to provide anxiety, sedation, and amnesia in adults and children [36,121,122]. The effects of preoperative administration of midazolam on EA in pediatric patients were inconsistent [86,123]. Specifically, in a meta-analysis published in 2010 [85], prophylactic administration of midazolam showed no preventive effect against EA in children anesthetized with sevoflurane, desflurane, or both. In contrast, another meta-analysis (published in 2013) indicated that prophylactic administration of midazolam reduced sevoflurane-induced EA [123]. In adults, premedication with benzodiazepines or a patient history of long-term benzodiazepine use increased the risk of EA [18,21,37]. Avoidance of benzodiazepine premedication can be helpful for preventing EA in adults [124].

Interestingly, in contrast with the effects of benzodiazepine premedication, perioperative administration of midazolam reduced EA in both children and adults. Intravenous injection of 0.03 mg/kg of midazolam immediately before the end of the operation reduced EA in children undergoing strabismus surgery with sevoflurane anesthesia [125]. In addition, infusion of midazolam from 15 minutes before anesthesia induction to the end of surgery provided an EA reduction effect similar to that of dexmedetomidine infusion in adult patients undergoing nasal surgery with sevoflurane anesthesia [126].

Regional analgesic techniques

Because postoperative pain is a major risk factor for EA, several studies have been conducted to investigate whether effective pain control through regional blockade can reduce the incidence and/or severity of EA, while reducing the side effects of systemic analgesics. In a prospective randomized double-blind study of 2 to 6-year-old children undergoing inguinal hernia repair under sevoflurane anesthesia, preoperative caudal block was found to reduce the incidence of EA compared to intraoperative intravenous fentanyl (4.5% vs. 59%, respectively) [35]. Peripheral nerve blockade also reduced the incidence or severity of EA in pediatric patients following sevoflurane anesthesia [127,128]. Infraorbital nerve block reduced the incidence and duration of EA in children undergoing cleft lip repair surgery [127], while fascia iliaca compartment block reduced the severity of EA in children undergoing orthopedic surgery that involved the anterior or lateral thigh [128]. Wang et al. [127] speculated that EA may have been reduced as a result of reduction in the amount of intraoperative sevoflurane, as well as reduction in pain caused by the infraorbital nerve block performed at the start of surgery. However, a randomized controlled trial involving different concentrations of
sevoflurane did not show significant reduction of EA in children [24]. Further studies are needed to determine the mechanism by which regional analgesia reduces EA.

**Multimodal analgesia**

Ketamine, magnesium, tramadol, nefopam, α₂-adrenoreceptor agonists (e.g., clonidine or dexmedetomidine), acetaminophen, nonsteroidal anti-inflammatory drugs (e.g., ketorolac), dexamethasone, gabapentinoids, and regional analgesia are included in multimodal analgesia [129]. However, only a few studies have evaluated the effects of multimodal analgesic regimens on EA. In a prospective randomized double-blind controlled study, administration of low-dose ketamine (0.15 mg/kg) followed by dexametomidine (0.3 μg/kg), both administered intravenously approximately 10 minutes before the end of surgery, was found to reduce the incidence and severity of EA in pediatric patients undergoing adenotonsillectomy using sevoflurane anesthesia compared to the administration of volume-matched saline [130]. Notably, ketamine administration at the end of surgery in children undergoing sevoflurane anesthesia (after performing caudal block prior to surgery) could not further reduce EA compared to the placebo group [131]. In children aged 2–10 years, who received preemptive analgesia using acetaminophen and ketorolac, intravenous administration of clonidine (2 μg/kg) reduced the incidence of EA, but lengthened the duration of PACU stay and frequency of postoperative sleepiness compared to children who received preemptive analgesia alone [132].

Further prospective randomized controlled studies with multimodal analgesic regimens are needed to identify drug combinations with better EA preventive effects and fewer adverse effects.

**Non-pharmacological methods**

Informing patients of predictable surgical pain or discomfort from the presence of invasive devices during emergence, prior to the induction of anesthesia, is expected to aid in prevention of EA by reducing sudden embarrassment. Early removal of indwelling invasive devices is expected to aid in relief of EA [3,39]. However, there remains a lack of scientific evidence for the EA reduction effects of these methods in adult patients.

In pediatric patients, preoperative anxiety is a risk factor for EA; recovery in strange environments can also cause EA [63]. Parental presence during induction of anesthesia was found to improve the effect of oral midazolam on EA in children aged 1–3 years undergoing sevoflurane anesthesia [133]; parental presence upon the patient’s arrival in the PACU is also expected to help reduce EA in pediatric patients [131]. In addition, family-centered behavioral preparation for surgery, which includes preoperative education and training of children and their parents, was found to reduce the incidence of EA in pediatric patients aged 2–10 years compared to administration of oral midazolam (0.5 mg/kg) at 30 minutes prior to surgery [134].

**Management of emergence agitation**

EA is a self-limiting phenomenon, which lasts for only a short period (1–15 minutes) [5,11]. The elimination of causative factors (e.g., pain, anxiety, presence of invasive devices) is the mainstay of EA management [3,39]. Differential diagnosis and prompt treatment should also be performed for conditions that can lead to disorientation, such as increased intracranial pressure, bladder distention, upper airway obstruction, hypop- and hyperglycemia, hypotension, hypoxia, and hypercarbia [11]. Two web-based surveys conducted by pediatric anesthesiologists in Canada and Germany [36,91] revealed that sedatives (e.g., propofol and midazolam) and opioids (e.g., fentanyl and morphine) were preferred therapeutic pharmacological treatments for EA. Rarely, some anesthesiologists chose “wait for spontaneous resolution” and/or “parental presence” as the first choice of therapy for EA [36]. To the best of our knowledge, there has only been one randomized controlled trial to evaluate the effects of therapeutic strategies on EA, which compared physostigmine and placebo as its treatments [135]. Further studies are needed to determine the efficacy of pharmacological or non-pharmaceutical interventions (e.g., parental presence) for treatment of established EA.

There have been few EA-related studies in adults compared to studies performed in children. Since the results of the studies in children cannot be extrapolated to adults, it is necessary to verify the consistency of the results for children by performing randomized controlled trials in adults. The establishment of standardized clinical research practice guidelines and the development of objective assessment tools for EA are needed to reduce the discrepancies of EA incidence among various studies, and facilitate better interpretation of the results from published studies. Effective EA prevention involves the identification of risk factors, elimination of correctable risk factors, and the application of pharmacological and non-pharmacological strategies on patients or during surgeries with high risks of EA. Strategies to reduce EA may vary with patient age (i.e., children vs. adults). Considerations for the dosage, timing, and method (e.g., bolus or continuous infusion) of administration of the agent should be made before applying pharmacological methods. In the future, prediction through objective indicators (before or during surgery) is expected to aid in preventing EA.
Conflicts of Interest

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

Author Contributions

Seok-Jin Lee (Conceptualization; Writing – original draft; Writing – review & editing)
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Anesthesia guidelines for COVID-19 patients: a narrative review and appraisal

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The coronavirus disease 2019 (COVID-19) pandemic has challenged health systems globally and prompted the publication of several guidelines. The experiences of our international colleagues should be utilized to protect patients and healthcare workers. The primary aim of this article is to appraise national guidelines for the perioperative anesthetic management of patients with COVID-19 so that they can be enhanced for the management of any resurgence of the epidemic. PubMed and EMBASE databases were systematically searched for guidelines related to SARS-CoV and SARS-CoV-2. Additionally, the World Federation Society of Anesthesiologists COVID-19 resource webpage was searched for national guidelines; the search was expanded to include countries with a high incidence of SARS-CoV. The guidelines were evaluated using the Appraisal of Guidelines for Research and Evaluation II tool. Guidelines from Australia, Canada, China, India, Italy, South Africa, South Korea, Taiwan, the United Kingdom, and the United States of America were evaluated. All the guidelines focused predominantly on intubation and infection control. The scope and purpose of guidelines from China were the most comprehensive. The UK and South Africa provided the best clarity. Editorial independence, the rigor of development, and applicability scored poorly. Heterogeneity and gaps pertaining to preoperative screening, anesthesia technique, subspecialty anesthesia, and the lack of auditing of guidelines were identified. Evidence supporting the recommendations was weak. Early guidelines for the anesthetic management of COVID-19 patients lacked quality and a robust reporting framework. As new evidence emerges, national guidelines should be updated to enhance rigor, clarity, and applicability.

Keywords: Anesthesia; Coronavirus infections; COVID-19; Guidelines; Perioperative management; Perioperative medicine; Review.

Introduction

China reported the first outbreak of the novel severe acute respiratory syndrome-related coronavirus (SARS-CoV-2) in Wuhan on 7 January 2020 [1]. As of 25 June 2020, coronavirus disease 2019 (COVID-19) had become a pandemic with more than 9 million cases with 2% critically ill and 9% deceased [2]. Importantly, healthcare workers accounted for 3.8% of the cases in China and 11% in Italy [3]. Virus transmission is through respiratory droplets and fomites, which places anesthetic staff at a high risk of nosocomial infection. Although the virus has been reported to be air-borne [4], this has not yet been
confirmed in clinical studies.

Following the rapid and global spread of the virus, numerous guidelines have been published by national anesthesia societies to provide anesthetists with insights into the management of COVID-19 patients and the risk of infection during aerosol-generating procedures (intubation, extubation, airway suctioning) associated with anesthesia [5]. Ideally, guidelines should have scientific rigor, and they should be presented with clarity. They should also apply to practitioners internationally, irrespective of the minor variations in practice. An objective framework for developing and appraising clinical guidelines is provided by the Appraisal of Guidelines for Research and Evaluation (AGREE) II tool [6]. As various countries move from the containment phase to the gradual relaxation of community restrictions, the second surge of infections is anticipated.

The primary aim of our review was to appraise national guidelines on the anesthetic considerations for COVID-19 patients presenting for surgery and evaluate their quality with the AGREE II tool. Through updates, guidelines can be refined to ensure that they are more robust, and they can equip anesthetists for the potential viral resurgence.

Materials and Methods

Search strategy and selection of sources of evidence

We conducted a systematic search of the PubMed and EMBASE databases using the combination of Medical Subject Heading (MeSH) and keywords ("anesthesia" or “anesthesiology”) OR ["airway management"] OR ["intubation"] AND ("SARS" OR “SARS-CoV” OR "SARS-CoV-2" OR "COVID-19" OR "Coronavirus") for guidelines/studies published between 1 Jan 2002 and 16 May 2020. To capture new guidelines that had not been indexed in these databases, national anesthesia organizations, with links to their official websites listed on the World Federation of Societies of Anesthesiologists (WFSA) [7] COVID-19 resource webpage (up to 28 May 2020), were interrogated because it represents anesthesia societies from over 150 countries. We also expanded our search for guidelines from countries (China, Hong Kong, Singapore, and Taiwan) that were affected by the SARS-CoV epidemic in 2003 [8]. Guidelines from Hong Kong and Singapore, which reported SARS previously, were not endorsed by their official national societies, and they were excluded. The bibliographies of the retrieved articles were manually screened for additional relevant material.

Eligibility criteria

Only articles written in English and Chinese were included because the two co-authors who conducted the search were proficient in both languages. Articles that reported relevant aspects of perioperative anesthetic management of patients with COVID-19 were included. Two reviewers (SO and WYL) conducted the search independently and screened all article types for eligibility using their titles and abstracts. Duplicate and irrelevant articles were excluded. Articles that did not address the primary objective and those that were correspondences and editorials were also excluded. Discrepancies were discussed and resolved by PK.

Critical appraisal of sources of evidence

SO and PK independently appraised each eligible national guideline using the AGREE II instrument [6] (Supplementary Table 1). The AGREE II instrument has six domains (with 23 items) and two global rating items. The six domains were scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence. Each item in the domain is scored on a seven-point scale (1 = minimum to 7 = maximum). Total scores were scaled to a percentage of the maximum score in each domain; for example, 0% if each reviewer scored 1 and 100% if each reviewer scored 7. The AGREE II instrument has been validated and tested for inter-rater reliability.

In addition, full manuscripts of extracted articles from the literature search were analyzed independently by SO and WYL and graded according to the level of evidence as defined by the Centre for Evidence-Based Medicine, Oxford [9].

Results

Nineteen national guidelines from Australia, Canada, China, India, Italy, South Africa, South Korea, Taiwan, the UK, and the USA described the anesthetic management of COVID-19 patients [10–28]. China had the highest score for Scope and Purpose of guidelines followed by South Korea and the UK. The UK and South Africa scored the highest for the Clarity of guidelines. Among the domains, editorial independence had the lowest score, followed by rigor of development and applicability. Spearman correlation analysis of reviewer scores of all domain items demonstrated good inter-rater reliability ($\rho = 0.714, P < 0.001, 95\% CI: 0.436–0.868$). A summary of the results is provided in Table 1.

There was a paucity of high-quality evidence supporting the current recommendations. Of the 63 articles retrieved from the literature search, only one systematic review (level 2) in 2012 re-
lated aerosol-generating procedures to the infections of health care workers [29], and one prospective single-center study (level 3) in 2006 focused on simulation [30]. The remainder of the reports were predominantly retrospective studies, case reports/series (level 4), and expert opinions (level 5) that focused on infection control and intubation. The results of the literature search are shown in Supplementary Table 2.

Guidelines on preoperative management

Preoperative evaluation, screening, and prioritization for surgery

The details on preoperative guidance varied. China and India detailed preoperative screening of history, symptoms, and investigations while South Africa used a brief checklist [15,17,20]. Australia recommended using telemedicine for preoperative assessment, counseling, consent, and a thorough airway assessment [10]. The UK through the Difficult Airway Society focused specifically on the MACOCHA (Mallampati III or IV; Apnea syndrome [obstructive]; Cervical spine limitation; Opening mouth-3 cm; Coma; Hypoxia; Anesthesiologist-non trained) score to assess and predict a difficult airway [24,31]. Only the USA linked preoperative screening with viral testing and prioritization for surgery involving a multidisciplinary team [26]. Recommendations on scheduling elective surgery during the pandemic were provided by Canada, India, South Africa, the UK, and the USA [12,17,20, 24,26].

Infection control and personal protective equipment

This was the focus of all the guidelines. All countries recommended airborne precautions and Personal protective equipment (PPE) training [10–28]. There was unanimous agreement on the use of full PPE (N95 mask or powered air-purifying respirator (PAPR), face shield or goggles, gown, hat, double gloves) for aerosol-generating procedures and hand hygiene when donning and after doffing PPE [10–28]. All countries (apart from India and South Korea), recommended a buddy system for PPE donning. High-risk healthcare personnel who were pregnant, immunocompromised, or older than 60 years with cardiorespiratory diseases were advised by the UK to refrain from airway management [23,24]. The number and position of staff present in the inner and the outer rooms, the types of PPE, including the position of equipment and monitors, were detailed by Italy and the UK [19,24]. Other recommendations included using a negative pressure operating theater with warning signs [10–21,23–28], placing a hydrophobic filter interposed between the face mask/endotracheal tube and the breathing circuit or the reservoir bag [10–28], and using disposable equipment [10–16,18–28] where possible. A clear plastic sheet to limit the aerosol spread and the use of forced-air warming blankets only in intubated patients were recommended by Australia [10].

Training and resource planning

Simulation training for the provision of anesthetic care was advocated by Australia, Canada, China, India, Italy, the UK, and the USA [10–19,23–28]. In addition, team briefing before surgery was recommended by Australia, Italy, South Africa, the UK, and the USA [10,11,18,23–28]. China, India, and South Korea addressed fatigue by deploying several airway and anesthetic teams to support hospitals and operating theaters [14–17,21]. All guidelines (except those from Canada and Taiwan) detailed the most direct route for patient transfer to the operating theatre: bypassing the holding area with the patient wearing a surgical mask [10,11,14–28].

Evidence

Apart from one level 2 and one level 3 evidence studies, the evidence relating to preoperative management was weak (level 4 and 5 evidence), and it focused on infection control [29,30]. Reports from the SARS outbreak in 2003 detailed risk factors for the infection of healthcare workers related to PPE use and aerosol generation [29,30,32–34]. Recent reviews on the preoperative management of COVID-19 patients also described operating room opti-

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Table 1. Summary of AGREE II Results on National Anesthesia Guidelines for the Management of a COVID-19 Patient

<table>
<thead>
<tr>
<th>AGREE II Domains</th>
<th>Australia/ New Zealand</th>
<th>Canada</th>
<th>China</th>
<th>India</th>
<th>Italy</th>
<th>South Africa</th>
<th>South Korea</th>
<th>Taiwan</th>
<th>UK</th>
<th>US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Domain 1 Scope and purpose</td>
<td>63.9</td>
<td>27.8</td>
<td>75.0</td>
<td>50</td>
<td>44.4</td>
<td>61.1</td>
<td>66.7</td>
<td>44.4</td>
<td>66.7</td>
<td>63.9</td>
</tr>
<tr>
<td>Domain 2 Stakeholder involvement</td>
<td>58.3</td>
<td>33.3</td>
<td>69.4</td>
<td>58.3</td>
<td>58.3</td>
<td>69.4</td>
<td>58.3</td>
<td>58.3</td>
<td>63.9</td>
<td>58.3</td>
</tr>
<tr>
<td>Domain 3 Rigor of development</td>
<td>11.5</td>
<td>3.1</td>
<td>22.9</td>
<td>13.5</td>
<td>8.3</td>
<td>15.6</td>
<td>13.5</td>
<td>17.7</td>
<td>25.0</td>
<td>19.8</td>
</tr>
<tr>
<td>Domain 4 Clarity of presentation</td>
<td>69.4</td>
<td>41.7</td>
<td>69.4</td>
<td>58.3</td>
<td>63.9</td>
<td>77.8</td>
<td>61.1</td>
<td>52.8</td>
<td>83.3</td>
<td>63.9</td>
</tr>
<tr>
<td>Domain 5 Applicability</td>
<td>39.6</td>
<td>25.0</td>
<td>43.8</td>
<td>27.1</td>
<td>31.3</td>
<td>50.0</td>
<td>29.2</td>
<td>35.4</td>
<td>43.8</td>
<td>31.3</td>
</tr>
<tr>
<td>Domain 6 Editorial Independence</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>41.7</td>
<td>0.0</td>
<td>0.0</td>
<td>82.6</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Values are presented as percentage. Spearman correlation analysis of reviewer scores of all domain items demonstrated good inter-rater reliability; \( \rho = 0.714 \) (\( P < 0.001 \), 95% CI: 0.436–0.868).
mization and infection control and the rational use of PPE [35,36].

**Guidelines on intraoperative management**

**Intubation**

All guidelines focused on the reduction of aerosol generation during procedures and limiting the exposure of healthcare personnel [10–28]. Recommendations included a rapid sequence induction and intubation by the most experienced airway personnel and the use of a videolaryngoscope [10–28]. Canada and the UK recommended using intravenous ketamine for induction in patients with hemodynamic instability [12,23]. Manual ventilation was to be avoided and, if required, small tidal volumes were to be delivered via two-handed facemask ventilation, with the VE hand position preferred to the C hand position [24] for a better mask seal. The Difficult Airway Society in the UK also recommended meticulous attention to preoxygenation, including optimizing patient positioning at induction to maximize a safe apnea time [24]. Only Italy suggested apneic nasal oxygenation delivery at a flow rate of 3 L/min during airway manipulation [18]. Positive pressure ventilation was only to be commenced after intubation and inflation of the tracheal tube cuff [10–20,22–28] to at least 5 cmH2O above the peak inspiratory pressure [24]. Awake fiberoptic intubation, including the use of high-flow nasal oxygen and non-invasive ventilation was discouraged by all guidelines (except for Canada and South Africa). Only Australia, Italy, and the UK provided specific recommendations for the management of a difficult airway [10,11,18,19,23,24]. These included using the VORTEX approach [37], intubation via a supraglottic airway device (SAD), and employing the scalpel bougie over the needle cannula approach in front of neck access in “cannot intubate, cannot oxygenate” scenarios [10,19,24]. Other heterogeneous recommendations included a smaller sized endotracheal tube, avoidance of cricoid pressure (to minimize coughing) [19], and loading the endotracheal tube routinely with an introducer [10,11].

**Use of SAD**

There is no consensus on its use as the primary airway device for general anesthesia. China recommended its use [15]; Australia, Canada, Italy, and the UK recommended it only for airway rescue [10,12,19,23,24]. If a second-generation device is used, ensuring a leak-free seal is recommended [24].

**Regional anesthesia**

Regional anesthesia, where possible, has been advocated by Australia, China, India, and the USA [10,14–17,25–28]. Thrombocytopenia and coagulopathy should be excluded before neuraxial techniques, especially in patients with severe COVID-19 disease [38]. Although SARS-CoV-2 has been demonstrated in cerebrospinal fluid and brain tissue on autopsy, spinal anesthesia in obstetric parturients with COVID-19 has been reported to be safe [39]. For peripheral nerve blocks near the head and neck area, airborne precautions may be considered [40]. In addition, confirming the success of the block reduces the need for emergent conversion to general anesthesia [40].

**Extrusion**

Extrusion recommendations targeted at minimizing cough varied, and they included deep extubation, SAD exchange, administration of opioids, lidocaine, dexmedetomidine [10,11,24], glycopyrrolate [22], and prophylactic antiemetics [12,17,27,28].

**Evidence**

Evidence supporting airway management and endotracheal intubation was initially derived from a systematic review on aerosol-generating procedures and infection in healthcare workers (level 2 evidence) and case reports (level 4 evidence) published on SARS [29,33,34,41–44]. Recent reports on COVID-19 patients (level 4 and 5 evidence) have been published [14–16,45–51]. A recent retrospective review (which included an expert panel) of the emergency intubation of 202 patients with COVID-19 reported that hypoxemia (oxygen saturation < 90%) was common and associated with hypotension, cardiac arrest, and pneumothorax [14]. The authors recommended head elevation for intubation with propofol dose reduction, fluid boluses, or inotropes (to avoid hypotension). A ventilation protective strategy utilizing small tidal volumes to minimize barotrauma was recommended [14].

**Guidelines on postoperative management**

**Patient transfer**

Most guidelines proposed that the patient should be recovered in the operating theater [10,11,15,16,25–28]. If disconnection from the breathing circuit is required, clamping the endotracheal tube before disconnection was recommended [10–12,19,24,26,27].

**Postoperative cleaning and disinfection**

Australia, Canada, China, India, Taiwan, the UK, and USA detailed environmental disinfection [10–17,22–28]. Australia and the UK recommended waiting 20 to 30 minutes between cases to allow for operating theater cleaning and air changes [10,23]. All guidelines advocated the disposal of waste into labeled bins [10–
Additionally, Australia, China, India, South Africa, South Korea, Taiwan, and the USA recommended sealing all contaminated equipment for disinfection in double zip-locked bags [10,11,15,17,20–22,26]. China and South Korea proposed the replacements of the end-tidal carbon dioxide sample line and water trap [15,21].

Staff monitoring and welfare

Australia, Italy, the UK, and the USA [10,19,23,26] recommended a team debriefing event, while Canada encouraged incident reporting of adverse events [12]. With regards to staff surveillance, Australia and the USA required staff to maintain a logbook of clinical exposure, while China required daily surveillance of temperature and respiratory symptoms [10,15,16,26,28]. Additionally, Australia, Canada, South Africa, the UK, and the USA provided support services on mental well-being [10,12,20,23,26].

Evidence

There was little evidence on postoperative management apart from a retrospective study (level 4 evidence) from China that reported surveillance and a 14-day quarantine of a team of anesthesiologists who performed intubation on all COVID-19 patients in two hospitals [52].

A summary of guidelines for the anesthetic management of COVID-19 patients is provided in Tables 2–4.

Guidelines on subspecialty anesthesia

Obstetric anesthesia

National guidelines on the perioperative anesthetic management of obstetric patients with COVID-19 were scarce. Australia, China, Taiwan, the UK, and the USA recommended neuraxial anesthesia as the technique of choice for cesarean delivery [10,15,22,23,25–28]. The use of nitrous oxide/oxygen mixture for labor analgesia was controversial. The UK endorsed its use with a viral filter, but Australia and Taiwan did not [10,22,23]. Evidence from retrieved articles was mainly of level 4 and 5 quality. An expert panel review recommended screening patients for COVID-19 symptoms remotely and observing droplet and contact precautions in the labor ward [53]. Parturients were to wear surgical masks as increased ventilation during labor and symptoms could predispose to airborne transmission [54]. Two studies reported safe administration of epidural and spinal in COVID-19 patients who underwent cesarean section [39,55]. However, a higher incidence of maternal hypotension was reported [55]. Combined spinal and epidural was recommended for anticipated prolonged procedures to minimize conversion to general anesthesia [56]. Thrombocytopenia, which may be present in COVID-19 infections, was to be excluded. Epidural was recommended for labor analgesia to reduce the need for general anesthesia if urgent delivery is required. Category 1 cesarean section delivery should be avoided by close fetal monitoring [42,56]. Patients should be informed of potential delays due to PPE donning [42].

Pediatric anesthesia

Australia, Canada, and the UK provided guidelines for pediatric anesthesia [10,13,23]. Aerosol generation from crying was to be minimized by sedation, parental presence, and deep extubation [10,13]. Inhalation induction was to be best performed with a circle system, utilizing the lowest gas flows. Airway management was to be performed by trained pediatric staff, and a cuffed endotracheal was recommended [10,13,23]. Recommendations for difficult airway management included using video laryngoscopy primarily, followed by fiberoptic intubation through a SAD, combined video laryngoscopy with fiberoptic bronchoscopy, and fiberoptic bronchoscopy alone [13]. The UK also highlighted the need to exclude pediatric multisystem inflammatory syndrome associated with COVID-19 [23]. The literature review revealed only expert opinions and narrative reviews (level 5 evidence) that supported the guidelines from Australia, Canada, and the UK [13,57].

Cardiothoracic anesthesia

Advanced hemodynamic monitoring such as transesophageal echocardiography can be used to guide fluid therapy and vasopressor drugs, especially for COVID-19 patients with multi-organ dysfunction presenting for cardiac surgery. In addition, blood conservation and rigorous evaluation of coagulation are needed for coagulation abnormalities [58]. For thoracic anesthesia, viral filters and clamps should be placed on the double-lumen tube before opening it to the atmosphere so that the release of positive pressure within the lung occurs through a viral filter. In addition, ventilation should be withheld and a swivel connector with a self-sealing valve should be used if the breathing circuit is to be accessed for procedures. Bronchoscopes are significantly contaminated, and disposable flexible bronchoscopes should be used where possible. Suctioning of the airways should be performed before reversing neuromuscular blockades [59,60].

Neuroanesthesia

Full PPE for aerosol-generating procedures should be used for trans-sphenoidal surgeries, as there is a high incidence of viral shedding. Patients undergoing awake craniotomy should be lightly sedated to avoid an emergent airway, and low-dose lidocaine or remifentanil can be used to minimize coughing. For the endovascular treatment of acute ischemic stroke, a low threshold for gen-
Table 2. Comparison of National Guidelines on the Perioperative Preparation and Management of a Suspected/Confirmed COVID-19 Patients

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</thead>
<tbody>
<tr>
<td>Training</td>
<td>Donning &amp; doffing PPE</td>
<td>Donning &amp; doffing PPE; Streaming lectures online</td>
<td>Donning &amp; doffing PPE</td>
<td>Donning &amp; doffing PPE</td>
<td>Donning &amp; doffing PPE</td>
<td>Donning &amp; doffing PPE</td>
<td>Donning &amp; doffing PPE</td>
<td>Donning &amp; doffing PPE</td>
<td>Donning &amp; doffing PPE</td>
<td>Donning &amp; doffing PPE</td>
</tr>
<tr>
<td>Simulation</td>
<td>e.g. Category 1 Caesarean delivery, airway crisis, major hemorrhage</td>
<td>e.g. Category 1 Caesarean delivery</td>
<td>Intubation/ extubation drills wearing PPE</td>
<td>Possible scenarios and multi-disciplinary teams</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
<td>e.g. Category 1 Caesarean delivery &amp; airway crisis</td>
<td></td>
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</tr>
<tr>
<td>Patient screening</td>
<td>History taking including respiratory symptoms; appropriate triage &amp; prompt isolation of patients</td>
<td>Perform airway assessment with PPE on</td>
<td>Elective cases</td>
<td>History taking (including fever, cough, sore throat and travel history) should be elicited</td>
<td>Not stated</td>
<td>Preoperative screening for acute respiratory illness, pneumonia, contact and travel history, contact with healthcare facility managing COVID-19 patients</td>
<td>Not stated</td>
<td>MACOCHA score to predict difficult intubation and prepare strategy</td>
<td>Screen patient for fever, cough, dyspnea, diarrhea &amp; contact history</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Telemedicine for anesthesia consult</td>
<td>History (travel &amp; contact history, respiratory symptoms) &amp; examination</td>
<td>Referral to infection control if temp &gt; 37.3°C</td>
<td>Emergency cases</td>
<td>As above plus</td>
<td>Chest Xray or CT</td>
<td>Actively counsel patient to postpone elective surgery</td>
<td>Phone or video assessment for pre-anesthesia encounter</td>
<td>PCR Testing based on population prevalence</td>
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<table>
<thead>
<tr>
<th>Country</th>
<th>Resource planning</th>
<th>Patient transfer</th>
<th>Infection control</th>
<th>PPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia [10,11]</td>
<td>Team-brief</td>
<td>To OT with surgical mask</td>
<td>Airborne precautions</td>
<td>N95 mask, face shield or goggles, gown, hat, double gloves for airway procedures</td>
</tr>
<tr>
<td>Canada [12,13]</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Airborne precautions</td>
<td>N95 mask or PAPR, face shield or goggles, gown, shoe covers, hood, and double gloves</td>
</tr>
<tr>
<td>China [14–16]</td>
<td>Smaller group to lead airway management in COVID-designated hospitals</td>
<td>To OT with surgical mask</td>
<td>Airborne precautions</td>
<td>N95/N99 mask, eye protection, gown, boot covers, hat, double gloves</td>
</tr>
<tr>
<td>India [17]</td>
<td>Multiple tracheal intubation teams</td>
<td>To OT with surgical mask</td>
<td>Airborne precautions</td>
<td>N95 mask or PAPR device, face shield or goggles, gown, shoe covers, and double gloves (PAPR for intubation &amp; extubation)</td>
</tr>
<tr>
<td>Italy [18,19]</td>
<td>Team-brief</td>
<td>From OT with surgical mask</td>
<td>Airborne precautions</td>
<td>N95 mask, face shield or goggles, gown, shoe covers, and double gloves (PAPR for intubation &amp; extubation)</td>
</tr>
<tr>
<td>South Africa [20]</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Airborne precautions</td>
<td>N95 mask, eye protection, gown, double gloves</td>
</tr>
<tr>
<td>South Korea [21]</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Airborne precautions</td>
<td>N95 mask or PAPR device, face shield or goggles, gown, and double gloves</td>
</tr>
<tr>
<td>Taiwan [22]</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Airborne precautions</td>
<td>N95 mask or PAPR device, face shield or goggles, gown, and double gloves</td>
</tr>
<tr>
<td>UK [23,24]</td>
<td>Team-brief</td>
<td>Not stated</td>
<td>Airborne precautions</td>
<td>N95 mask or PAPR device, face shield or goggles, gown, and double gloves</td>
</tr>
<tr>
<td>US [25–28]</td>
<td>Team-brief</td>
<td>Not stated</td>
<td>Airborne precautions</td>
<td>N95 mask or PAPR device, face shield or goggles, gown, and double gloves</td>
</tr>
</tbody>
</table>

*PAPR only for trained staff or if performing multiple procedures

Warning signs on OT doors
Do not keep patient in holding area
Direct route to OT with surgical mask
Porters to clear the path

Negative pressure OT
Negative pressure isolation room
Negative pressure isolation room
Negative pressure isolation room
Negative pressure OT
Negative pressure OT
Negative pressure OT
Negative pressure OT
Negative pressure OT
Negative pressure isolation OT

Hand hygiene is essential before donning and after doffing PPE
Use “anti-fog” for goggles

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Buddy System when donning PPE. Hand hygiene is essential before donning and after doffing PPE.

Hand hygiene is essential before donning and after doffing PPE.

Staff to handover all personal belongings to buddy/runner to avoid them becoming fomites.

**Equipment**

- 2 viral filters placed in circuit
- Hydrophobic/HEPA filter between circuit & ETT
- 2 viral filters placed in circuit (between ETT & circuit; & between circuit & machine)
- Filter placed in circuit
- High efficiency Hydrophobic filter on every oxygen interface
- HEPA filter between circuit & ETT
- HEPA filter between circuit & ETT
- HME filter between catheter mount & circuit
- HEPA or HME filter between circuit & ETT, gas sampling tubing protected by HEPA filter

- Forced air warming blankets only in intubated patients
- Use disposable equipment if possible
- Use disposable equipment if possible
- Dedicated equipment
- Preload closed suction device on anesthesia circuit
- Use disposable equipment if possible
- Use disposable equipment if possible
- Create a COVID-19 tracheal intubation trolley
- Use disposable equipment if possible

PPE: personal protective equipment, MACOCHA: Mallampati III/IV, sleep apnea, decreased cervical mobility, mouth opening < 3 cm, Coma GCS < 8, severe Hypoxemia, practitioner not an Anesthetist. CT: computed tomography, PCR: polymerase chain reaction, OT: operating theatre, PAPR: powered air-purifying respirator, HEPA: high-efficiency particulate air, ETT: endotracheal tube, HME: heat and moisture exchanger.
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</thead>
<tbody>
<tr>
<td><strong>Anesthesia Technique</strong></td>
<td>Regional technique where possible</td>
<td>Regional technique where possible</td>
<td>Regional technique where possible</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Regional technique where possible</td>
</tr>
<tr>
<td><strong>Induction</strong></td>
<td>Limit staff present due to potential aerosolization</td>
<td>Limit staff present due to potential aerosolization</td>
<td>Limit staff present due to potential aerosolization</td>
<td>Limit staff present due to potential aerosolization</td>
<td>Limit staff present due to potential aerosolization</td>
<td>Limit staff present due to potential aerosolization</td>
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<td>Limit staff present due to potential aerosolization</td>
<td>Limit staff present due to potential aerosolization</td>
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<tr>
<td><strong>Airway Management</strong></td>
<td>Most experienced clinician</td>
<td>Most experienced clinician</td>
<td>Most experienced clinician</td>
<td>Most experienced clinician</td>
<td>Most experienced clinician</td>
<td>Most experienced clinician</td>
<td>Most experienced clinician</td>
<td>Most experienced clinician</td>
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</tr>
<tr>
<td><strong>Intubation</strong></td>
<td>Use of video-laryngoscope; optimize position</td>
<td>Consider induction with Ketamine or use vasopressors in hemodynamic instability</td>
<td>Use of video-laryngoscope (Asleep fiberscope intubation by trained staff)</td>
<td>Use of video-laryngoscope</td>
<td>Use of video-laryngoscope with pre-loaded introducer</td>
<td>Use of video-laryngoscope</td>
<td>Use of video-laryngoscope</td>
<td>Use of video-laryngoscope</td>
<td>Consider induction with Ketamine or use vasopressors in hemodynamic instability</td>
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</tbody>
</table>

- Clear plastic cover over patient (RSI) (Intubation recommended over SAD) Introducer for intubation (stylet/bougie)
- Neuromuscular blocker
- Avoid PPV until ETT cuff inflation. Disconnect mask & HME from circuit to avoid ongoing flow of oxygen out through filter
- Ensure tracheal tube cuff pressure ≥ 5 cm H₂O above peak inspiratory pressure

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<tbody>
<tr>
<td><strong>Awake fiberoptic intubation</strong></td>
<td>Avoid</td>
<td>Not stated</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid aerosol with topicalization &amp; rescue – Insert SAD if failed 2nd attempt</td>
<td>Not stated</td>
<td>Avoid; Avoid aerosol with topicalization</td>
<td>Avoid</td>
<td>Avoid</td>
<td>Avoid</td>
</tr>
<tr>
<td><strong>Difficult Airway</strong></td>
<td>Vortex approach if cannot intubate and oxygenate</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Intubate through SAD with flexible endoscope CICO, for early cricothyroidotomy</td>
<td>After failed intubation Plan B: 2nd generation SAD; Plan C: Two-handed mask ventilation</td>
<td>Plan D: Emergency FONA</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Safe, Accurate, Swift; Emergency FONA (Scalpel bougie); Consider intubation via SAD (blind/bronchoscope assisted)</td>
</tr>
<tr>
<td><strong>Supraglottic airway device (SAD)</strong></td>
<td>Insert SAD if failed intubation (2nd generation SAD preferred)</td>
<td>SAD for airway rescue</td>
<td>SAD preferred to intubation to minimize coughing at extubation</td>
<td>For airway rescue</td>
<td>Insert SAD if failed intubation (2nd generation SAD preferred)</td>
<td>SAD for airway rescue for manual ventilation instead of face mask ventilation</td>
<td>SAD for airway rescue</td>
<td>2nd generation SAD preferred. Careful patient selection; controlled ventilation &amp; low peak airway pressures; Intubate if leak is significant</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td><strong>Methods of oxygenation</strong></td>
<td>AvoidHFNO; minimize sedation &amp; supplemental oxygen; lung protective ventilation</td>
<td>AvoidHFNO &amp; non-invasive ventilation</td>
<td>Not stated</td>
<td>Avoid high flow oxygen</td>
<td>Use nasal apneic oxygenation 3 L/min Balance risk of viral transmission vs HFNO</td>
<td>Avoid high flows and extreme positive pressure ventilation</td>
<td>Avoid high flows and HFNO</td>
<td>Avoid HFNO &amp; non-invasive ventilation</td>
<td>Avoid HFNO &amp; non-invasive ventilation</td>
<td>Not stated</td>
</tr>
<tr>
<td><strong>Extubation</strong></td>
<td>Closed loop suctioning; Deep extubation, Consider opioids, lidocaine/Dexmedetomidine</td>
<td>SAD exchange to avoid coughing</td>
<td>Prophylactic antiemetics to minimize vomiting</td>
<td>Closed-loop suctioning</td>
<td>Closed-loop suctioning: prophylactic antiemetics to minimize vomiting</td>
<td>Consider antiemetics Plastic sheet to reduce droplet dispersion</td>
<td>Not stated</td>
<td>Consider glycopyrrolate or atropine to minimize secretions</td>
<td>Closed-loop suctioning: consider opioids, lidocaine/Dexmedetomidine</td>
<td>Closed-loop suctioning: Prophylactic antiemetics to minimize vomiting and possible viral spread.</td>
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<tbody>
<tr>
<td>Recovery of patient</td>
<td>Recover in OT; Surgical mask placed over oxygen mask</td>
<td>Not stated</td>
<td>Recover in OT</td>
<td>Patient to wear surgical mask; oxygen mask over surgical mask</td>
<td>Not stated</td>
<td>Recover in OT</td>
<td>Recover in OT</td>
<td>Not stated</td>
<td>Recover in OT</td>
<td>Surgical mask placed over oxygen mask/na- sal prong</td>
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<td>Ventilators on standby for circuit disconnection</td>
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Table 4. Comparison of National Guidelines for the Postoperative Management of a Suspected/Confirmed COVID-19 Patient

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<tbody>
<tr>
<td>Patient transfer</td>
<td>ICU transfer plan; minimize circuit disconnection; clamp ETT, paralyze before disconnection</td>
<td>Minimize circuit disconnection, clamp ETT</td>
<td>Single-use Ambu bags preferred for intubated patients, avoid ventilator use</td>
<td>Single-use Ambu bag preferred for intubated patients;</td>
<td>Minimize circuit disconnection, clamp ETT; ventilator on standby</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
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</tr>
<tr>
<td>Post-operative cleaning &amp; disinfection</td>
<td>OT cleaning as per local protocol</td>
<td>As per hospital terminal cleaning protocol</td>
<td>Environmental disinfection</td>
<td>Environmental disinfection</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
<td>OT cleaning as per local protocol</td>
<td></td>
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<tr>
<td></td>
<td>Maintain airborne precautions for staff entering OT for at least 30 min</td>
<td></td>
<td>(2–3% hydrogen peroxide spray disinfection, 2–5 g/L chloride disinfectant/75% alcohol wiping of solid surfaces of equipment &amp; floor)</td>
<td>(2–3% hydrogen peroxide, 2–5 g/L chloride disinfectant/75% alcohol wiping of solid surfaces of equipment &amp; floor)</td>
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## Post-op handling of equipment

- **Australia [10,11]**: Waste disposal in labelled bins
- **Canada [12,13]**: Waste disposal in labelled bins
- **China [14–16]**: Waste disposal in labelled bins (double-bagged)
- **Italy [18,19]**: Waste disposal in labelled bins
- **South Africa [20]**: Waste disposal in labelled bins
- **South Korea [21]**: Waste disposal in labelled bins
- **Taiwan [22]**: Waste disposal in labelled bins

**Replacement of filters & breathing circuits; seal equipment in zip-lock bag**

**Replace end-tidal carbon dioxide sample lines & traps**

**Dispose all used airway equipment in double zip-locked bag**

**Debriefing**

- **Debriefing post event**
  - **Australia [10,11]**: Not stated
  - **Canada [12,13]**: Not stated
  - **China [14–16]**: Debriefing post event
  - **Italy [18,19]**: Not stated
  - **South Africa [20]**: Not stated
  - **South Korea [21]**: Not stated
  - **Taiwan [22]**: Not stated

**Timely feedback, encourage incident reporting**

**Social distancing measures for staff**

**Consider influenza vaccination**

**Pregnant staff deployed to areas away from COVID-19 patients**

**Wellness resources**

**Staff monitoring & welfare**

- **Staff: complete log book of clinical exposures**
  - **Australia [10,11]**: Not stated
  - **Canada [12,13]**: Daily temperature check
  - **China [14–16]**: Monitor respiratory symptoms and inform occupational med team
  - **Italy [18,19]**: Social distancing measures for staff
  - **South Africa [20]**: Not stated
  - **South Korea [21]**: Not stated
  - **Taiwan [22]**: Not stated

**Wellness resources on mental health and communicating with empathy**

**Regular communication updates**

**Wellness resources**

**Consider influenza vaccination**

**Pregnant staff deployed to areas away from COVID-19 patients**

**Wellness resources**

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Table 4. Continued

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<tbody>
<tr>
<td>Post-op handling of equipment</td>
<td>Waste disposal in labelled bins</td>
<td>Waste disposal in labelled bins</td>
<td>Waste disposal in labelled bins (double-bagged)</td>
<td>Waste disposal in labelled bins (double-bagged)</td>
<td>Waste disposal in labelled bins</td>
<td>Dispose all used airway equipment in double zip-locked bag</td>
<td>Dispose all used airway equipment in double zip-locked bag</td>
<td>Dispose all used airway equipment in double zip-locked bag</td>
</tr>
<tr>
<td>Debriefing</td>
<td>Debriefing post event</td>
<td>Timely feedback, encourage incident reporting</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Debriefing post event</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Staff monitoring &amp; welfare</td>
<td>Staff: complete log book of clinical exposures</td>
<td>Not stated</td>
<td>Daily temperature check: monitor respiratory symptoms and inform occupational med team</td>
<td>Not stated</td>
<td>Social distancing measures for staff</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td></td>
<td>Regular communication updates</td>
<td>Wellness resources</td>
<td>May require blood tests and chest CT; consider isolation</td>
<td>Wellness resources</td>
<td>Wellness resources</td>
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</table>

ICU: intensive care unit, ETT: endotracheal tube, OT: operating theatre, CT: computed tomography.
eral anesthesia with intubation by airway personnel in a negative pressure room is preferred over the urgent conversion from sedation [61]. In addition, a lead gown can be worn under the PPE gown [62].

**Anesthesia for otolaryngology**

For airway surgery such as airway dilatation and tracheostomy, closed-loop communication between the surgeon and anesthesiologist is important to ensure that ventilation is held-off every time the endotracheal cuff is deflated, the tube is removed, or the circuit is disconnected [63].

**Trauma anesthesia**

Regional anesthesia is recommended where possible. Cricoid pressure during induction of general anesthesia should be used with caution, as it can stimulate coughing. Blood conservation is recommended and thromboprophylaxis should be instituted where possible [38].

## Discussion

The strength of this review is that it provides a comprehensive appraisal of all the available guidelines; it also summarizes their strengths and limitations. Our review found that national guidelines for the anesthetic management of COVID-19 patients were moderately comprehensive, but they scored poorly for rigor of development, editorial independence, and applicability. Evidence underpinning guidelines was weak, leading to heterogeneity in recommendations. Gaps in preoperative screening, prioritization for surgery, and anesthesia for specific groups were identified and addressed, albeit with low-quality evidence consisting of retrospective studies, case reports, narrative reviews, and expert opinions.

The Institute of Medicine defines clinical guidelines as “statements that include recommendations, intended to optimize patient care, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options” [64]. Clinical guidelines assist physicians in providing the best care, and they should adhere to a robust reporting framework. Given the rapid spread of the pandemic, initial guidelines were undoubtedly subjected to time-sensitive pressure in development and publication. As the virus is highly contagious, early guidelines focused on defining aerosol-generating procedures, mitigating aerosolization, and appropriate PPE and infection control practices. These were largely based on retrospective studies and case series during the SARS outbreak in 2003 [30,33,34,42-44]. These initial guidelines have served their purpose in successfully limiting disease spread to healthcare workers. Moving forward, national guidelines should be updated as new data emerge to include the entire perioperative process. Dagens et al. [65] suggested that pandemic guidelines should have transparent timelines for revision and amendment to ensure that they are more robust, especially for the potential viral resurgence. The recommendations should describe how they were derived and indicate their strengths and limitations and whether they were reviewed by experts, including infectious disease physicians and epidemiologists. Importantly, recommendations should be linked to an evaluation of supporting evidence and presented clearly with the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system [66]. GRADE is widely used by many organizations globally, and it is a transparent and reproducible framework that helps clinicians to understand the underlying logic and principles of the guidelines. The GRADE system comprises a two-level representation of the strength of recommendation (weak or strong) and a four-level representation of the certainty of the evidence (very low, low, moderate, and high) [67]. In addition, conflict of interest, which is essential for any scientific publication, should be disclosed, as many involved experts may have industry affiliations. Non-declaration implies bias, and it reduces the quality and reliability of the recommendations. Contributions from experts in subspecialty interest groups make national guidelines more inclusive and comprehensive. Although attempts to address difficult airway management were addressed by the Difficult Airway Society in the UK and Safe Airway Society in Australia and New Zealand, guidance for other patient groups was scarce.

With countries resuming elective surgeries, gaps in current guidelines would need to be addressed. Of relevance would be preoperative screening, which has important implications for resource utilization, especially PPE, processes, facilities, and manpower. Preoperative screening for COVID-19 and prioritization for surgery is also important, as morbidity and mortality have been reported in pre-symptomatic carriers who have undergone elective surgeries [68]. The USA has proposed two approaches to the perioperative testing of COVID-19 depending on the local prevalence of SARS-CoV-2. The American College of Surgeons recommends that a committee comprising surgeons, anesthesiologists, and nurses (guided by the Elective Surgery Acuity Scale) should assist with the prioritization of patients for surgery [69].

Categorizing COVID-19 to mild, moderate, severe, or critical may also help to refine anesthetic plans [70]. For COVID-19 patients with moderate to severe pneumonia, careful airway assessment is important, as hypoxemia during intubation is common and the options for oxygenation or awake intubation are limited. Critically ill patients with organ dysfunction would require pre-
emptive inotropes, fluid resuscitation, careful titration of drugs, and a lung-protective ventilation strategy [14].

Areas of controversy relating to anesthetic technique, the use of airway devices, the extent of aerosol dispersion, and the management of specific groups require further research and guidance updates as new evidence emerges. Further research on temperature, blood, and fluid management, including the degree of staff surveillance for infection and burnout is also needed.

This review was limited by the language restriction of our search and the quality of evidence available. Evidence was mostly from retrospective studies involving small samples, case reports, narrative reviews, and expert opinions.

Conclusion

National anesthetic guidelines published in the early phase of the COVID-19 pandemic were largely guided by weak evidence, and they lacked robust reporting. As countries move into easing lockdown during the second phase of the pandemic, recommendations need to be updated as new data become available. Guidelines should be subjected to established grading and appraisal systems such as GRADE and AGREE II to provide clarity, especially during a pandemic.

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Conflicts of Interest

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

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John Ong (Data curation; Formal analysis; Methodology; Supervision; Validation; Writing – review & editing)
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Supplementary Materials

Supplementary Table 1. AGREE II Instrument [6]
Supplementary Table 2. Combined results from guidelines and database search

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Introduction

Most parametric statistical analysis methods require normality assumptions. When violated, statistical results from non-normally distributed data could be a cause of serious error. These are apparent obstacles for confident scientific results. Even though the central limit theory could cover normality when the size of the sample is sufficient, many clinical and experimental data fail to satisfy normality assumptions despite a relatively large sample size. Back-transformation is crucial for the interpretation of the estimated results. This article introduces general concepts about variable transformation, mainly focused on logarithmic transformation. Back-transformation and other important considerations are also described herein.

Keywords: Back-transformation; Box-Cox transformation; Homoscedasticity; Logarithmic; Normality; Power; Retransformation; Skewed distribution; Transformation.
Distribution of each variable and relationship between variables

Before commencing statistical analysis, checking data distribution, the relationship between variables, missing data, and outlier controlling are appropriate method of statistical analysis and inference, which allow us to overcome issues that may occur during analysis. Data distribution and relationships between variables determine unsuitable variables of skewed distribution and reveal the possibility of planned linear regression.

The shape of data distribution is often couched in terms of representative values, including mean, median, and values of dispersion such as standard deviation (SD), quartiles, range, maximum, and minimum. In addition, skewness and kurtosis reveals the more detailed shape of data distribution [2] and most statistical software provides extensive information about these factors. If one variable violates the normality assumption, distribution plot or skewness/kurtosis provide a clue regarding data distribution. A quantile-quantile plot (Q-Q plot) with a normality test could imply the skewness of data distribution [3]. Normally distributed data appears as a rough straight line while skewed data presents a curved line on a Q-Q plot (Fig. 1).

In a clinical situation, various data follow positively or negatively skewed distributions. For example, in terms of mean arterial pressure, most people have normal blood pressure and some patients with hypertension would present higher mean arterial pressure with a small portion of aggregate data. Randomly sampled mean arterial pressure data from the general population will have a positively skewed distribution. Plasma hemoglobin concentration from the general population will have a negatively skewed distribution if the incidence of anemia is higher than polycythemia.

According to the characteristics of data distribution, various transformation methods can be used to achieve satisfaction for the normality test (Table 1). These kinds of transformations could help improve the normality of the data distribution.

<table>
<thead>
<tr>
<th>Skewness</th>
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<tbody>
<tr>
<td>Nomenclature</td>
<td>Positively skewed distribution</td>
<td>Negatively skewed distribution</td>
</tr>
<tr>
<td>Characteristics</td>
<td>Skewed right</td>
<td>Skewed left</td>
</tr>
<tr>
<td>Recommended transformation to achieve normality</td>
<td>Square root</td>
<td>Long right tail relative to left</td>
</tr>
<tr>
<td></td>
<td>Reciprocal</td>
<td>Long left tail relative to right</td>
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<tr>
<td></td>
<td>Logarithmic</td>
<td>Power (square, cubic)</td>
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Fig. 1. Quartile-Quartile plot (Q-Q plot) of original data and logarithmically transformed data. (A) Q-Q plot of original data. Upper tail of the plot seems to be going off from the straight line. This means that data has a probability of non-normal distribution. Mean and SD of this data is 20.52 and 4.117. The skewness of this distribution is 0.56, and it is a positively skewed distribution. Shapiro-Wilk normality test statistics = 0.974, P = 0.047. (B) Q-Q plot of natural logarithmic transformed data. Non-normality of data distribution seems to be improved in the part of the upper tail. Mean and SD of transformed data is 3.0 and 0.201. Skewness of transformed data is −0.14, Shapiro-Wilk normality test statistics = 0.988, P = 0.477.
make the data symmetrically distributed and the absolute value of the skewness close to zero [1]. These transformation methods could be applied to ensure the linear relationship between variables. It is well known that many statistical modeling methods are based on the linear relationship between treatment and response variables, and forming an apparent linear relationship through variable transformation enhances statistical model estimation. A typical example is logit transformation, which is used for binomial logistic regression. The logit transformation converts the probability of an event to log odds, allowing regression analysis between the dichotomous outcome variable and the independent variable, which plays the role of the linear predictor. The odds ratio can be used to interpret logit transformed regression. However, if a transformation is conducted with a variable using complex methods or if treatment and response variables are simultaneously transformed, interpretation of estimated results may be challenging. Therefore, transformation should remain as simple as possible to ensure a comprehensive interpretation of statistically inferred results.

Non-linear transformations

Adding, subtracting, multiplying, or dividing with a constant is commonly considered as the linear transformation, because these transformations rarely affect the distribution of data, they only shift the geometric mean and SD to some extent by their nature. In contrast, other transformations, including logarithmic transformation are referred to as non-linear transformation. They stabilize dispersion, create a linear relationship between variables, and enable parametric statistical estimation with the normality assumption assured.

Although these transformation methods provide a satisfying statistical result, the transformation itself forms an obstacle in terms of interpreting and reporting the statistical results. The transformed variable itself is sometimes meaningful without back-transformation. For example, a certain cancer incidence is proportional to the square of the smoking period. This result is based on the linear regression analysis with observed cancer incidence and squared period of smoking, and its interpretation has meaning without back-transformation. We can present the collected data with median and 1st and 3rd quartiles of the smoking period when the original data have violated the normality assumption. If we compare the smoking periods between two groups and they require square transformation to keep the normality assumption, it is hard to interpret the clinical meaning of the mean difference of squared data. The difference between each squared value is not the same as the squared difference between the two original scaled values. In this situation, non-parametric analysis makes it easier to interpret the results.

A non-linear transformation may sometimes be required to obey the assumptions for a specific statistical analysis such as multiple linear regression. If we use undiscerning transformation methods for numerous variables, it is hard to interpret estimated results. For complex statistical analysis, it is therefore better to use an interpretable transformation method. In addition, using a more liberal statistical method such as generalized linear or non-linear models may be more appropriate.

Logarithmic transformation

Applying a logarithmic transformation, each value is changed by the characteristics of the logarithm. Considering its features, the differences between transformed values become smaller than the original scale (Fig. 2). The logarithmic transformation compresses the differences between the upper and lower part of the original scale of data. For example, for data with 100 cases, its skewness of 0.56 changes to −0.14 after natural logarithmic transformation. The results of the normality test using the Shapiro-Wilk test also changes its statistics from 0.974 (P = 0.047) to 0.988 (P = 0.477). The Q-Q plot also is stabilized after logarithmic transformation (Fig. 1). As shown here, a logarithmic transformation has a normalizing effect on the positively skewed distribution. This transformed distribution is referred to as ‘log-normal distribution.’ An interesting finding from the logarithmic transformation is that its effects cover normalizing the density of data and decreasing the SD, the latter provides greater opportunity to satisfy the equal variance test, which is frequently used for various parametric statistical inferences. From Fig. 1, the mean and SD of the original data are 20.52 and 4.117 become 3.0 and 0.201 after logarithmic transformation. The coefficients of variances are 20.1% and 7.0% for original and logarithmically transformed data, respectively. The coefficient of variance is a representative value for a standardized measure of the dispersion of data distribution. A large value implies that one value from the data has a high risk of being far from the mean. With decreased SDs, the results of the equal variance test could be satisfied, and several comparison methods including Student’s t-test could be possible after logarithmic transformation of a variable [1].

Although we can generate the data for intended statistical analysis, the interpretation of statistically inferred data is another ob-

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[1] In the case of violated equal variance assumption, means comparison is possible through unequal variance t-test or unequal variance ANOVA using Welch’s test, which is based on the corrected degree of freedom.
Transformed values of dilutions should be repeated five times until the last seropositive results \(2^5 = 32\). Antibody titer itself has a characteristic of the powered value of dilution numbers, which is always reported as \(1:2^{\text{dilution numbers}}\). Hence, the geometric mean should be presented as \(2^{\text{mean dilution number}}\), not the mean of titers.

Furthermore, mean difference obtained from the t-test does not imply a simple difference between estimated means when a logarithmic transformation is used. Back-transformation from logarithmic transformation leads to arithmetic difference of transformed variables to ratio. The mean difference from two natural logarithmic transformed samples is \(X_1 - X_2\), and back-transformation results in \(e^{X_1}e^{X_2} = e^{X_1 + X_2}\). That is, the logarithmic transformed mean difference should be interpreted as a ratio of means when back-transformation is applied. For example, if the mean difference is 0.5, \(e^{0.5} = 1.65\), mean from one sample has 65% higher value compared to the other mean. This should not be interpreted as 165%, and we should consider the difference, not a simple ratio. The CI of the mean difference also can be interpreted in a similar way. If the estimated 95% CI of the above sample is 0.4–0.6, the back-transformed range is 1.49–1.83, its interpretation is ‘mean from one sample has a 65% higher value with a 95% CI ranging from 49% to 83% compared to the other mean.’ Reporting statistics can be estimated using logarithmically transformed data. When reporting this, the information regarding transformation should be accompanied. Corresponding effect sizes and P values can also be reported as estimated. This interpretation approach can be applied to the statistical method of mean comparison.

Pearson’s correlation analysis and linear regression analysis also require data normality. When the logarithmic transformation is applied to the data for the former, the result can be described as estimated. The correlation coefficient is a statistic that has the characteristics of effect size, and we do not need to conduct further back-transformation. Only one thing should be done reporting results with the information about transformation. If logarithmic transformation is applied for linear regression, it produces more complex considerations in terms of results interpretation. Linear regression requires several assumptions, including the linear relationship between independent and dependent variables.

To fulfill this assumption, variable transformation may be necessary. If the dependent variable requires logarithmic transformation, the meaning of the regression coefficient changes from unit change to a ratio. Basically, the definition of the regression coefficient is that ‘a one-unit change in the independent variable produces an increase (decrease) in the dependent variable by the amount of regression coefficient.’ Arithmetic increment (decrement) of the transformed dependent variable will be changed into a ratio with back-transformation of an exponential function. For example, the estimated regression coefficient is 0.1, \(e^{0.1} = 1.105\),
means ‘for a one-unit increase in the independent variable, dependent variable increases by 10.5%’. Similar to the explanation of the mean difference, it should be noted that the interpreted value is not 110.5%. If the dependent variable is a common logarithmic transformed variable, a one-unit change in the independent variable is the same as a tenfold increment in the original matric variable. That is, a tenfold increment in independent variable produces dependent variable changes by the estimated regression coefficient. Description with a 1% increment of the independent variable is also possible. For the convenience, common logarithmic transformation is better for independent variable transformation. If natural logarithmic transformation is applied, interpretation is not easy with e as the base of the natural logarithm; the approximated value is 2.71828. If both dependent and independent variables are transformed with logarithmic transformation, we can interpret the result as a percentile increment of the independent variable produces a percentile change in the dependent variable following the rule explained above. These interpretation rules can be applied to the other kind of general linear modeling method including ANCOVA and MANOVA.

Several problems are reported regarding logarithmic transformation [7]. Such transformation is impossible when the values have negative or zero in its original metric. To overcome this problem, adding a positive constant to the original data is a common practice. However, the shape of the logarithmic graph subtly changes in the early stage from zero and then enters the fluent curve section in the later stage (Fig. 2). That is, the dispersion of logarithmically transformed data could be varied according to the added value from original scaled data. For example, assume two normally distributed data sets with mean = 0, SD = 1, n = 100 and mean = 1, SD = 3, n = 100 using a random number creation function. Then, we add the integers that make all data have positive values. Logarithmic transformation with a base of 10 is applied to all datasets. Then, plotting their mean and SD in one graph, we can see the mean differences and SDs become smaller according to an increment of an added constant (Fig. 3). As a result, estimated t-statistics and P values are also changed, which increases the statistical errors. These kinds of errors could only occur when the mean difference and SD are relatively small, but estimated t-statistic could increase as the added value increases even if mean difference and SD are large. These kinds of errors originate from the nature of logarithmic transformation; it increases the difference when the values are small and reduces the difference when the values are large. From the null hypothesis significance testing viewpoint, the significance of the t-test may not change except when t-statistics are very near to the significance level. However, it should be noted that estimated statistics and performed power also change because logarithmic transformation stabilizes SD values.

**Power transformation and Box-Cox transformation**

Power transformation is a transformation method that uses a power function. If we use a number greater than 1 as an index of a power function, it could transform left-skewed data into near-normally distributed data. A specialized form of power transformation is the Box-Cox transformation [8], which is frequently applied to stabilize the variance of errors estimated during linear regression or correlation analysis. There are several extended forms of Box-Cox transformation [9], the traditional method is as shown in (Equation 1) below.

\[
y'_i = \begin{cases} 
\frac{(y_i - 1)}{\lambda} & : \lambda \neq 0 \\
\log y_i & : \lambda = 0
\end{cases} \quad \text{(Equation 1)}
\]

According to the value of \(\lambda\), this performs various types of non-linear transformation. For example, \(\lambda = -1\) produces a reciprocal transformation, \(\lambda = 2\) a square transformation, and \(\lambda = 0.5\) a square root transformation. Because it contains a constant, a somewhat linear transformation is also applied as we already know the linear transformation hardly effects the estimated statistics. However, we should be cautious as such transformation could affect the statistical results, as described in the previous section. If \(\lambda = 0\), the Box-Cox transformation is same as logarithmic trans-
Data transformation. Then, how can we determine the value of $\lambda$ and how the Box-Cox transformation stabilizes the variance? We consider this using linear regression. Linear regression requires several assumptions including homoscedasticity, which means all observed values are equally scattered from the estimated regression line. Several residual diagnostics provide about homoscedasticity. When the homoscedasticity is violated, the Box-Cox transformation could stabilize the variance of residuals. Using $y^\lambda$ instead of $y$ in the linear regression model, for example, $y^\lambda = \alpha x + \beta + \epsilon$ ($\alpha$: regression coefficient, $\beta$: constant, $\epsilon$: error), several statistical software programs find best estimated values of $\lambda$ and its 95% CI based on the maximal likelihood method. Using this result, we can estimate the linear regression model with homoscedasticity. Although the Box-Cox transformation is an excellent tool to obtain the best results of linear regression, it also has a serious problem of result interpretation. Back-transformation for this is not as simple as other non-linear transformations because it includes the error term, which is essential for the linear regression. There are several proposed back-transformation methods from the Box-Cox transformation [10,11], which require complex statistical process. If we try to interpret as the transformed variable itself, we should also consider the transformed unit, which could lose its real meaning after transformation. Only when the other measures for stabilizing variance (homoscedasticity) have failed, should the Box-Cox transformation be considered.

Conclusion

Parametric statistical analysis is frequently used in medical research. Unfortunately, many physicians have not recognized that these analytic methods require the normality of data distribution and other assumptions. There are many other analytic methods with more generous assumptions such as generalized linear or non-linear models. Nevertheless, we need simplified and intuitive analysis, including $t$-test and analysis of variances (ANOVA). Variable transformation is a powerful tool to make data normally distributed or to form a linear relationship of data. However, almost all of the transformed data should be back-transformed for the interpretation of the results. The transformation could be easy, it is possible to calculate the transformation in commonly used spreadsheet programs. However, back-transformation is not an easy process if complex or a combination of several transformations are used. Result interpretation also depends on the role of the transformed variable. It is relatively simple for a transformed independent variable to be compared to the transformed dependent variable. When the dependent variable is transformed, back-transformation should rely on the transformed error term.

Variable transformation provides an attractive and convenient method of enabling parametric statistical analysis, and data preparation should be considered a priori. Information about data distribution, such as skewness, range, mean, SD, median, and quartiles, and the relationship between variables (scatter plot) can be used to derive the best method. Outlier controlling, missing data evaluation, and adequacy of sample size should be prioritized before variable transformation. If possible, using statistical analysis with generous assumptions is an option and non-parametric statistical analysis also guarantees a scientific result.

Conflicts of Interest

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

References


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3One easy way to perform the Box-Cox transformation is using the ‘MASS’ package included in R system, which provides the command ‘boxcox’.
Nebulized heparin and salbutamol versus salbutamol alone in acute exacerbations of chronic obstructive pulmonary disease requiring mechanical ventilation: a double-blind randomized controlled trial

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Background: Nebulized heparin has been effectively used in the management of many pulmonary diseases. However, its effect on mechanically ventilated patients with acute exacerbation chronic obstructive pulmonary disease (AECOPD) has never been studied. This study aimed to assess the efficacy of nebulized heparin and salbutamol to increase ventilator-free days (VFD) in mechanically ventilated AECOPD patients and the effect of nebulized heparin on respiratory and coagulation functions.

Methods: In this double-blind controlled study, 60 mechanically ventilated adult patients with AECOPD were randomly allocated into two groups; heparin and salbutamol (HS) group and salbutamol only (S) group. In the Group HS, patients received nebulized heparin (25,000 IU) and salbutamol (5 mg) every 6 hours. Patients in the Group S received nebulized salbutamol only (5 mg). The treatment was continued while patients remained ventilated for a maximum of 14 days. The primary outcome was VFDs at day 14. PaCO₂, PaO₂/FiO₂ ratio, number of nebulizations withheld, C-reactive protein (CRP) titer and activated partial thromboplastin time (APTT) were secondary outcomes.

Results: Patients in the Group HS had significantly more VFDs 4.7 ± 3.3 compared with those in the Group S 2.4 ± 2.6, P = 0.007. PaCO₂ levels, PaO₂/FiO₂, the decrease in the CRP level and the increase in the APTT from the baseline showed no evidence of difference in both groups.

Conclusions: The co-administration of nebulized heparin and salbutamol, compared with salbutamol alone, significantly increased (VFDs) among mechanically ventilated AECOPD patients without increasing bleeding risks.

Keywords: Albuterol; Artificial respiration; Asthma chronic obstructive pulmonary disease overlap syndrome; C-reactive protein; Heparin; Nebulizers.

Introduction

Chronic obstructive pulmonary disease (COPD) is considered the fifth leading cause of mortality in the world and is subjected to be the fourth by 2030 [1]. The prevalence of COPD in Egypt is almost 10% [2]. COPD is a progressive disease and is associated with acute exacerbation (AE) periods [1]. Despite the widespread use of non-invasive positive
pressure ventilation (NIPPV) in the management of AECOPD, it is not suitable for all patients and may be associated with a 60% risk of intubation [1,3,4]. The leading pathophysiologic causes of AE-
COPD are peribronchial inflammation and broncho-constriction. Accordingly, short-acting β₂ agonists (e.g., salbutamol), antibiotics, and corticosteroids are considered cornerstones in the management of COPD [1,5].

Besides its anticoagulant effect, heparin decreases the adherence of bacteria and viruses to the bronchial surface and it has an anti-inflammatory effect [6,7]. Recently nebulized heparin has been added for the management of many pulmonary conditions including the exacerbation of bronchial asthma, smoke inhalational injuries and critically ill mechanically ventilated patients [8–10]. However, its effect on mechanically ventilated AECOPD patients is unknown and has not yet been studied. In theory, adding nebulised heparin to ventilated AECOPD treatment may shorten the duration of mechanical ventilation (MV).

This study aimed to assess the efficacy of nebulized heparin and salbutamol (albuterol) to increase ventilator-free days (VFDs) among mechanically ventilated AECOPD patients (primary outcome) and its effect on respiratory, coagulation functions and C-reactive protein (CRP) (secondary outcomes).

Materials and Methods

This double-blind randomized controlled study was approved by the ethics committee of the Faculty of Medicine, Ain Shams University, Cairo, Egypt (FMASU R 26/2017) and registered at ClinicalTrials.gov (NCT03333395). The study was conducted between the 1st of February 2017 to the 30th of September 2017 at the Internal Medicine Intensive Care Unit of Ain-Shams University Hospital. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Sixty adult patients with COPD and primary respiratory failure that were not responding to NIPPV were included in this study [11]. The randomization was done using a computer-generated table of random numbers. Allocation concealment was achieved by drawing a sequential numbered, opaque, and sealed envelope to randomize the patients into two groups: heparin and salbutamol (HS) group and salbutamol (S) group. There were 30 patients allocated to each group. The randomization day was considered to be day 0. Written informed consent was taken from all the patients, and their parents or guardians if applicable before the study were commenced. Patients were aged between 18 and 70 years old, had a body mass index of ≤ 40 kg/m² with stage II to IV COPD, according to the Global Initiative for Chronic Obstructive Lung Disease spirometric classification [12]. The research team excluded patients who had already been mechanically ventilated for more than 24 h, were expected to be extubated within 48 h, pregnant, or had a history of ischemic heart disease, pulmonary bleeding (within the previous three months), bleeding diathesis, allergy to heparin, or history of heparin induced-thrombocyto-
penia (HIT).

According to our intensive care unit (ICU) policy and guidelines, on patient admission, an arterial cannula (in the radial artery of the non-dominant hand) and a central line were inserted and daily blood samples were taken. Patients received standard medications, including analgesics, sedatives, fluid management, antibiotics according to a sputum culture, steroids and thrombo-prophy-
laxis (enoxaparin 40 IU SC once/day) [13].

All patients received nebulization of a 5 ml solution; 2.5 ml (5 mg) of nebulized salbutamol solution (preservative-free Ventolin, GlaxoSmithKline, UK) added to 2.5 ml normal saline (NS). This was followed by either nebulization of heparin (25,000 IU, hepa-
rin sodium; Nile Company for Pharmaceuticals and Chemical Indus-
tries, Egypt) in the Group HS or 5 ml of NS in the Group S. The medication for the second nebulization was prepared by the ICU pharmacist and then handed to the nurse in charge who was blinded to the nature of the medication and did not further take part in the study. All data were recorded by ICU resident doctors who followed-up the patients and were unaware of the contents used in the second nebulization medication. Additionally, they were not involved in any other part of the study.

The nebulization session lasted for at least 10 min for each medication. This regimen was repeated every 6 h and continued while patients remained ventilated for a maximum of 14 days.

The nebulization medication was added to a nebulization chamber (Ameco Technology; particle size: 0.5–10 μm, nebuli-
zation rate: > 0.3 ml/min) connected to the inspiratory limb of the breathing circuit 15 cm from the Y of the circuit. The heat and moisture exchanger was removed during nebulization. All pa-
tients were mechanically ventilated using the Synchronized Intermi-
ttent (SIMV) mode with or without pressure support (PS), with a targeted tidal volume: 6–8 ml/kg, rate: 12–14 breaths/min inspi-
ratory : expiratory ratio (I : E ratio) = 1 : 3, positive end-expirato-
ry pressure (PEEP): 5–10 cmH₂O, fraction of inspired oxygen (FiO₂) (40–60%) and upper pressure levels were maintained at or below 35 cmH₂O to target arterial oxygen saturation (SpO₂) of 88–92%. PS ventilation was used to wean the patient.

The weaning process was started by optimizing the mechanical and biochemical respiratory parameters; i) treatment of the cause of exacerbation, ii) spontaneous respiratory volume (Vt) > 0.005 L/kg of body weight, iii) maximal spontaneous inspiratory effort (PImax) ≤ 25 cmH₂O, iv) heart rate < 140/min, v) body tempera-
ture < 37.5°C, vi) hemoglobin > 100 g/L, vii) partial arterial oxygen pressure (PaO$_2$) > 60 mmHg with inspired oxygen fraction (FiO$_2$) ≤ 0.4, extrinsic PEEP < 5 cmH$_2$O, viii) no need for vasoactive and/or inotropic support, PaO$_2$/FiO$_2$ ratio > 200, and RR/Vt ratio < 100. Patients who fulfilled those criteria were given a two-hours spontaneous breathing trial (SBT) using PSV with an initial positive pressure of 15 cmH$_2$O. Patients who withheld the SBT were extubated, while those who had a spontaneous respiratory rate > 25/min, SatO$_2$ < 90%, FiO$_2$ ≤ 0.4, heart rate > 140/min (or more than 20% change from the initial heart rate), PaO$_2$ ≤ 60 mmHg, pH ≤ 7.30, and restlessness were tagged as failing to wean and (MV) with SIMV was continued.

The duration of VFDs (the primary outcome) was evaluated at day 14. The number of patients successfully weaned from MV, changes in PaCO$_2$, the PaO$_2$/FiO$_2$ and PaCO$_2$ were measured each day at 7 AM. No changes in the ventilator settings or the patient's position were permitted for the 10 min before these measurements were taken. In cases of suction or lavage of blood-tinged sputum, the next nebulization cession was withheld, and the number of those cessions were evaluated and were added to the secondary outcomes. In cases of HIT occurrence, increased APTT more than double the normal, evident pulmonary bleeding, or death the patient was dropped out of the study.

To facilitate blinding, the study medications were prepared by a pharmacist and given by the nurse in charge. Both of those staff members were not involved in any other part of the study.

The PaCO$_2$, the PaO$_2$/FiO$_2$ and CRP titer were assessed daily. They were presented every other day to avoid redundancy of data.

### Statistical analysis

Based on a similar previous study [14], 26 patients were required in each group, assuming a power of 0.80 and a 5% alpha error (2-tailed) [15]. To compensate for dropouts, 30 patients in each group were recruited. Coded data were tabulated and statistically analyzed using the Statistical Package for Social Sciences version 22.0 (IBM Corp., USA). Data are presented as mean ± SD, numbers, frequencies and percentages. Data were analyzed using the independent t-test, repeated measures analysis of variance (RMANOVA), chi-square test, or the log-rank test as appropriate. The level of significance was set to a P value of < 0.05.

### Results

A total of 55 patients completed the study, of which 28 were in the Group HS and 27 in the Group S (Fig. 1). Patients' characteristics, associated co-morbidities, basal respiratory variables, known risk factors, and laboratory results showed no evidence of difference (Table 1).

The patients in the Group HS had significantly longer VFDs (4.7 ± 3.3 vs. 2.4 ± 2.6, P = 0.007; Table 2). The survival curve showed that the percentage of ventilated patients in the Group HS was lower than the Group S during the 14 days (P = 0.009, Fig. 2). The other respiratory variables; PaCO$_2$ levels (P = 0.075, Fig. 3), PaO$_2$/FiO$_2$ (P = 0.069, Fig. 3) and the rate of decrease in CRP (P = 0.185, Fig. 4) showed no evidence of difference in both groups. Generally, the study medications were well tolerated by patients in both groups. The number of withheld of nebulisations/patient in the Group HS showed no evidence of difference to that of the Group S (5.8 ± 2.2 vs. 4.8 ± 1.4, P = 0.064; Table 2). Similarly, blood product usage did not show any significant differences between the groups, with only nine patients requiring blood transfusions in the Group HS and seven in the Group S. None of the patients in both groups had suspected HIT (a decrease in platelet count). The maximum increase in the APTT from baseline over

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**Fig. 1.** CONSORT flow diagram. Group HS: heparin and salbutamol group, Group S: salbutamol only group.
the study period was higher in the Group HS. However, this was not statistically significant (39.5 ± 2.5 vs. 39.1 ± 1.0, P = 0.407; Table 2).

**Discussion**

Invasive or noninvasive MV is a form of life support until the cause of underlying acute respiratory failure is reversed with medi-

cal therapy. This study demonstrated that the Group HS was associated with higher VFDs as compared to the Group S. This effect may be due to an improvement of oxygenation, ventilation (Fig. 3), and/or inflammation (Fig. 4). Despite not reaching statistical significance an improving trend in the Group HS was observed.

Many studies have confirmed the anti-inflammatory and immune-modulatory effects of heparin [16,17] (Fig. 5). A variety of clinical trials studying patients with inflammatory processes e.g.
Table 2. Outcomes, Tolerability, and Safety

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Group HS (n = 28)</th>
<th>Group S (n = 27)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator free days</td>
<td>4.7 ± 3.3</td>
<td>2.4 ± 2.6</td>
<td>0.007*</td>
</tr>
<tr>
<td>Number of doses of nebulization withheld/patient</td>
<td>5.8 ± 2.2</td>
<td>4.8 ± 1.4</td>
<td>0.064</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>9</td>
<td>7</td>
<td>0.612</td>
</tr>
<tr>
<td>APTT Max (s)</td>
<td>39.5 ± 2.5</td>
<td>39.1 ± 1.0</td>
<td>0.407</td>
</tr>
<tr>
<td>APTT elevation (s)</td>
<td>0.9 ± 1.8</td>
<td>0.2 ± 0.9</td>
<td>0.053</td>
</tr>
<tr>
<td>APTT Max ≥ 40.0 (s)</td>
<td>13</td>
<td>9</td>
<td>0.322</td>
</tr>
<tr>
<td>Double APTT</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>HIT</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
<td>3</td>
<td>0.669</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or a frequency as appropriate. Group HS: heparin and salbutamol group, Group S: salbutamol only group. APTT: activated partial thromboplastin time, HIT: heparin-induced thrombocytopenia, VFDs: ventilator free days. *Statistically significant with P < 0.05.

Fig. 2. The survival curve showed that the percentage of ventilated patients in the Group HS was lower than the Group S during the 14 days (P = 0.009). Group HS: heparin and salbutamol group, Group S: salbutamol only group.

Fig. 3. (A) PaCO₂ levels showed no evidence of difference in both groups (P = 0.075). (B) PaO₂/FiO₂ ratios (P = 0.069) showed no evidence of difference between groups. Group HS: heparin and salbutamol group, Group S: salbutamol only group.

Fig. 4. Rate of decrease of the CRP levels in both groups showed no evidence of difference and is presented by a line graph with error bars. An RMANOVA was used for the analysis; Group effect (P = 0.185). Group HS: heparin and salbutamol group, Group S: salbutamol only group. CRP: C-reactive protein, RMANOVA: repeated-measures analysis of variance.
inflammatory bowel disease and cardiopulmonary bypass have confirmed this \[18,19\]. It was even found to reduce the histological and clinical evidence of pulmonary microvascular thrombosis in patients with acute pulmonary inflammation following cardiac surgery \[20\]. Moreover, inhalational heparin has anti-asthmatic properties as confirmed by different clinical models of bronchial asthma \[8,21\] and inpatients with smoke inhalational injuries \[8,9,21,22\]. Heparin nebulization also improved oxygenation and increased the VFDs in critically ill mechanically ventilated patients and was found to be comparable to a nebulized corticosteroid (budesonide) in decreasing the risk of ventilator-induced lung injury \[14,23\], highlighting its anti-inflammatory effect. Subcutaneous low-molecular-weight heparin also improved the pulmonary functions and decreased the days of MV among AECOPD ventilated patients \[24,25\].

In contrast to our study, a retrospective review designed by Kashei et al. \[26\] concluded that alternating treatments of heparin and N-acetylcysteine/albuterol nebulization every 4 h on adult inhalation injury patients did not reduce mortality or duration of MV. This finding may be explained by the low dose of (5,000 IU/per dose) used.

In a trial studying the effects of different doses of nebulized heparin on the coagulation activation, nebulized heparin was found to increase APTT in a dose-dependent manner. However at a dose of 100,000 IU/day this increase was modest and was not associated with any adverse events \[27\].
Also, Shute et al. [28], proved that nebulized heparin of 75,000 or 150,000 IU/day days in moderate to very severe COPD patients significantly increased FVC following 7 days of treatment. These results might be explained by an earlier study on intrapulmonary administered heparin. This study proved that it was absorbed rapidly by the alveolar membrane and released gradually into the blood. A study done by Bendstrup et al. concluded that nebulized heparin slowly dissipated form the lungs, and that 39% of it was still present in the lungs 24 h after nebulization [29,30]. Based on such results, the research team decided to adjust the treatment protocol to add enoxaparin SC as a prophylaxis against thromboembolic complications and to withhold heparin nebulisation if APTT increased more than double the normal or serious bleeding occurred. Our results correlated well with all the studies done on the nebulized heparin regarding the absence of any bleeding hazards in response to its usage [8,10,14,23–25,27,28].

Heparin nebulization on the other hand, did not prove to be effective in reversing histamine-induced bronchospasm, suggesting its effects are mediated by mechanisms not involving smooth muscles [8,16]. This finding mandated the addition of bronchodilators to the management of histamine-induced bronchospasm. In this context, short-acting β2 agonists alone or in combination are recommended [5].

The dose of 5.0 mg of nebulized salbutamol was based on a review study on the management of COPD exacerbations by Rodriguez-Roisin [5]. He found that inspiratory capacity increased significantly at 30 and 90 min after the administration of 5.0 mg of nebulized salbutamol to acute-on-chronic air trapping and lung hyperinflation patients.

Dixon et al. [14] showed that the pulmonary lavage markers of coagulation activation did not decrease in the heparin group. However, later, he contradicted this in a letter to the editor when he studied higher doses (up to 400,000 IU/day) and was allowed to do further coagulation markers [31].

In this study, the team chose CRP as a biomarker of inflammation. CRP is not only an easy and important marker in COPD but is also an early marker of exacerbation [32]. Its increase indicates bacterial infection in AECOPD and the need for antibiotics in the treatment [32–35]. Its serial measurements were beneficial in assessing the efficacy of treatment [33,34]. Despite the absence of a statistical significance between the two groups regarding CRP, the research team observed a decreasing trend of CRP in the heparin treated patients (Fig. 4). It could be explained that heparin decreases the adherence of bacteria and viruses to the bronchial surface and has an anti-inflammatory effect [6,7].

This study had several limitations. First, this study was carried out at a single center. However, the research team believe that the study provides valuable clinical information for assessing ICU outcomes of using nebulized heparin and salbutamol in AECOPD patients, as the study population was disease-specific. Second, the results of this study were evaluated at day 14 and not at day 28 because 28 days would be a relatively long duration considering that most of AECOPD patients would be extubated before this. Additionally, mortality cases were omitted from the assessment. We assumed a timeframe of 14 days would be enough. Our results show that nearly 20% of patients remained ventilated after the 14-days timeframe (Fig. 2) which makes the timeframe (and not the VFDS) a limitation in our study. The research team recommends increasing the timeframe of VFDSs evaluated in future studies regarding mechanically ventilated AECOPD. Third, a larger sample size is required to achieve significant differences in the side effects encountered. Fourth, the time from admission to hospital discharge, which is important outcome because of its economic implications, was not examined. This should be considered in future randomized clinical trials.

Nevertheless, this study also has some strengths. First, all the patients were subjected to prolonged (MV) along with its potential of lung damage. Second, the randomized and double-blind design decreased the possibility of bias. Third, the use of VFDS as an outcome provided added value because of its statistical power to detect treatment effects rather than the binary outcome measure of mortality [36]. Survivors of respiratory failure from COPD tend to return to baseline lung function very slowly (i.e., weeks to months). However, the risk for re-hospitalization and re-intubation for patients with COPD is increased markedly after an episode of respiratory failure requiring MV. COPD patients continue to experience significantly increased rates of severe exacerbations and use of healthcare resources, indicating a potential unmet need in this Group S of patients [37]. The need for new pharmaceutical therapies and protocols of treatments to reduce severe exacerbations is evident and may in the future be of benefit for this high-risk population.

Possible roles of heparin and salbutamol nebulization in targeting the pathophysiology of AECOPD were presented in Fig. 5 [1,6,17,38–40].

In conclusion, the co-administration of nebulized heparin and salbutamol, compared with salbutamol alone, significantly increased VFDS among mechanically ventilated AECOPD patients without increasing bleeding risks.

Acknowledgements

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Ain Shams University Hospital for their valuable help in this work.

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**Conflicts of Interest**

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

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Ahmad Mahmoud Hasseb (Formal analysis; Writing – review & editing)
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**References**

5. Rodríguez-Roisin R. COPD exacerbations.5: management. Thorax 2006; 61: 535-44.


Incidence of newly developed postoperative low back pain with median versus paramedian approach for spinal anesthesia

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Background: The effects of anesthetic techniques on postdural puncture backache (PDPB) have not been specifically evaluated. The purpose of this study was to compare the incidence and severity of PDPB between median and paramedian techniques.

Methods: Patients were randomized to receive spinal anesthesia by either a median (Group M, n = 50) or paramedian (Group P, n = 50) approach. We recorded each patient’s personal number of puncture attempts, surgical position, and operation duration. We investigated the incidence and intensity of back pain 1 day, 1 week, and 1, 2, and 3 months postoperatively.

Results: The overall incidence of PDPB was higher in the Group M (18/50, 36%) than in the Group P (8/50, 16%) (P = 0.023). Twenty-four hours after surgery, 8 patients in Group M and 6 patients in Group P complained of back pain. Seven days after the surgery, 16 patients in the Group M and 5 patients in the Group P complained of pain (P = 0.007). After 1 month, 5 patients in the Group M and 1 patient in the Group P complained of pain. Only one patient in each group complained of pain after 3 months. No significant differences were noted in NRSs between the groups during study period.

Conclusions: The results of this study suggest that spinal anesthesia using the paramedian approach reduces the incidence of PDPB during the early postoperative period.

Keywords: Adverse effects; Anesthesia; Low back ache; Median-paramedian; Numeric rating scale; Spinal.
nique, the needle is inserted 1 cm lateral and 1 cm caudal to the caudal edge of the most superior spinous process in the sagittal plane. In this technique, the interspinous and supraspinous ligaments are not penetrated, and the ligamentum flavum is the first structure the needle encounters.

Previous studies suggested that patients are more likely to experience PDPB after spinal anesthesia using a large-bore spinal needle due to the increased degree of tissue injury [5]. The effect of the anesthetic technique on PDPB has not been specifically investigated. The median approach technique may aggravate stretching of the spinal ligaments, resulting in increased rates of PDPB. We postulated that avoiding penetration of the supraspinous and interspinous ligaments may decrease spinal ligament stretch and reduce the incidence of PDPB. The purpose of this study was to compare the incidence and severity of PDPB following the performance of the median and paramedian techniques.

Materials and Methods

This study was conducted under the approval of the Institutional Review Board of Gwangju Christian Hospital in 2017 (KCHIRBM-2017-045). All patients signed an informed consent form before undergoing surgery. Data were collected from March 2017 to August 2017. One hundred and twenty-four patients with the American Society of Anesthesiologists physical status classification I–II, who were between the ages of 20–70 years and were scheduled for elective surgery under spinal anesthesia, were enrolled. The types of surgery included urological, orthopedic, gynecological, and general surgeries. Patients with pre-existing low back pain and those who were unable to converse or ambulate after surgery were excluded. Patients with traumatic deformity of the spine or congenital abnormalities of the lumbar spine, as well as those with contraindications for spinal anesthesia, were also excluded. Patients were classified into either the median (Group M) or the paramedian group (Group P) by computer-generated randomization. Patients were excluded from the analysis when two or more punctures were attempted or when spinal anesthesia failed.

In the operating room, the blood pressure, heart rate, electrocardiogram, peripheral oxygen saturation, and respiratory rate of all patients were monitored. After infiltration of the puncture site with 5 ml of 2% lidocaine (Lidocaine HCl Hydrate Inj. 2%, Daiban), spinal anesthesia was performed with 0.5% hyperbaric bupivacaine (Bupivacaine HCl Heavy Injection 0.5%, Hana Pharm Co., Korea) at the L3–4 or L4–5 intervertebral space. All spinal anesthesia was performed in the lateral position by the same practitioner (Dr. Lee) using a 25-gauge (G) pencil point needle (Pencan, B. Braun, Malaysia). All patients were equipped with an IV patient-controlled analgesia (PCA) device for 48 hours for postoperative pain control. The total volume of analgesic solution was 100 ml, with a combination of 500 μg fentanyl (Fentanyl citrate, Hana Pharm Co., Korea) and 6 g propacetamol (Denogan, Youngjin Pharm Co., Korea). The IV-PCA was infused at 2 ml/h, and the bolus dose was 2 ml (30 minutes lock-out times) in all patients.

We recorded the patients’ personal data, including sex, age, weight, medical history, method of approach, puncture site, bupivacaine capacity, number of puncture attempts, sensory nerve block height, surgical position, operation time, and rescue analgesics (diclofenac, ketorolac, tramadol, and meperidine) added to V-PCA. The doses of tramadol and meperidine used on the nursing floor were converted into equivalent morphine doses according to the Opioid Conversion Ratios-Guide to Practice 2010. We designed the questionnaire specifically to evaluate back pain and non-transient neurological symptoms (e.g., unilateral or bilateral pain or radicular pain in the buttock, thigh, calves, or legs, as defined by Hampl and colleagues, Appendix 1) [6]. Twenty-four hours after operation, we interviewed patients and assessed their level of low back pain. If patients had back pain, we inquired about the characteristics, aggravating factors, and degree of pain using a numeric rating scale (NRS, NRS-11) [7]. We interviewed the patients and asked the same questions over the telephone after 7 days, 1 month, 2 months, and 3 months. The interviewer was not aware of the injection approach. Patient satisfaction was assessed at the end of the survey by asking whether the patient would choose to receive spinal anesthesia again (Appendix 1).

Previous studies indicated that the incidence of PDPB ranges from 2% to 29% [5,8,9]. To detect a difference of 0.3 between the two groups, sample size calculation suggested 44 subjects per group for a two-group 0.05 one-sided t-test with 80% power. Since we planned to use a non-parametric test, 50 subjects in each group were considered adequate for the present study (12% more than the calculated sample size). Data are presented as mean ± SD for continuous data and frequencies for categorical data. Statistical analyses were performed using SPSS ver. 18.0 software (SPSS, Inc., USA). Independent-samples t-tests for quantitative data and Chi-square test for qualitative data were applied. P values less than 0.05 were considered statistically significant.

Results

One hundred and twenty-four patients were enrolled in this study. Three patients in Group M were excluded due to failure of spinal anesthesia. Nine patients in Group M and 9 in Group P were excluded from the analysis because two or more attempts
were required for successful needle placement. Two patients in Group M and 1 in Group P were lost to follow-up. Thus, a total of 100 patients were included in this study (Fig. 1). Demographic data are shown in Table 1 and did not differ between groups. Surgery type, operative time, surgical position, and bed resting time showed no evidence of differences between the groups (Table 2).

In total, 18 (36%) patients in the Group M and 19 (38%) patients in the Group P received additional analgesia. Five patients in the Group M and 8 patients (16%) in the the Group P received additional analgesia with tramadol and meperidine. Consumption of tramadol and meperidine was similar in both groups (0.8 ± 0.2 vs. 0.7 ± 0.1 mg by opioid conversion ratio) (Table 3).

During the 3-month follow-up period, 26 participants reported back pain (newly occurring) at least once. In the questionnaire administered 24 hours after surgery, 8 patients in the Group M and 6 in the Group P complained of back pain (P = 0.569); the NRS scores were 3.5 and 4.1, respectively (P = 0.828). Seven days after the surgery, 16 patients in the Group M and 5 in the Group P complained of pain (P = 0.007), with NRS scores of 3.9 vs. 3.8, respectively. After 1 month, 5 patients in the Group M and 1 in the Group P complained of pain (P = 0.095). The NRS score was 3.0 in both groups. One patient in the Group M and 1 in the Group P reported pain continuously for 3 months (Table 4, Fig. 2). Interestingly, both patients were operated upon in the lithotomy position.

Overall, 46/50 (92%) of patients in the Group M and 48/50 (96%) of patients in the Group P were satisfied with the spinal anesthesia.

### Table 1. Demographic Data

<table>
<thead>
<tr>
<th></th>
<th>Group M (n = 50)</th>
<th>Group P (n = 50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>49.4 ± 13.2</td>
<td>49.6 ± 13.0</td>
<td>0.949</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>33/17</td>
<td>38/12</td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>169.7 ± 9.1</td>
<td>169.7 ± 8.7</td>
<td>0.575</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>70.1 ± 14.6</td>
<td>70.0 ± 8.9</td>
<td>0.967</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.0 ± 4.9</td>
<td>25.3 ± 3.2</td>
<td>0.761</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number of patients (%). Group M: median group, Group P: paramedian group. BMI: body mass index. P value less than 0.05 were considered statistically significant.

### Table 2. Operative Information

<table>
<thead>
<tr>
<th></th>
<th>Group M (n = 50)</th>
<th>Group P (n = 50)</th>
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</thead>
<tbody>
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<td>Operative type</td>
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<td>37</td>
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<td></td>
</tr>
<tr>
<td>Rectoanal</td>
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<td>3</td>
<td></td>
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<tr>
<td>Orthopedic</td>
<td>7</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Operative time (h)</td>
<td>1.4</td>
<td>1.6</td>
<td>0.651</td>
</tr>
<tr>
<td>Bed rest time (h)</td>
<td>10.9</td>
<td>10.6</td>
<td>0.651</td>
</tr>
<tr>
<td>Surgical position</td>
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<td>Supine</td>
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<td>18</td>
<td></td>
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<tr>
<td>Lithotomy</td>
<td>27</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Prone</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean or number of patients (%). Group M: median group, Group P: paramedian group. P values less than 0.05 were considered statistically significant.

### Table 3. Additional Use of Analgesics

<table>
<thead>
<tr>
<th></th>
<th>Group M (n = 50)</th>
<th>Group P (n = 50)</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>NSAIDs</td>
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<tr>
<td>Diclofenac</td>
<td>5 (10)</td>
<td>6 (12)</td>
<td>0.677</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>9 (18)</td>
<td>7 (14)</td>
<td>0.550</td>
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</table>

Opioids

<table>
<thead>
<tr>
<th></th>
<th>Group M (n = 50)</th>
<th>Group P (n = 50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative morphine (mg)*</td>
<td>0.8 ± 0.2</td>
<td>0.7 ± 0.1</td>
<td>0.157</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or number of patients (%). Group M: median group, Group P: paramedian group. NSAIDs: non-steroidal anti-inflammatory drugs. P values less than 0.05 were considered statistically significant. *Opioid Conversion Ratios-Guide to Practice 2010. Available from https://swarh2.com.au/assets/A/4404/5e7e89de2ffbc6655c11e38b7a85d53/OpioidConversion2010Final(2).pdf
Discussion

We found that the overall incidence of PDPB was higher in the Group M than in the Group P, and the median approach technique was more frequently associated with PDPB 7 days postoperatively. Additionally, the pain intensity showed no evidence of differences between groups during the entire survey period, and PDPB lasting over 3 months was rare regardless of the technique.

One of the most common complications of spinal anesthesia is low back pain. Rhee et al. [10] studied patient dissatisfaction after spinal anesthesia and found that 54/1,191 (4%) patients were not satisfied. Twenty-nine percent of these dissatisfied patients identified back pain as the reason for their dissatisfaction. The risk factors for PDPB are as follows: preexisting back pain, immobilization of the spine for > 2.5 hours, lithotomy position during surgery, body mass index > 32 kg/m², and multiple attempts made for needle placement [5,8,11–14]. The mechanisms which initiate PDPB include injury to the ligaments, fascia, or bone, with localized inflammation [13,15,16]. Potential exacerbating mechanisms include immobilization of the spine, relaxation of the paraspinal muscles due to spinal anesthesia, flattening of the normal lumbar convexity curve, and stretching and/or straining of the paraspinal ligaments and facet joints, especially in the lithotomy position [11,12].

PDPB is characterized by mild intensity, local tenderness at the site of injection, and responsiveness to oral anti-inflammatory drugs or spontaneous resolution [9]. A recent study reported that the incidence of PDPB decreased from 29% 1 day after spinal anesthesia to 5% 4 weeks after spinal anesthesia, and the intensity of pain also diminished over time [5]. The findings of the present study were consistent with those of previous studies. Two patients (1 patient in each group) complained of back pain that persisted for over 3 months.

Many studies have reported no effect of spinal needle parameters (needle type and size, and the use of an introducer) on PDPB [17–20]. On the other hand, a randomized study comparing the incidence and duration of back pain after spinal (24 G Sprotte spinal needle) and epidural (18 G Touhy epidural needle) anesthesia noted that the incidence of back pain was significantly higher on postoperative days 1, 2, and 3 after epidural anesthesia [21]. Additionally, a recent review article examining back pain and neuraxial anesthesia concluded that the incidence of back pain was higher after epidural anesthesia compared to spinal anesthesia [1]. Factors which may be responsible for the increased incidence of PDPB in the epidural group are the needle size and/or tip design. This result may suggest that greater degrees of penetration result in more back pain.

![Fig. 2. Total incidence of back pain was significantly higher in the median group. During the time course, the median group showed significantly higher incidence of back pain on day 7. Group M: median group, Group P: paramedian group. *Statistically significant with P < 0.05.](https://doi.org/10.4097/kja.19409)

Table 4. Incidence and Severity of Pain

<table>
<thead>
<tr>
<th></th>
<th>Group M (n = 50)</th>
<th>Group P (n = 50)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total incidence</td>
<td>18 (36)</td>
<td>8 (16)</td>
<td>0.023</td>
</tr>
<tr>
<td>Incidence of pain after 24 hours</td>
<td>8 (16)</td>
<td>6 (12)</td>
<td>0.569</td>
</tr>
<tr>
<td>NRS after 24 hours</td>
<td>3.5 ± 0.9</td>
<td>4.1 ± 1.0</td>
<td>0.828</td>
</tr>
<tr>
<td>Incidence of pain after 7 days</td>
<td>16 (32)</td>
<td>5 (10)</td>
<td>0.007</td>
</tr>
<tr>
<td>NRS after 7 days</td>
<td>3.9 ± 1.0</td>
<td>3.8 ± 1.1</td>
<td>0.956</td>
</tr>
<tr>
<td>Incidence of pain after 1 month</td>
<td>5 (10)</td>
<td>1 (2)</td>
<td>0.095</td>
</tr>
<tr>
<td>NRS after 1 month</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Incidence of pain after 2 months</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>NRS after 2 months</td>
<td>3</td>
<td>3</td>
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<tr>
<td>Incidence of pain after 3 months</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td></td>
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<tr>
<td>NRS after 3 months</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as number of patients (%) or mean ± SD. Group M: median group, Group P: paramedian group. NRS: numeric rating scale. P values less than 0.05 were considered statistically significant.
The majority of studies that compared different needle insertion techniques have reported that the incidence of PDPB is significantly lower in the Group P compared to the Group M [22–24]. In a recent randomized control study by Singh et al. [24], the incidence of back pain in the Group P and Group M was 2% and 10%, respectively. However, these studies have a few limitations; they focused on postdural puncture headache rather than back pain. They also lacked detailed exclusion criteria such as pre-existing back pain, patient position, immobilization time, and multiple needle placement trials. In addition, studies examining the occurrence of back pain after spinal or epidural anesthesia frequently fail to describe the characteristics of the back pain. Most studies did not comment on the characteristics of the back pain, and only a few studies noted the occurrence of radicular pain in the buttock and/or lower extremities [12,16].

In our study, the overall incidence of PDPB was significantly higher in the Group M compared to the Group P. At some time points, the incidence of back pain was higher in the Group M to a non-significant degree, and pain intensity was not different in both groups, except on day 7. Our results indicate that the median approach for spinal anesthesia may be a risk factor for PDPB in the early postoperative period, but is not correlated with long-term and/or chronic back pain. Because all patients received an IV-PCA device after surgery in our study, it is possible that back pain was underreported at the 24-hour time point. Despite the potential problem it might cause during data analysis, we equipped all patients with an IV-PCA device for ethical reasons.

The strengths of our study include the exclusion of patients with pre-existing back pain. Schwabe and Hopf [8] concluded that back pain after spinal anesthesia is almost exclusively associated with pre-existing back pain. Furthermore, a recent review article evaluating back pain and neuraxial anesthesia noted that pre-existing back pain is a risk factor for persistent back pain after neuraxial anesthesia [1]. We excluded patients with pre-existing back pain because our main goal was to evaluate newly occurring back pain following spinal anesthesia. In addition, our questionnaire, which has previously been used to evaluate back pain after epidural anesthesia, was designed specifically to evaluate PDPB and not transient neurological symptoms [14]. We also excluded results obtained from patients with multiple spinal needle insertions.

Our study has several limitations. First, we did not monitor the use of postoperative supplemental analgesics, such as non-steroidal anti-inflammatory drugs, due to ethical constraints. Second, we did not exclude patients who underwent surgery in the lithotomy position. Finally, although we found no significant difference in the incidence of PDPB between the two groups, definitive conclusions could not be drawn due to the small sample size.

We conclude that the paramedian approach for spinal anesthesia reduces the incidence of PDPB in the early postoperative period. Future studies involving a more detailed description of patients’ symptoms and an appropriate physical examination will help define the precise nature of the back pain and also assist in determining the appropriate treatment for such pain.

**Conflicts of Interest**

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

**Author Contributions**

Jung Ha Lee (Data curation; Investigation)
Dae Hun Yoon (Investigation; Software)
Bong Ha Heo (Conceptualization; Supervision; Writing – original draft; Writing – review & editing)

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**References**

Appendix

Appendix 1.

Checklist for Postoperative Evaluation for Postdural puncture back pain

1. Do you have Pain at the site of injection?
   □ Yes    □ No

If yes,
1) Characteristics of these symptoms
   □ Dull       □ Aching
   □ Burning    □ Tingling   □ Numbness   □ Hypesthesia
   □ Others
2) Aggravating factor
3) Relieving factor
4) NRS (numeric rating scale)

Unusual sensations
   □ Yes    □ No

If yes, where?
If pain or any unusual sensations in the legs or buttocks was mentioned, regard as inappropriate for this study.

2. Did you recuperate completely from your anesthetic?
   □ Yes    □ No

If no, what are your problems?
   □ Back pain   □ Headache
   □ Fatigue     □ Nausea/vomiting
   □ Dizziness   □ Difficulty urinating or defecating
The immunosuppressive effects of volatile versus intravenous anesthesia combined with epidural analgesia on kidney cancer: a pilot randomized controlled trial

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Background: The aim of this study was to test the hypothesis that the use of inhalational anesthesia leads to higher suppression of the cell-mediated immunity compared to total intravenous anesthesia in patients undergoing kidney cancer surgery under combined low thoracic epidural analgesia and general anesthesia.

Methods: Patients were randomly allocated to either propofol-based (intravenous anesthetic) or sevoflurane-based (volatile anesthetic) anesthesia group with 10 patients in each group, along with epidural analgesia in both groups. Amounts of natural killer (NK) cells, total T lymphocytes, and T lymphocyte subpopulations in the blood samples collected from the patients before surgery, at the end of the surgery and postoperative days 1, 3 and 7 were determined by flow cytometric analysis. The NK cell count served as the primary endpoint of the study, whereas the total T lymphocyte count and cell counts for T lymphocyte subpopulations were used as the secondary endpoint.

Results: Our study showed that there were no significant differences in the amount of NK cells, total T lymphocytes, regulatory T cells, and T-helper cells, cytotoxic T lymphocytes, and their subpopulations between the propofol- and sevoflurane-based anesthesia groups when the anesthesia was administered in combination with epidural analgesia.

Conclusions: The results of this pilot study did not support the hypothesis that the use of inhalational anesthesia leads to higher suppression of the cell-mediated immunity than that of total intravenous anesthesia in patients undergoing kidney cancer surgery under combined low thoracic epidural analgesia and general anesthesia.

Keywords: Anesthesia; Cancer; Epidural analgesia; Immunity; Propofol; Sevoflurane.

Introduction

Kidney cancer is the sixth most common cancer among men, and the eighth most common cancer among women [1]. Nephrectomy and surgical resection are the primary
methods of choice for the treatment of renal cancer. Perioperative stress is associated with neuroendocrine and immune de-arrangements and contributes to the survival of circulating tumor cells and minimal residual disease [2]. Several in vivo, animal, and retrospective clinical studies showed that anesthesia contributes to the perioperative stress and may affect cancer recurrence and survival [3].

Suppression of cell-mediated immunity has been hypothesized to be associated with poor long-term outcomes of cancer surgery [4]. Several studies demonstrated that the use of volatile anesthetics during cancer surgery is associated with poor outcomes as compared to the use of intravenous anesthetic, propofol [5–7]. These differences in the outcomes are contributed through various effects of anesthetic agents on various immune cells, such as natural killer (NK) cells, cytotoxic T lymphocytes (CTL), and T-helper ($T_h$) cells [8–11].

Although epidural analgesia is routinely used and widely accepted in cancer patients, the selection of an appropriate type of anesthesia (inhalational versus total intravenous anesthesia) remains a matter of debate. Furthermore, studies have so far not standardized the effects of combined anesthetic interventions (e.g., regional and opioid analgesia) on cell-mediated immunity.

The aim of this study was to test the hypothesis that the use of inhalational anesthesia as compared to total intravenous anesthesia leads to the higher suppression of the cell-mediated immunity in patients undergoing kidney cancer surgery under combined low thoracic epidural analgesia and general anesthesia, by conducting a pilot, randomized, controlled trial (RCT).

Materials and Methods

Study population

The RCT was approved by the ethics committee of E. Meshalkin National Medical Research Center, Novosibirsk, Russian Federation (Approval number 14/2018). The trial was registered prior to patient enrollment at clinicaltrials.gov (NCT03514550, Principal investigator: Efremov Sergey, Date of registration: May 2, 2018). Written informed consent was obtained from all participants. All patients were operated in E. Meshalkin National Medical Research Center.

Patients with renal cancer scheduled for open nephrectomy or kidney resection were eligible for the study; inclusion criteria were as follows: surgery for renal cancer and signed informed consent; exclusion criteria: propofol or sevoflurane intolerance, contraindications to epidural analgesia, renal failure, liver failure, congestive heart failure, previous chemotherapy, and co-morbid hematological diseases.

Before anesthesia induction, patients were randomly allocated to either propofol-based (intravenous) or sevoflurane-based (inhalational) anesthesia groups with 10 patients in each group. Random allocation sequence generation, enrollment, and the allocation of the participants to the interventions were performed by an investigator not involved in the intervention and outcome assessment. A simple randomization sequence was generated electronically (https://www.sealedenvelope.com). Patients were allocated to the intervention using numbered-opaque-sealed envelopes, and the procedure for the allocated intervention was performed immediately after opening the envelope. Flank incision was used for surgical access to the kidney.

Clinical characteristics

Demographic and perioperative data were collected and analyzed, including age, height, weight, gender, cancer stage, minimal body temperature during operation, duration of surgery (defined as the period between skin incision and skin closure), duration of anesthesia (defined as the period between induction to anesthesia and end of the administration of the anesthetic agents, sevoflurane or propofol), ventilation time, intensive care unit stay and duration of hospitalization.

Anesthesia

The enrolled patients were not premedicated. Intraoperative monitoring included ECG, pulse oximetry, body temperature, and invasive arterial pressure. Forced-air warming with a blanket covering legs were used for the maintenance of normothermia. Epidural analgesia was performed using an 18-gauge (G) Touhy needle using the median or para-median approach at the T10–11 or T11–12 vertebral level. After confirmation of the needle tip placement, using saline for the loss of resistance technique, catheterization of epidural space with a 20 G epidural catheter was performed, and 7 ml of 0.75% ropivacaine was administered. Epidural block in relevant dermatomes has been confirmed using an alcohol swab test for 20 minutes after ropivacaine administration. Repeated epidural 0.75% ropivacaine injection was performed after 1–3 hours of initial dose in accordance with the anesthesiologist decision.

Anesthesia induction was performed by administering propofol at a dosage of 1.5–2.5 mg/kg intravenously, in the propofol-based anesthesia group, and sevoflurane 5–8% inspired concentration with 50% oxygen, in the sevoflurane-based anesthesia group. Lidocaine (1 mg/kg) and fentanyl (2 µg/kg) were given intravenous-
ly, 3 min before intubation to all the patients. After loss of consciousness and confirmation of adequate mask ventilation, rocuronium (0.6 mg/kg) was administered intravenously for muscle relaxation. Tracheal intubation was performed 1–2 min after rocuronium injection. Antiobiotic prophylaxis was performed using Cefuroxime (1500 mg, intravenous administration).

Anesthesia was maintained with a dosage of 0.1–0.2 mg/kg/min propofol in the propofol-based group, and with 1 minimal alveolar concentration of sevoflurane in the sevoflurane-based group. Opioids were not used for anesthesia maintenance. During anesthesia, the mean blood pressure was maintained above 60 mmHg. At the end of the surgery, the administration of propofol or sevoflurane was stopped, the patients were transferred to the post-anesthesia care unit, and the epidural analgesia was continued with 0.25% ropivacaine for up to 2 days after surgery. The rate of postoperative epidural ropivacaine infusion was set as 3–8 ml/h and delivered by syringe pump in accordance to individual requirements and tolerability. In the absence of contraindications, non-steroid anti-inflammatory drugs (ketoprofen) and/or acetaminophen were used routinely for multimodal analgesia in all patients. Parenteral opioids were allowed for analgesic rescue postoperatively in cases when multimodal analgesia was insufficient.

Blood samples

Venous blood samples were collected before surgery, at the end of the procedure, and on postoperative days (POD) 1, 3, and 7. Blood samples were collected in ethylenediaminetetraacetic acid tubes. Flow cytometric analysis was performed immediately after blood collection.

Determination of frequencies of natural killer cells and T lymphocytes by flow cytometric analysis

The primary endpoint of the study was NK cell count, and the secondary endpoint was the total T lymphocyte count and counts for the T lymphocyte subpopulations, such as T<sub>h</sub> cells, CTL, naive, central memory (CM), effector memory (EM), terminally differentiated effector memory (TEMRA) of T<sub>h</sub> cells and CTL cells, natural killer T cells (NKT), and regulatory T cells (T<sub>reg</sub>).

Frequencies of NK cells and the different types of T lymphocytes in the blood samples were determined based on the expression of cell-type-specific cluster of differentiation (CD) antigens. Anti-human antibodies specific to the various CD antigens and conjugated to specific fluorophores, allophycocyanin (APC), APC-Alexa Fluor (AF)-700, APC-AF-750, phycoerythrin (PE), phycoerythrin-Texas-Red-x (ECD), phycoerythrin-Cyanin 7 (PC7), phycoerythrin-Cyanin 5 (PC5), pacific blue (PB), were purchased from Beckman Coulter (France), and flow cytometry analysis was performed based on the antibody staining. Investigators, blinded to the allocated intervention, performed the flow cytometry analysis. For that, 100 μl of whole blood samples were stained with the specific fluorophore-conjugated monoclonal antibodies at room temperature (20–25°C), in the dark, for 15 min, in accordance with the manufacturer’s instructions. Red blood cells were lysed using the IQTest 3 Lysing Solution (IM3514, Beckman Coulter, France) at room temperature, in the dark, for 10 min. The various immune cells in the peripheral blood were identified using the Navios flow cytometer (Beckman Coulter, USA), and analysis was performed according to the manufacturer’s protocol. Flow cytometric analysis was performed with at least 10,000 events in every measurement.

The use of antibodies for the determination of circulating NK and NKT cells

The amount of circulating NK and NKT cells in the peripheral blood samples was determined using APC-AF 750-conjugated anti-human CD3 antibody (A66329), PC7-conjugated anti-human CD16 antibody (6607118), and PC7-conjugated anti-human CD56 antibody (A51078). All antibodies were purchased from Beckman Coulter, France. The specific cell types were identified based on the expression of the specific CD antigens: CD3<sup>+ </sup>CD16<sup>-</sup> CD56<sup>-</sup> for NK cells, CD3<sup>+</sup> CD16<sup>+</sup> CD56<sup>-</sup> for NKT cells.

The use of antibodies for the determination of total T lymphocytes and its subpopulations

The quantity of circulating total T lymphocytes, Th cells, CTL and its subpopulations in the peripheral blood samples were determined using APC-AF 750-conjugated anti-human CD3 antibody (A66329), APC-conjugated anti-human CD8 antibody (IM2469U), PC7-conjugated anti-human CD4 antibody (A6607101), ECD-conjugated anti-human CD62L antibody (IM2713U), PE-conjugated anti-human CD45RO antibody (IM1307U), and PB-conjugated anti-human CD45RA antibody (A82946). All antibodies were purchased from Beckman Coulter, France. The specific cell types were identified based on the expression of the specific CD antigens: CD3<sup>+</sup> for mature T lymphocytes; CD3<sup>+</sup> CD4<sup>-</sup>; CD3<sup>+</sup> CD8<sup>-</sup> for T<sub>h</sub> cells; CD3<sup>+</sup> CD4<sup>+</sup> CD62L<sup>-</sup> CD45RA<sup>-</sup> for CM T<sub>h</sub> cells; CD3<sup>+</sup> CD8<sup>-</sup> CD62L<sup>-</sup> CD45RA<sup>-</sup> for CM CTL cells; CD3<sup>+</sup> CD4<sup>+</sup> CD62L<sup>-</sup> CD45RA<sup>-</sup> for EM Th cells; CD3<sup>+</sup> CD8<sup>-</sup> CD62L<sup>-</sup> CD45RA<sup>-</sup> for EM CTL cells; CD3<sup>+</sup> CD4<sup>+</sup>
CD62L⁺ CD45RA⁺ for naive T<sub>H</sub> cells; CD3⁺ CD8⁺ CD62L⁺ CD45RA⁺ for naive CTL cells; CD3⁺ CD4⁺ CD62L⁺ CD45RA⁺ for TEMRA T<sub>H</sub> cells; CD3⁺ CD8⁺ CD62L⁻ CD45RA⁻ for TEMRA CTL cells.

The use of antibodies for the determination of circulating regulatory T cells

The amount of circulating regulatory T cells in the peripheral blood samples was determined using APC-AF 750-conjugated anti-human CD3 antibody (A66329), PC7-conjugated anti-human CD4 antibody (A6607101), PC5-conjugated anti-human CD25 antibody (IM2646U), and APC-AF 700-conjugated anti-human CD127 antibody (A71116). All antibodies were purchased from Beckman Coulter, France.

Statistical analysis

Comparisons within each group, as well as between the two anesthesia groups, were performed using mixed-effects model (with time and patient as random effects and group as fixed effects), incorporating multiplicity correction by Tukey’s method. Levene’s test was performed, and sphericity was confirmed to be valid. Qualitative characteristics were compared using the χ² test and Fisher’s exact test, wherever appropriate. The level of significance was set at P < 0.05 (two-tailed). Statistical analysis was performed using MedCalc statistical software version 13.1.0 (MedCalc Software, Belgium). Data were summarized and presented as median and Q1–Q3. Cellular distributions are represented in numbers and percentages.

Results

In total, 20 patients were enrolled from May 2018 to April 2019, and 10 patients were randomly allocated to each the propofol- or sevoflurane-based anesthesia groups (Fig. 1). Groups showed no evidence of differences in terms of baseline and perioperative clinical characteristics (Table 1). Epidural block was successful in all patients. No hemodynamic reactions during skin incision or wound traction were observed. Norepinephrine infusion in order to maintain mean arterial pressure above 60 mmHg was required in (20%, n = 2) patients of propofol and (20%, n = 2) of sevoflurane groups.

The extent of postoperative pain in accordance with 10-points visual analog scale (VAS) showed no evidence of difference in both groups. Thus, VAS values were equal to 2.5 (2–3) and 2 (2–3) at the day of surgery, 2 (2–3) and 3 (3–3) at the first POD 2 (2–3) and 2 (2–2) at the third POD in the propofol and sevoflurane groups, accordingly. One patient in the propofol group and 2 patients in the sevoflurane group needed rescue analgesia with tramadol after discharge from the post-anesthetic care unit.

Detailed cell count data are provided in Table 2. We used NK cell count as the primary endpoint of the study, and our analysis showed that there were no significant differences in the amount of

![Fig. 1. CONSORT flow diagram.](https://doi.org/10.4097/kja.19461)
NK cells between the propofol- and sevoflurane-based anesthesia groups. NK cell counts, observed during the different stages and represented as median [interquartile range], were: 169 (105–466) and 187 (147–453) at baseline, 109 (67–262) and 166 (51–245) at the end of the surgery, 116 (69–150) and 128 (71–226) at POD 1, 121 (55–223) and 128 (63–186) at POD 3, 148 (96–245) and 151 (131–206) at POD 7; in the propofol-based and sevoflurane-based anesthesia group, respectively (P = 0.055). The secondary end-point was the total T lymphocyte count and counts for T-cell subpopulations. Our analysis showed that there were no significant differences in the amount of total T lymphocyte, T<sub>reg</sub> cells, T<sub>H</sub> cells, CTL, and their subpopulations between the propofol- and sevoflurane-based anesthesia groups. However, a small reduction in NK cell counts was observed during the first 3 POD in both groups. Significant within-group differences in the total T lymphocytes count (P < 0.001) and T<sub>reg</sub> cells (P < 0.005) were observed in both groups. Significant within-group differences in the total count of T<sub>H</sub> cells (P < 0.001), and its subpopulations, naive T<sub>H</sub> cells (P < 0.001), CM T<sub>H</sub> cells (P < 0.001), EM T<sub>H</sub> cells (P < 0.001) were observed during surgery, POD 1, and POD 3 in both groups and the corresponding levels were recovered to the normal by POD 7. Similarly, significant differences in the total count of CTL (P < 0.001), and its subpopulations, naive CTL (P < 0.001), CM CTL (P < 0.005), EM CTL (P < 0.05) were observed during surgery, POD 1 and POD 3, in both groups and the levels were recovered by POD 7.

Table 1. Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Propofol (n = 10)</th>
<th>Sevoflurane (n = 10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>59 (58–67)</td>
<td>62 (57–62)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Sex (F)</td>
<td>5 (50)</td>
<td>4 (40)</td>
<td>0.659</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>168 (159–172)</td>
<td>166 (164–171)</td>
<td>0.873</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>87 (75–97)</td>
<td>79 (68–85)</td>
<td>0.271</td>
</tr>
<tr>
<td>Cancer stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3 (30)</td>
<td>3 (30)</td>
<td>0.380</td>
</tr>
<tr>
<td>2</td>
<td>1 (10)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>6 (60)</td>
<td>5 (50)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>2 (20)</td>
<td></td>
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<tr>
<td>Distal metastases at diagnosis</td>
<td>0</td>
<td>2 (20)</td>
<td>0.138</td>
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<td>Invasion to inferior vena cava</td>
<td>0</td>
<td>1 (10)</td>
<td>0.325</td>
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<tr>
<td>Redo surgery</td>
<td>0</td>
<td>1 (10)</td>
<td>0.325</td>
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<td>ASA score</td>
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<tr>
<td>II</td>
<td>6 (60)</td>
<td>4 (40)</td>
<td>0.382</td>
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<tr>
<td>III</td>
<td>4 (40)</td>
<td>6 (60)</td>
<td></td>
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<tr>
<td>Surgery type</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nephrectomy</td>
<td>7 (70)</td>
<td>8 (80)</td>
<td>0.611</td>
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<tr>
<td>Kidney resection</td>
<td>3 (30)</td>
<td>2 (20)</td>
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<td>Intraoperative characterisitcs:</td>
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<tr>
<td>Total ropivacain dose (mg)</td>
<td>75 (53–75)</td>
<td>75 (53–120)</td>
<td>0.633</td>
</tr>
<tr>
<td>Lowest mean arterial pressure (mmHg)</td>
<td>57 (51–67)</td>
<td>65 (61–67)</td>
<td>0.082</td>
</tr>
<tr>
<td>Blood transfusion</td>
<td>0 (0)</td>
<td>1 (10)</td>
<td>0.317</td>
</tr>
<tr>
<td>Crystalloids infusion (ml)</td>
<td>1500 (1000–1500)</td>
<td>1500 (1500–2500)</td>
<td>0.153</td>
</tr>
<tr>
<td>Diuresis (ml)</td>
<td>305 (200–470)</td>
<td>345 (180–420)</td>
<td>0.970</td>
</tr>
<tr>
<td>Minimal body temperature (°C)</td>
<td>36.0 (35.7–36.1)</td>
<td>36.0 (35.5–36.5)</td>
<td>0.559</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>60 (50–100)</td>
<td>90 (60–210)</td>
<td>0.090</td>
</tr>
<tr>
<td>Duration of anesthesia (min)</td>
<td>132 (100–170)</td>
<td>125 (105–270)</td>
<td>0.628</td>
</tr>
<tr>
<td>Postoperative characteristics:</td>
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<tr>
<td>Ventilation time (h)</td>
<td>1.5 (0–2)</td>
<td>1 (0–2)</td>
<td>0.973</td>
</tr>
<tr>
<td>PACU stay (days)</td>
<td>1 (1–1)</td>
<td>1 (1–1)</td>
<td>0.470</td>
</tr>
<tr>
<td>Hospitalization (days)</td>
<td>7 (6–7)</td>
<td>6 (5–7)</td>
<td>0.262</td>
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</tbody>
</table>

Values are presented as median (Q1–Q3) or number (%). PACU: post anesthetic care unit.

https://doi.org/10.4097/kja.19461
Table 2. T lymphocyte Subtype Counts

<table>
<thead>
<tr>
<th>Lymphocyte subpopulation</th>
<th>Group</th>
<th>Baseline</th>
<th>End of surgery</th>
<th>1 day</th>
<th>3 days</th>
<th>7 days</th>
<th>P value*</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-cells (cells/μl)</td>
<td>Propofol</td>
<td>1256 (996–1695)</td>
<td>957 (857–1032)</td>
<td>722 (514–806)</td>
<td>898 (615–1048)</td>
<td>957 (905–1333)</td>
<td>0.861</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>T-helpers (cells/μl)</td>
<td>Propofol</td>
<td>727 (556–851)</td>
<td>591 (520–784)</td>
<td>775 (623–921)</td>
<td>801 (526–1201)</td>
<td>1307 (1059–1441)</td>
<td>0.818</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Sevoflurane</td>
<td>786 (565–961)</td>
<td>958 (538–1460)</td>
<td>1307 (1059–1441)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Naive CD4⁺ cells (cells/μl)</td>
<td>Propofol</td>
<td>169 (110–215)</td>
<td>129 (80–178)</td>
<td>722 (514–806)</td>
<td>898 (615–1048)</td>
<td>957 (905–1333)</td>
<td>0.859</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>CM CD4⁺ cells (cells/μl)</td>
<td>Propofol</td>
<td>339 (224–535)</td>
<td>256 (193–364)</td>
<td>722 (514–806)</td>
<td>898 (615–1048)</td>
<td>957 (905–1333)</td>
<td>0.314</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>EM CD4⁺ cells (cells/μl)</td>
<td>Propofol</td>
<td>131 (101–245)</td>
<td>175 (120–188)</td>
<td>722 (514–806)</td>
<td>898 (615–1048)</td>
<td>957 (905–1333)</td>
<td>0.613</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Sevoflurane</td>
<td>156 (94–216)</td>
<td>140 (64–201)</td>
<td>898 (615–1048)</td>
<td>957 (905–1333)</td>
<td>1307 (1059–1441)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEMRA CD4⁺ cells (cells/μl)</td>
<td>Propofol</td>
<td>11.6 (5.9–27.7)</td>
<td>12.1 (4.8–45.4)</td>
<td>722 (514–806)</td>
<td>898 (615–1048)</td>
<td>957 (905–1333)</td>
<td>0.772</td>
<td>0.267</td>
</tr>
<tr>
<td></td>
<td>Sevoflurane</td>
<td>14 (6.6–56.1)</td>
<td>17 (3.6–55.9)</td>
<td>898 (615–1048)</td>
<td>957 (905–1333)</td>
<td>1307 (1059–1441)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTL (cells/μl)</td>
<td>Propofol</td>
<td>423 (372–573)</td>
<td>387 (294–452)</td>
<td>722 (514–806)</td>
<td>898 (615–1048)</td>
<td>957 (905–1333)</td>
<td>0.488</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Naive CTL (cells/μl)</td>
<td>Propofol</td>
<td>90 (68–132)</td>
<td>83 (53–127)</td>
<td>722 (514–806)</td>
<td>898 (615–1048)</td>
<td>957 (905–1333)</td>
<td>0.780</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Sevoflurane</td>
<td>118 (69–147)</td>
<td>79 (45–93)</td>
<td>898 (615–1048)</td>
<td>957 (905–1333)</td>
<td>1307 (1059–1441)</td>
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</tr>
<tr>
<td>CM CTL (cells/μl)</td>
<td>Propofol</td>
<td>67.4 (55–104)</td>
<td>47.3 (22.8–80.1)</td>
<td>722 (514–806)</td>
<td>898 (615–1048)</td>
<td>957 (905–1333)</td>
<td>0.515</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Sevoflurane</td>
<td>57 (39–83)</td>
<td>47.5 (26.1–61.6)</td>
<td>898 (615–1048)</td>
<td>957 (905–1333)</td>
<td>1307 (1059–1441)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EM CTL (cells/μl)</td>
<td>Propofol</td>
<td>102 (65–118)</td>
<td>79 (39–148)</td>
<td>722 (514–806)</td>
<td>898 (615–1048)</td>
<td>957 (905–1333)</td>
<td>0.266</td>
<td>0.022</td>
</tr>
<tr>
<td></td>
<td>Sevoflurane</td>
<td>119 (98–125)</td>
<td>70 (40–124)</td>
<td>898 (615–1048)</td>
<td>957 (905–1333)</td>
<td>1307 (1059–1441)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TEMRA CTL (cells/μl)</td>
<td>Propofol</td>
<td>151 (75–281)</td>
<td>148 (83–199)</td>
<td>722 (514–806)</td>
<td>898 (615–1048)</td>
<td>957 (905–1333)</td>
<td>0.868</td>
<td>0.011</td>
</tr>
<tr>
<td>Treg (cells/μl)</td>
<td>Propofol</td>
<td>24.1 (16.5–41.7)</td>
<td>22.4 (15–36.9)</td>
<td>722 (514–806)</td>
<td>898 (615–1048)</td>
<td>957 (905–1333)</td>
<td>0.543</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>Sevoflurane</td>
<td>30.2 (24.7–34.8)</td>
<td>25.3 (19.5–43.4)</td>
<td>898 (615–1048)</td>
<td>957 (905–1333)</td>
<td>1307 (1059–1441)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NK cells (cells/μl)</td>
<td>Propofol</td>
<td>169 (105–466)</td>
<td>109 (67–262)</td>
<td>722 (514–806)</td>
<td>898 (615–1048)</td>
<td>957 (905–1333)</td>
<td>0.504</td>
<td>0.053</td>
</tr>
<tr>
<td></td>
<td>Sevoflurane</td>
<td>187 (147–453)</td>
<td>166 (51–245)</td>
<td>898 (615–1048)</td>
<td>957 (905–1333)</td>
<td>1307 (1059–1441)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNK cells (cells/μl)</td>
<td>Propofol</td>
<td>101 (65–168)</td>
<td>89 (45–103)</td>
<td>722 (514–806)</td>
<td>898 (615–1048)</td>
<td>957 (905–1333)</td>
<td>0.753</td>
<td>0.174</td>
</tr>
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</table>

Values are presented as median (Q1–Q3). EM: effector memory, CM: central memory, TEMRA: terminally differentiated effector memory cells, CTL: cytotoxic T lymphocytes, NK: natural killer, Treg: regulatory T lymphocytes, TNK: natural killer T lymphocytes. *Between-group differences in accordance with a mixed-effects model, †Within-group differences using a mixed-effects model.
Discussion

An important observation from this study is that the suppression of the cell-mediated immunity under the use of inhalational anesthesia was similar to that during total intravenous anesthesia in patients undergoing kidney cancer surgery under combined low thoracic epidural analgesia and general anesthesia. Our analysis showed that there were no significant differences in the amounts of NK cells, total T lymphocytes, regulatory T cells, T<sub>reg</sub> cells, CTL, and their subpopulations between the propofol- and sevoflurane-based anesthesia groups when the anesthesia was administered in combination with epidural analgesia.

NK cells are essential defensive cells for attenuation of cancer progression [12], and due to their anti-tumor activity, which is independent of recognition of tumor-specific antigens that are anyway poorly presented on a majority of the malignant cells, are particularly attractive for cancer treatment. Regulatory T cells inhibit anti-tumor activity of NK cells and CTL, promote cancer growth, recurrence, and metastasis [13].

The results of our study are in accordance with the existing data on the pattern of perioperative-stress-mediated immunosuppression. Several studies have shown that perioperative stress is responsible for suppression of cell-mediated immunity lasting up to 1 week, and the effect is directly related to the extent of surgical stress and incidence of postoperative complications, adversely affecting the long-term outcomes [3].

Furthermore, there are reports on the suppressive effects of volatile anesthetics on lymphocyte proliferation [14,15] and their ability to induce lymphocyte apoptosis [16], whereas propofol was shown to have a neutral effect on the lymphocyte function [17]. Moreover, advantages of using propofol over sevoflurane on the anti-tumor activity of immune cells were investigated in an in vitro study, performed on breast cancer tissue samples. These samples were obtained from the participants of a large ongoing randomized trial aimed to explore the effect of combined use of propofol with paravertebral anesthesia in comparison to sevoflurane with opioid anesthesia (NCT00418457). These pilot studies showed that the combined use of propofol and paravertebral anesthesia increase the levels of NK and T<sub>reg</sub> cell infiltration in the breast cancer tissue samples [18], induce the apoptosis of estrogen receptor-negative breast cancer cells [11], and are associated with increased NK cell cytotoxicity [9] in comparison to sevoflurane. However, in this study, propofol was administered together with paravertebral block, whereas sevoflurane was administered with opioids. Of note, previous studies have demonstrated the dose-dependent detrimental effects of opioids on NK cell cytotoxicity [19], whereas regional anesthesia was shown to attenuate the immunosuppressive effects of surgery by reducing the neuroendocrine stress due to the lesser anesthetic drug requirements.

Further, epidural analgesia is hypothesized to be protective for cancer patients by attenuating inflammation [20], immunosuppression, catecholamine response, sympathetic blockade [21], and eliciting inhibitory effects on perioperative lymph flow, thus lowering the risk of intraoperative cancer cell dissemination [22]. A meta-analysis of two independent retrospective clinical trials showed a favorable impact of regional anesthesia on the mortality in cancer patients [23,24]. Nevertheless, a study of Myles et al. [25], provided conflicting evidence. Our study did not observe a difference between propofol- and sevoflurane-based anesthesia groups, probably because the immunosuppression, induced by the volatile anesthetics, may be modified when used in combination with regional analgesia.

In a recently published RCT by Oh et al. [10], 201 patients scheduled for breast cancer surgery were randomly assigned to propofol or sevoflurane anesthesia, and no significant differences were observed between the two groups in T<sub>reg</sub> cells (CD39<sup>+</sup>, CD73<sup>+</sup>), T<sub>reg</sub> type 1 and type 17 cells, NK cells, CTL, cytokines, or in the neutrophil-to-lymphocyte ratio. Although the patients enrolled in this study were not administered epidural analgesia, findings of our study are in accordance with these observations.

We have herein discussed some of the essential considerations and strengths of the current study. Our decision on the enrollment of kidney cancer patients in RCT was based on several reasons. First, open nephrectomy is associated with considerable tissue trauma, and perioperative pain is controlled by epidural analgesia in many occasions. Further, none of the patients enrolled in the study received chemotherapy before surgery. The major strength of our study is that the confounders that are capable of influencing cell immunity are uniform between the two groups, and epidural analgesia, opioid-less anesthesia, and maintenance of normothermia were applied in both groups. Furthermore, this is the first study that is assessing the effects of anesthesia on cell-mediated immunity in patients undergoing surgery for kidney cancer. Although several large randomized trials on the investigation of the effects of anesthesia on clinical outcomes among cancer patients are ongoing (NCT01975064, NCT03034096, NCT02813044, NCT03193710, NCT02660411, NCT02840227), it should be noted that none of these trials are designed to administer regional anesthesia to all the participants.

Nevertheless, there are also some limitations of the current study. First, it was a pilot trial with a small number of participants and hence, it is not powered for the primary endpoint. Second, the effect of fentanyl that was administered to all patients during the procedure (a single dose of 2 μg/kg) on cell-mediated immu-
nity is not known. Third, the level of anesthesia using the bispectral index was not monitored during the surgery, and comparative data of anesthesia depth are not provided. However, successful epidural block in all patients, no cases of intraoperative awareness, and end-tidal anesthetic gas guided anesthesia in sevoflurane-based group likely overcome this limitation. Fourth, our study measures cell counts, which may not comprehensively reflect the function and actual difference in cytotoxic activity.

In conclusion, the results of this pilot study do not support the hypothesis that the suppression of cell-mediated immunity is higher under the use of inhalational anesthesia than total intravenous anesthesia in patients undergoing kidney cancer surgery under combined low thoracic epidural analgesia and general anesthesia. Our study indicates that the effect of different types of anesthesia on cell-mediated immunity might be modulated when used in combination with regional analgesia. These findings are of importance for designing clinical trials in the future.

**Conflicts of Interest**

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

**Author Contributions**

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Sergey Valeriievich Yarmolshuk (Data curation; Investigation)

Alexandr Alexandrovich Zheravin (Data curation; Investigation)

Giovanni Landoni (Conceptualization; Writing – review & editing)

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**References**

Presently, many thoracic surgeries require one-lung ventilation (OLV) to improve the operation field and expedite the operation. During OLV, maintenance of adequate arterial oxygenation is a major concern to anesthesiologists. In previous studies, 4–27% of patients undergoing OLV developed arterial hypoxemia [1–3]. Because a collapsed lung is not ventilated but perfused, a transpulmonary shunt is inevitably developed, which leads to impairment of oxygenation. In addition, atelectatic and hypoventilated areas are increased in the dependent ventilated lung by the positional effects during thoracic surgery with OLV in the lateral position, which contributes to ventilation/perfusion mismatch and decreases arterial oxygen partial pressure (PaO₂).

Hypoxic pulmonary vasoconstriction (HPV) is a physiologic mechanism that decreas-
es blood flow to hypoxic or atelectatic lung regions by arteriolar vasoconstriction via a pathway involving nitric oxide and/or cyclooxygenase synthesis inhibition [4]. HPV diverts pulmonary blood flow from poorer ventilated areas to better areas of the lung, reducing the shunt fraction, and improving oxygenation [5,6]. Although HPV reduces shunt flow, 15–40% of pulmonary blood shunts to the left heart during OLV [7]. Recommendations to prevent arterial hypoxemia during OLV include the use of high inspired fraction of oxygen (FiO₂), application of positive end-expiratory pressure (PEEP) to the dependent lung, and continuous positive airway pressure (CPAP) to the non-dependent lung [8]. However, these techniques are inadequate for maintaining adequate oxygenation in some patients undergoing OLV.

In clinical practice, many patients have hypercarbia due to decreased minute ventilation and increased dead-space ventilation during OLV compared to two-lung ventilation (TLV). Carbon dioxide (CO₂) is a potent vasodilator in cerebral and systemic circulation [9,10]. However, the effect of CO₂ on pulmonary circulation is unclear. In previous studies [10–14], the effects of CO₂ on pulmonary vessels varied by the experiment species and pulmonary vascular tone. Most previous studies were conducted on ventilated lungs, but studies OLV subjects are rare. If CO₂ dilates the pulmonary artery in the ventilated lung or constricts the pulmonary artery in the non-ventilated lung, then hypercarbia may increase arterial oxygenation during OLV. If CO₂ has the opposite effects, then hypercarbia should be avoided.

We hypothesized that hypercarbia increases arterial oxygenation compared to normocarbia during OLV. The primary purpose of this prospective, randomized crossover study was to evaluate the effects of hypercarbia on arterial oxygenation during OLV.

Materials and Methods

The clinical research was done following the ethical principles for medical research involving human subjects in accordance with the Helsinki Declaration 2013. This prospective, randomized crossover study was approved by the Institutional Review Board of Chonbuk National University Hospital and registered with the WHO International Clinical Trials Registry Platform (KCT0003185). Written informed consent was obtained from all participants. Fifty adult patients who were assigned American Society of Anesthesiologists physical status I or II, and who underwent elective video-assisted thoracoscopic lobectomy or pneumonectomy due to lung cancer were enrolled in the study. Patients who presented cardiac arrhythmia, heart failure, chronic obstructive pulmonary disease, restrictive pulmonary disease or increased intracerebral pressure were excluded. Arterial oxygenation can be greatly affected by surgical process such as ligation of the pulmonary vessels in the collapsed surgical lung. Therefore, we divided the patients into two groups by order of intervention, although it was a crossover comparison. After initiation of OLV, Group I patients were first maintained at normal arterial CO₂ partial pressure (normocarbia, PaCO₂: 38–42 mmHg) for 30 min (OLV-1) and then at high PaCO₂ (hypercarbia, 45–50 mmHg) for 30 min (OLV-2). In Group II patients, PaCO₂ was maintained in the reverse order (OLV-1, hypercarbia; and OLV-2, normocarbia). Subjects were randomly assigned using a computer-generated block randomization scheme to one of two groups (1 : 1 allocation ratio).

The anesthetic regimen was standardized for all patients. After placement of the electrocardiogram, pulse oximetry, non-invasive blood pressure, bispectral index (BIS) and peripheral nerve stimulator, anesthesia was induced with 1.0–1.5 mg/kg propofol, 4–6 ng/ml effect-site concentration of remifentanil, and 1.0 mg/kg rocuronium. Remifentanil was administered using a Minto model effect-site target-controlled infusion pump (Orchestra® Base Primea, Fresenius Vial, France). Patients were manually ventilated using a face mask with sevoflurane (4.0 vol% in 50% oxygen) until a train-of-four count of 0 in the peripheral nerve stimulator was obtained. Female and male patients were intubated with a 35 or 37 Fr. and 37 or 39 Fr. left-sided double-lumen tube (Shiley™ Endobronchial tube left, Covidien, USA), respectively. The double-lumen tube was positioned using a fiberoptic bronchoscope. After induction of anesthesia, a 20-gauge arterial catheter was inserted into the brachial artery in the non-dominant hand. The brachial artery catheter was connected to the FloTrac™ transducer (Edwards Lifesciences, USA) coupled to both an anesthesia workstation (Primus Infinity® Empowered, Dräger, Germany) and EV1000™ (software version 1.5, Edwards Lifesciences) for hemodynamic measurements, including invasive blood pressure (IBP), cardiac index (CI), stroke volume variation (SVV), and systemic vascular resistance index (SVRI). The right subclavian vein was catheterized under ultrasono-guide for intravenous fluid line, central venous blood gas analysis, and central venous pressure (CVP) measurement. Pressure transducers were zeroed at the cardiac level to atmospheric pressure.

Lungs were mechanically ventilated with 0.5 of FiO₂ using a tidal volume (TV) of 6–8 ml/kg predicted body weight, an inspiratory to expiratory ratio of 1 : 2, an inspiratory pause of 25% of total inspiration time, and 5 cmH₂O of PEEP. The ventilatory rate was adjusted to maintain normocapnia. Anesthesia was maintained with sevoflurane and remifentanil. Fresh gas flow was fixed 3 L/min. The end-expiratory sevoflurane concentration was fixed
to 1.0 vol%. Arterial blood pressure was kept within 20% of preanesthetic values by adjustment of remifentanil concentration. Initially, the end-tidal CO$_2$ (ETCO$_2$) and BIS value were maintained at 35–38 mmHg and 40–60, respectively. If the patient showed > 60 BIS value, the patient received midazolam and was excluded from the data analysis.

After changing to the lateral position, the double-lumen tube position was reconfirmed using a fiberoptic bronchoscope. An arterial and central venous blood sample was obtained in the lateral position with two-lung ventilation after an alveolar recruit maneuver. After arterial blood gas analysis, the difference between PaCO$_2$ and ETCO$_2$ was evaluated. During OLV, TV was not changed. The FiO$_2$ was initially set at 0.5 and adjusted to maintain arterial O$_2$ saturation above 90%. The FiO$_2$ was not changed during the study period. If the patients showed pulse oximetric oxygen saturation (SpO$_2$) lower than 90% in FiO$_2$ 0.5, the FiO$_2$ was increased and the patients were excluded from the data analysis. The ventilatory rate was adjusted to maintain the preset target PaCO$_2$. In all patients, normocarbia and hypercarbia periods were stable for 30 min because HPV reaches a plateau by 20–30 min [15,16].

The primary endpoint of the study was PaO$_2$ in normocarbia and hypercarbia during OLV. The PaO$_2$ was recorded at TLV and at normocarbia and hypercarbia during OLV. At the time of measurement, the following respiratory and hemodynamic variables were recorded: expiratory TV, ventilatory rate, peak inspiratory pressure (P$_{IP}$), plateau pressure (P$_{plat}$), IBP, CVP, CI, SVV, and SVRI. The dynamic ($C_{dyn}$) and static compliances ($C_{stat}$) were calculated using the following equations: $C_{dyn} = TV / P_{IP} - PEEP$ and $C_{stat} = TV / P_{plat} - PEEP$. Arterial blood gas, hemoglobin (Hg) concentration, and lactate concentration were also recorded. Central venous blood gas analysis was performed to measure oxygen partial pressure (PcvO$_2$) and saturation (ScvO$_2$) of central venous blood. Arterial O$_2$ content (CaO$_2$) was calculated by the following equation: CaO$_2 = 1.39 \times$ Hg concentration $\times$ SaO$_2 + 0.0031 \times$ PaO$_2$. Oxygen delivery (DO$_2$) was calculated by the following equation: DO$_2 = CaO_2 \times CO$.

**Statistical analysis**

The sample size was predetermined by paired t-test sample size test using SigmaPlot 13.0 (Systat Software Inc., USA) based on the assumption that a pilot study of ten patients for PaO$_2$ difference between hypercarbia and normocarbia during OLV, which was the primary endpoint, showed an average of 10 mmHg and a standard deviation of 18 mmHg. For PaO$_2$ difference, a value of ≥10 mmHg was considered as clinically significantly different. It was determined that 34 patients were required to obtain a difference in mean PaO$_2$ of 10 mmHg for an expected standard deviation of 20 mmHg with a significance level of 0.05 (α = 0.05) and a power of 80% (β = 0.20). To allow for attrition, the sample size was increased to 50 patients.

The PaO$_2$ measured for OLV-1 and OLV-2 were analyzed via linear mixed-effects (LME) modeling using SPSS 23.0 (IBM Corp., USA). The linear mixed model included the variables id (random effect), presence of hypercarbia (OLV-1 and OLV-2), the sequence of ventilation (OLV-1 first versus OLV-2 first) and interaction between the presence of hypercarbia and the sequence of ventilation. The LME modeling produced a restricted maximum likelihood estimation fit. The LME modeling was used to assess whether there was a differential carryover effect of the first given treatment. Patient and clinical characteristics were analyzed with unpaired t-tests or Chi-square tests. The blood gas analysis, hemodynamic variables, and respiratory variables were compared with unpaired t-tests between Group I and II. Data are presented as the mean ± SD. The α value adjustment with Bonferroni correction was made to compensate for multiple comparisons within primary outcomes. The α value was adjusted to 0.016 instead of 0.05. The P values were compared with this adjusted α value in interpreting primary outcome measures. Otherwise, P values < 0.05 indicated statistical significance.

**Results**

Of the 50 allocated surgical patients, five patients, whose pulmonary artery was ligated before final measurement, and five patients, who showed arterial oxygen saturation less than 90% despite FiO$_2$ 1.0, thus, requiring CPAP to the non-dependent lung, were excluded from the analysis (Fig. 1). During OLV, 40, four, and six patients were maintained with FiO$_2$ 0.5, 0.8, and 1.0, respectively. No patient required transfusion during the operation. The demographic and preoperative clinical characteristics of the patients are shown in Table 1. The differential carryover effect of a preceding ventilation technique over the following ventilation technique and interaction between presence of hypercarbia and the sequence of ventilation were statistically insignificant (P = 0.771 and P = 0.713).

The PaCO$_2$ values during normocarbia and hypercarbia were 38.8 ± 2.6 and 48.2 ± 2.4 mmHg (mean ± SD), respectively. In both groups, PaO$_2$ was significantly decreased to convert from TLV to OLV, but PaO$_2$ was higher during hypercarbia than normocarbia. PaO$_2$ values during normocarbia and hypercarbia were 66.5 ± 10.6 and 79.7 ± 17.3 mmHg, respectively, (mean difference: 13.2 mmHg, 95% CI for difference of means: 17.0 to 9.3, P
Arterial O₂ saturation (SaO₂) values during normocarbica and hypercarbia were 92.5 ± 4.8% and 94.3 ± 3.1% (P = 0.009), respectively. For individual patients, PaO₂ was increased by changing the PaCO₂ from normocarbia to hypercarbia in 37 of 40 patients (93%) (Fig. 2). During normocarbia, pH was 7.42 ± 0.04, but 7.35 ± 0.04 during hypercarbia (P < 0.001).

Although fixed TV was applied, PIP and PPL were significantly lower during hypercarbia than normocarbia in both groups. Based on these results, Cdyn and Cstat were higher during hypercarbia than normocarbia (Table 2). The hemodynamic variables, including IBP, HR, CI, CVP, SVV, and SVRI, as well as the Hg con-
centration and BIS during normocarbia, were comparable to hypercarbia in both groups. However, CaO₂ and DO₂ were significantly higher during hypercarbia than during normocarbia (Table 3). PcvO₂, ScvO₂, and lactate concentration were significantly different between normocarbia and hypercarbia in both groups (Table 4).

**Discussion**

Although OLV provides optimum surgical conditions during thoracic surgery, it is associated with impairment of gas exchange. In addition to arterial hypoxemia, hypercarbia is commonly developed during OLV. Because atelectasis may readily occur in the dependent lung, the application of PEEP is necessary to prevent atelectasis during OLV. Increased lung volume and PEEP elevate airway pressure. Increased airway pressure may impede perfusion of the dependent lung, leading to dead-space ventilation. Increased dead-space ventilation may cause hypoventilation and hypercarbia [17]. Additionally, anesthesiologists are apt to reduce TV to prevent increased PIP during OLV. For these reasons, hypercarbia is common in arterial blood gas analysis during OLV in clinical practice. In the present study, moderate hypercarbia increased PaO₂, SaO₂, CaO₂, DO₂, PcvO₂, ScvO₂, Cdyn, and Cstat but decreased airway pressure and lactate concentration. These results were considered as positive effects on gas exchange during OLV.

The main cause of hypoxemia during OLV is the intrapulmonary shunt through the non-dependent, non-ventilated lung. The alveolar collapse in the non-dependent lung activates HPV, leading to an increase in resistance to flow in the dependent pulmonary artery, thus diverting more perfusion to the ventilated, dependent lung. In the present study, increased PaO₂ reflected as decreased intrapulmonary shunt during hypercarbia. Although the mechanism was not clarified, hypercarbia may increase pulmo-
nary vascular resistance in the non-dependent lung or decrease pulmonary vascular resistance in the dependent, ventilated lung. A pulmonary vasoconstrictor almitrine enhances HPV and prevents OLV-induced decrease in PaO₂ [18,19]. Inhaled nitric oxide has selective pulmonary vasorelaxation in the dependent, ventilated lung during OLV. Therefore, both almitrine and nitric oxide increase arterial oxygenation during OLV. Chuang et al. [11,20] reported that inhaled CO₂ has vasodilatory effects and reverses pulmonary hypertension induced by hypoxia in isolated perfused rat lungs. Previous studies have indicated that CO₂ is a mild vasoconstrictor during basal tone condition but is a potent vasodilator at high pulmonary vascular resistance [14,21–24]. Unfortunately, the present results did not provide a mechanism because pulmonary vascular resistance and pulmonary blood flow were not measured in both lungs.

In the present study, the pH value was decreased by 0.06–0.08 during hypercarbia compared to normocarbia. A low pH shifts the oxyhemoglobin dissociation curve to the right by Bohr effects. As the curve shifts to the right, the SaO₂ for given PaO₂ decreases, i.e., decreased Hg affinity for O₂ [25]. As the pH decreases from 7.40 to 7.35, like the decrease in the present study, Hg releases O₂ more readily to tissues, although oxygen uptake is reduced from the alveoli. Respiratory acidosis can potentiate HPV [26]. Although the increase of PaO₂ was not excluded by the effects of acidosis in our results, hypercarbia provides positive effects to the management of arterial hypoxemia during OLV in conjunction with increased CaO₂ and DO₂. Accordingly, blood lactate concentration was lower during hypercarbia than normocarbia in both groups, although the values were considered within normal ranges.

In the present study, Pp and Pl were significantly lower during hypercarbia than normocarbia in both groups although TV was not changed. Based on these results, Cdyn and Csat were higher during hypercarbia than normocarbia. These results may reflect that increased CO₂ relaxes bronchiolo and lung parenchyma. CO₂-dependent regulation of lung compliance and ventilation-perfusion matching have been explained by pH- and CO₂-dependent changes. Previous studies have reported that CO₂ relaxes lung parenchyma and increases lung compliance [27,28]. These hypercarbia effects provide positive effects on ventilation/perfusion matching and management of arterial hypoxemia during OLV. However, increased lung compliance during hypercarbia may be influenced by the respiratory rate change. The results require further studies to clarify the mechanism.

The key points of lung protective mechanical ventilation strategies of acute respiratory distress syndrome (ARDS) are low TV and increased PEEP. The unintended consequences of the protective ventilation are hypercapnia and hypercapnic acidosis owing to a reduction in minute ventilation and a worsening of ventilation/perfusion mismatch. Previously, acidosis has been permitted as an adverse side effect of protective ventilation. However, several studies have shown the ability of CO₂ to protect against lung injury and repair independently of low TV [29–33]. The concept has been changing from permissive hypercapnia to therapeutic hypercapnia in ARDS. OLV is associated with a high rate of postoperative pulmonary complications, and OLV is currently recognized as a risk factor for acute lung injury [34,35]. Although the pathophysiologic mechanism of acute lung injury after OLV is different for the ventilated and non-ventilated lung, hypercarbia may help prevent and/or repair acute lung injury after OLV.

There are two limitations to the current study. First, the results may be affected by the surgical process. To exclude this effect, patients were divided into two groups in a different order, although the study was designed for crossover comparison. Moreover, the study was discontinued if the pulmonary artery was ligated before the final measurement. Nevertheless, the results could be affected by operation. Therefore, it would be better if the study was performed before the operation. Second, the present results did not provide a mechanism that hypercarbia increased PaO₂ during OLV because the pulmonary vascular resistance and pulmonary blood flow were not measured in both lungs, as mentioned above. Further studies are needed to confirm the mechanism of hypercarbia.

In conclusion, hypercarbia increases PaO₂ and O₂ carrying capacity and improves pulmonary mechanics without significant hemodynamic changes during OLV. Thus, it may help manage oxygenation during OLV. Therefore, permissive hypercarbia may be a simple and valuable modality to manage arterial oxygenation during OLV.

Acknowledgements

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Conflicts of Interest

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

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References


Retrospective analysis of risk factors of hypotensive bradycardic events during shoulder arthroscopic surgery under interscalene blockade in the sitting position

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Background: Hypotensive bradycardic events (HBEs) are a frequent adverse event in patients who underwent shoulder arthroscopic surgery under interscalene block (ISB) in the sitting position. This retrospective study was conducted to investigate the independent risk factors of HBEs in shoulder arthroscopic surgery under ISB in the sitting position.

Methods: A total of 2,549 patients who underwent shoulder arthroscopic surgery under ISB and had complete clinical data were included in the study. The 357 patients who developed HBEs were included in the HBEs group, and the remaining 2,192 in the non-HBEs group. The potential risk factors for HBEs, such as age, sex, past medical history, anesthetic characteristics, and intraoperative medications were collected and compared between the groups. Statistically significant variables were included in a logistic regression model to further evaluate the independent risk factors for HBEs in patients who received shoulder arthroscopic surgery under ISB.

Results: The incidence of HBEs was 14.0% (357/2549). Logistic regression analysis revealed that the intraoperative use of hydralazine (odds ratio [OR] 4.2, 95% CI 2.9–6.3), propofol (OR 2.1, 95% CI 1.3–3.6), and dexmedetomidine (OR 3.9, 95% CI 1.9–7.8) before HBEs were independent risk factors for HBEs in patients who received shoulder arthroscopic surgery under ISB.

Conclusions: The intraoperative use of antihypertensives such as hydralazine and sedatives such as propofol or dexmedetomidine leads to increased risk of HBEs during shoulder arthroscopic surgery under ISB in the sitting position.

Keywords: Brachial plexus block; Bradycardia; Hypotension; Logistic models; Risk factors; Shoulder arthroscopy; Syncope.

Introduction

Hypotensive bradycardic events (HBEs) in patients who underwent shoulder arthroscopic surgery in the sitting position under interscalene block (ISB), while usually not serious, are very challenging complications for anesthesiologists [1,2]. The position of the patient in shoulder arthroscopy largely depends on the choice of the surgeon. The sitting position has benefits, such as easier airway access, easier conversion to open surgery,
less bleeding, a familiar anatomical orientation, and low risk of brachial plexus injury. Despite these benefits, the sitting position can cause adverse cardiovascular events, such as HBEs and cerebrovascular desaturation events, as reported in many articles [2–7]. The incidence rate of HBEs in patients undergoing shoulder arthroscopic surgery ranges from 13% to 21% [1,3,4]. Severe systolic cardiac arrests can be caused by HBEs, and can be life-threatening without immediate correct treatment [5]. Several previous studies have suggested that HBEs may be related to intravenous (IV) drugs administrated intraoperatively [3,6,7]. Although antihypertensives, sedatives, and analgesics such as propofol, dexmedetomidine, and fentanyl may be involved in the development of HBEs, it has not yet been investigated which of these drugs are independent risk factors. In addition to these drugs, HBEs may be associated with the underlying mechanisms responsible for neurally mediated syncope, carotid sinus hypersensitivity, orthostatic hypotension, and other types of syncope [1,8,9]. Thus, HBEs may be associated with the patient’s age, sex, body mass index (BMI), past medical history, and the technical aspects of ISB, but the relationships between patient or anesthesia factors and HBEs in the clinical setting of shoulder arthroscopic surgery have not been studied. In this study, we retrospectively analyzed the records of 2,549 patients who underwent shoulder arthroscopic surgery in the sitting position to explore the independent risk factors of HBEs by logistic regression analysis.

**Materials and Methods**

**Patients**

The Institutional Review Board of Daegu Catholic University Medical Center approved this retrospective study (approval number, CR-16-005-L) and waived the requirement for written informed consent because of the retrospective study design. This study was registered at the Korea Clinical Research Information Service (registration number: KCT0004544). The data of 2,613 patients who underwent shoulder arthroscopic surgery in the sitting position under ISB from October 2002 to March 2018 were retrospectively analyzed. Among them, 64 patients were excluded by the following criteria: conversion from ISB to general anesthesia or intravenous general anesthesia; conversion from ISB to mask general anesthesia; and patients with additional brachial plexus block. Thus, this study analyzed the anesthetic records of 2,549 patients.

**Definition of HBEs**

HBEs were defined [3,6,7] as cases in which the minimum intraoperative systolic blood pressure (SBP) was under 90mmHg and ephedrine was administered to increase blood pressure, or in which the minimum intraoperative heart rate (HR) was under 50 beats/min and atropine was administered to increase HR.

**Potential risk factors of HBEs**

Demographic data, past medical history, preoperative medications, anesthetic characteristics of ISB, vital signs, and intraoperative use of vasoactive drugs and other medications were considered potential risk factors related to HBEs. The potential risk factors of HBEs were statistically analyzed using univariable analysis with the variables described in the following. Demographic data included: American Society of Anesthesiologists (ASA) physical status, operation type, age, sex (male versus female), height, weight, BMI, and preoperative diagnosis. Among the data related to past medical history or preoperative medication, the following were considered: hypertension, diabetes mellitus (DM), heart disease, pulmonary disease, liver disease, brain disease, antihypertensive medication, and diabetic medication. A previous study [4] has reported that the ISB site (right versus left) may be considered a risk factor of HBEs. Data related to ISB anesthesia included: guided device (ultrasound and/or nerve stimulator), ISB site (right or left), operation time, and total amount of local anesthetics (LA). Data about perioperative vital signs or intraoperative use of vasoactive drugs included: baseline SBP, baseline diastolic blood pressure (DBP), baseline HR, maximum and minimum SBP and DBP, maximum and minimum HR, use of ephedrine and atropine, and amount of IV fluid. Regarding intraoperative medications, the following were considered: hydralazine, diltiazem, nicardipine, fentanyl, propofol, midazolam, and dexmedetomidine.

**Statistical analysis**

For the univariate analysis, categorical data were analyzed using Chi-square tests, and continuous data were analyzed using an independent sample t-test.

For the multivariate analysis, the potential risk factors with \( P < 0.05 \) in univariate analysis were considered as independent variables in a binary logistic regression model to identify the independent risk factors, with HBEs as the dependent variable (\( Y: 1 = \text{Yes}, 0 = \text{No} \)). To solve the problem of multicollinearity, variable selection was performed with the forward conditional method. After variable selection, the analysis was performed adjusting for...
statistically significant covariates. P values < 0.05 were considered statistically significant. Odd ratios (ORs) and their 95% confidence intervals (CIs) were calculated. Data were analyzed using SPSS version 19.0 (SPSS Inc., USA).

Our standard ISB technique for shoulder arthroscopic surgery

The patient's neck was sterilized using iodine solution and sterile drapes were applied, then the patient's head was rotated contralaterally and the interscalene groove was identified. Local anesthesia infiltration was given with 1 ml lidocaine 2% in the needle insertion site. If using nerve stimulation, a 50-mm 22-gauge insulated needle (Stimuplex® insulated, B. Braun Medical, Germany) was introduced from lateral to medial parallel to the interscalene groove. A 2-Hz, 1-mA stimulus nerve stimulator (Stimuplex, HNS12, B. Braun Medical, Germany) was connected to the needle and the needle was inserted with 1 mA stimulus until muscle trigger was noted in the elbow and in the first and second fingers. The stimulus was then decreased to 0.3 mA, and while muscle trigger was still present 30–40 ml of a mixture of lidocaine 1% or mepivacaine 1% and ropivacaine 0.75%, or 25–30 ml of ropivacaine alone, were injected in divided doses with frequent aspiration. If using ultrasound, after disinfecting the skin and positioning the transducer (Alpha 7, Hitachi Aloka, Japan), a 50-mm 22-gauge insulated needle (Stimuplex® insulated, B. Braun Medical, Germany) was introduced from lateral to medial parallel to the interscalene groove in an in-plane technique, such that the entire needle was visualized. A total of 15–30 ml of the same type of LA was injected in divided doses with frequent aspiration and the LA spread was visualized with the ultrasound.

Intraoperative patient management

All shoulder arthroscopies were performed by the same surgeon, and three anesthesiologists were involved. The noninvasive blood pressure cuff was placed during surgery on the arm on the non-operative site. If needed, invasive arterial monitoring by catheter was performed on the radial artery of the non-operative site. If needed, invasive arterial monitoring by catheter was performed on the radial artery of the non-operative site. If needed, invasive arterial monitoring by catheter was performed on the radial artery of the non-operative site.

When sufficient ISB anesthesia was achieved, the surgeon started the operation. In case of pain when placing the port in the back of the shoulder, the surgeon performed local infiltration using 10 ml of 1% mepivacaine. In case of impaired visualization of the surgical field due to bleeding or if the patient's SBP increased above 170 mmHg during surgery, hydralazine (10 mg), nicardipine (0.25–5 mg) or diltiazem (5–10 mg) were administered intravenously, and induced hypotension was not used. Vasopressors, inotropes, or chronotropics (ephedrine, epinephrine, or atropine) were used at the discretion of the attending anesthesiologist in cases of HBEs. Routine sedation was not performed. In case of incomplete ISB blocks with the patient manifesting discomfort or strongly requesting sedation, a small dose of IV fentanyl (50 µg) or midazolam (1–3 mg) was administrated. Some patients received an IV bolus of propofol (20–30 mg) or propofol infusion (0.3–0.6 mg/kg/h) because of pain or discomfort not controlled by fentanyl and midazolam. Some patients received continuous IV infusion of dexmedetomidine (maintenance dose of 0.2–0.5 µg/kg/h) without loading infusion.

Results

The incidence of HBEs was 14.0% (357/2549). HBE incidence during shoulder arthroscopic surgery under ISB was examined using univariable analysis. The results revealed that demographic data, such as ASA physical status, age, sex, height, weight, and BMI were related to HBE incidence (P < 0.05, Table 1). However, preoperative diagnosis and the site of operation (right versus left) were not significantly correlated with the occurrence of HBEs (P > 0.05). The univariable analysis of the relationships between past medical history and preoperative medications and HBEs revealed that a history of hypertension and antihypertensive medication were risk factors for HBEs (P < 0.05, Table 2). However, history of DM, liver disease, heart disease, pulmonary disease, brain disease, and DM medication were not risk factors (P > 0.05). Regarding the anesthetic characteristics of ISB, univariable analysis revealed that a guided ISB device (sonography versus nerve stimulator), operation time, and total amount of LA (ropivacaine, mepivacaine, and lidocaine) were not related with HBEs (P > 0.05, Table 3). Table 4 shows the analysis of perioperative vital signs and intraoperative use of vasoactive drugs as risk factors for HBEs. Univariable analysis of the relationships between baseline vital signs and HBEs revealed that baseline SBP and DBP were significantly associated to HBEs (P < 0.05), while among intraoperative medications, the intraoperative use of IV hydralazine, propofol, midazolam and dexmedetomidine were significantly correlated with the occurrence of HBEs (P < 0.05, Table 5). However, the intraoperative use of nicardipine was not a risk factor for HBEs: Indeed the use of nicardipine in the HBEs group was significantly lower (P < 0.05, Table 5) than in the non-HBEs group. Furthermore, the intraoperative use of fentanyl was not significantly correlated with the occurrence of HBEs (P > 0.05).

The variables described above were examined through logistic regression analysis with the forward conditional method for variable selection, and the results indicated that the intraoperative use
Table 1. Univariate Analysis of the Relationship between Demographic Data and HBEs

<table>
<thead>
<tr>
<th></th>
<th>HBEs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 357)</td>
</tr>
<tr>
<td>ASA physical status</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>211 (59.1)</td>
</tr>
<tr>
<td>II</td>
<td>144 (40.3)</td>
</tr>
<tr>
<td>III</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Operation type</td>
<td></td>
</tr>
<tr>
<td>Elective</td>
<td>347 (97.2)</td>
</tr>
<tr>
<td>Emergency</td>
<td>10 (2.8)</td>
</tr>
<tr>
<td>Age</td>
<td>55.1 ± 15.1</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>186 (52.1)</td>
</tr>
<tr>
<td>F</td>
<td>171 (47.9)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>163.4 ± 9.0</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>62.2 ± 11.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.2 ± 3.1</td>
</tr>
<tr>
<td>Preoperative diagnosis</td>
<td></td>
</tr>
<tr>
<td>Rotator cuff tear</td>
<td>264 (74.4)</td>
</tr>
<tr>
<td>Shoulder instability</td>
<td>36 (10.1)</td>
</tr>
<tr>
<td>Calcified tendinitis</td>
<td>11 (3.1)</td>
</tr>
<tr>
<td>Impingement syndrome</td>
<td>8 (2.3)</td>
</tr>
<tr>
<td>SLAP or labral tear</td>
<td>10 (2.8)</td>
</tr>
<tr>
<td>Frozen shoulder</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Pyogenic arthritis</td>
<td>26 (7.3)</td>
</tr>
<tr>
<td>Site of operation</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>257 (72.0)</td>
</tr>
<tr>
<td>Left</td>
<td>100 (28.0)</td>
</tr>
</tbody>
</table>

Values are presented as frequency (%) or mean ± SD. HBEs: hypotensive bradycardic events, ASA: American Society of Anesthesiologists, BMI: body mass index, SLAP: superior labrum anterior to posterior. *Statistically significant with P < 0.05.

Table 2. Univariate Analysis of the Relationship between Past Medical History or Preoperative Medications and HBEs

<table>
<thead>
<tr>
<th></th>
<th>HBEs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 357)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>104 (29.1)</td>
</tr>
<tr>
<td>DM</td>
<td>36 (10.1)</td>
</tr>
<tr>
<td>Liver disease</td>
<td>9 (2.5)</td>
</tr>
<tr>
<td>Heart disease</td>
<td>14 (3.9)</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>6 (1.7)</td>
</tr>
<tr>
<td>Brain disease</td>
<td>8 (2.2)</td>
</tr>
<tr>
<td>Hypertension medications</td>
<td>94 (26.3)</td>
</tr>
<tr>
<td>DM medications</td>
<td>34 (9.5)</td>
</tr>
</tbody>
</table>

Values are presented as frequency (%). HBEs: hypotensive bradycardic events, DM: diabetes mellitus. *Statistically significant with P < 0.05.

of IV hydralazine, propofol, and dexmedetomidine were independent risk factors for developing HBEs during shoulder arthroscopic surgery under ISB (P < 0.05, Table 6). The results of the logistic regression analysis adjusted by age, sex, BMI, preoperative medical history, perioperative medication, and vital signs are shown in Table 7. The intraoperative use of hydralazine (OR 4.2, 95% CI 2.9–6.3), propofol (OR 2.1, 95% CI 1.3–3.6), and dexmedetomidine (OR 3.9, 95% CI 1.9–7.8) were identified as independent risk factors for the occurrence of HBEs during shoulder arthroscopic surgery (Table 7).
Table 3. Univariate Analysis of the Relationship between Anesthetic Characteristics of ISB and HBEs

<table>
<thead>
<tr>
<th></th>
<th>HBEs</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 357)</td>
<td>No (n = 2,192)</td>
</tr>
<tr>
<td>Guided device</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sonography</td>
<td>239 (67.0)</td>
<td>1385 (63.2)</td>
</tr>
<tr>
<td>Nerve stimulator</td>
<td>118 (33.1)</td>
<td>807 (36.8)</td>
</tr>
<tr>
<td>Operation time (min)</td>
<td>94.1 ± 35.9</td>
<td>92.3 ± 42.0</td>
</tr>
<tr>
<td>Total amount of LA (ml)</td>
<td>30.9 ± 8.7</td>
<td>31.4 ± 8.4</td>
</tr>
<tr>
<td>Ropivacaine (ml)</td>
<td>16.4 ± 4.8</td>
<td>16.5 ± 4.5</td>
</tr>
<tr>
<td>Mepivacaine (ml)</td>
<td>15.1 ± 5.1</td>
<td>15.6 ± 4.9</td>
</tr>
<tr>
<td>Lidocaine (ml)</td>
<td>7.8 ± 5.3</td>
<td>7.2 ± 6.4</td>
</tr>
</tbody>
</table>

Values are presented as frequency (%) or mean ± SD. ISB: interscalene block, HBEs: hypotensive bradycardic events, LA: local anesthetic.

Table 4. Perioperative Vital Sign and Intraoperative Use of Vasoactive Drugs

<table>
<thead>
<tr>
<th></th>
<th>HBEs</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 357)</td>
<td>No (n = 2,192)</td>
</tr>
<tr>
<td>Baseline SBP (mmHg)</td>
<td>139.3 ± 23.1</td>
<td>142.7 ± 21.2</td>
</tr>
<tr>
<td>Baseline DBP (mmHg)</td>
<td>78.2 ± 12.3</td>
<td>80.7 ± 12</td>
</tr>
<tr>
<td>Baseline HR (mmHg)</td>
<td>72.7 ± 13.7</td>
<td>72.7 ± 13.5</td>
</tr>
<tr>
<td>Maximum SBP (mmHg)</td>
<td>156.5 ± 24.1</td>
<td>160.4 ± 21.2</td>
</tr>
<tr>
<td>Minimum SBP (mmHg)</td>
<td>83.6 ± 11.2</td>
<td>125.2 ± 26.3</td>
</tr>
<tr>
<td>Maximum HR (mmHg)</td>
<td>86.5 ± 15.3</td>
<td>83.3 ± 16</td>
</tr>
<tr>
<td>Minimum HR (mmHg)</td>
<td>58.9 ± 12.6</td>
<td>68.5 ± 106.7</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>294 (82.4)</td>
<td>178 (8.1)</td>
</tr>
<tr>
<td>Atropine</td>
<td>57 (16.0)</td>
<td>70 (3.2)</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or frequency (%). HBEs: hypotensive bradycardic events, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate. *Statistically significant with P < 0.05.

Table 5. Univariate Analysis of the Relationship between Intraoperative Medications and HBEs

<table>
<thead>
<tr>
<th></th>
<th>HBEs</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes (n = 357)</td>
<td>No (n = 2,192)</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>49 (13.7)</td>
<td>91 (4.2)</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>5 (1.4)</td>
<td>34 (1.55)</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>37 (10.4)</td>
<td>370 (16.9)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>114 (31.9)</td>
<td>651 (29.7)</td>
</tr>
<tr>
<td>Propofol</td>
<td>20 (5.6)</td>
<td>68 (3.1)</td>
</tr>
<tr>
<td>Midazolam</td>
<td>64 (17.9)</td>
<td>303 (13.8)</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>14 (3.9)</td>
<td>23 (1.1)</td>
</tr>
</tbody>
</table>

Values are presented as frequency (%). HBEs: hypotensive bradycardic events. *Statistically significant with P < 0.05.

Table 6. Binary Logistic Regression Analysis of HBEs during Shoulder Surgery with Forward Conditional Method as Variable Selection

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine</td>
<td>3.9</td>
<td>2.7, 5.7</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Propofol</td>
<td>1.9</td>
<td>1.1, 3.2</td>
<td>0.018*</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>4.0</td>
<td>2.0, 7.8</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

HBEs: hypotensive bradycardic events, OR: odds ratio. *Statistically significant with P < 0.05.

Discussion

Shoulder arthroscopic surgery is commonly performed in the sitting position under ISB, and the anesthesiologist should focus on monitoring the patient vital signs, so as to allow early detection and treatment of HBEs occurring during surgery. We retrospectively analyzed the data of 2,549 patients who underwent shoulder surgery.
Table 7. Binary Logistic Regression Analysis of HBEs during Shoulder Surgery Adjusted by Age, Sex, BMI, Preoperative Medical History, Perioperative Medications, and Vital Signs

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydralazine</td>
<td>4.2</td>
<td>2.9, 6.3</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Propofol</td>
<td>2.1</td>
<td>1.3, 3.6</td>
<td>0.006*</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>3.9</td>
<td>1.9, 7.8</td>
<td>&lt; 0.001*</td>
</tr>
</tbody>
</table>

HBEs: hypotensive bradicardic events, BMI: body mass index, OR: odds ratio. *Statistically significant with P < 0.05.

arthroscopic surgery under ISB, and found that the incidence rate of HBEs was 14.0%. In addition, our results indicated that the use of hydralazine, propofol, and dexmedetomidine before HBE occurrence were independent risk factors for developing HBEs.

The use of intraoperative antihypertensives during shoulder arthroscopic surgery can be increased by the operator's demand for blood pressure control, because high blood pressure can increase bleeding and blur the operation field. For the anesthesiologist, it is very challenging to use IV antihypertensive drugs in conscious sitting patients under ISB. Our results show that vasodilators such as hydralazine were strong risk factors for HBEs, but calcium channel blockers (CCBs) such as nicardipine and diltiazem were not. Especially the use of nicardipine in the HBEs group was significantly lower than in the non-HBEs group in our results. Therefore, the intraoperative use of nicardipine was not a risk factor for HBEs despite of statistical significance. In a previous study [6], another antihypertensive drug, namely urapidil, was identified as a risk factor for HBEs in shoulder arthroscopic surgery. Urapidil [10], which is currently not approved by the U.S. Food and Drug Administration, acts as an α1-adrenoceptor antagonist and as a 5-HT1A receptor agonist. These findings suggest that the anesthesiologist should pay attention to the selection of antihypertensive agents during shoulder arthroscopic surgery under ISB.

Hydralazine is known to act directly on the vascular smooth muscle causing strong vasorelaxation and primary artery relaxation [11]. However, the action time of hydralazine is unpredictable, compared with other intravenous antihypertensives used for the treatment of malignant hypertension, and can be as long as 8 h in some cases [12]. The cause of such longer action time of hydralazine is not well known, but animal experiments confirmed that the active metabolite of hydralazine adheres to tissues in the vascular wall for a certain period of time, and that the hydralazine metabolites deposited on the vascular endothelial cells can continuously produce endothelial-dependent nitric oxide (NO) [12]. In contrast, CCBs block the L-type voltage-dependent calcium channels of the vascular smooth muscle, inhibiting calcium influx, thereby relaxing the vascular smooth muscle. The production of NO in vascular endothelial cells is usually caused by calcium-dependent nitric oxide synthase, and CCBs do not directly affect NO production [13]. Considering these aspects, when the need arises to use IV anti-hypertensive drugs during shoulder arthroscopy under ISB, it is safer to choose CCBs rather than hydralazine that alters NO production and has long-lasting effects.

A previous study [7] reported that a large single IV bolus dose of fentanyl (100 μg) was associated with the development of HBEs. However, the use of fentanyl in this study was not a risk factor for HBEs, possibly because we use fentanyl in a single bolus dose generally smaller than 50 μg. On the contrary, propofol was identified in this study as an independent risk factor for HBEs. However, Souron et al. [14] performed target-controlled propofol infusion (0.8–0.9 μg/ml) in 140 patients during shoulder arthroscopic surgery under ISB and found that the propofol infusion group had a low incidence of HBEs (5.7%). This discrepancy may be caused by the different purpose and protocol of propofol administration compared with this study. In our center, we do not routinely use patient sedation during shoulder arthroscopic surgery, and propofol is not used for patient sedation itself. In cases of insufficient block or strong patient’s demand, if analgesics or sedatives such as fentanyl or midazolam are not effective, an IV bolus injection and/or IV infusion of propofol are used. Therefore, the effect of propofol in this study should be interpreted as a combination effect of propofol with fentanyl and midazolam. Although dexmedetomidine was used for sedation in a small number of patients, we found it to be an independent risk factor for HBEs. Since the stability of dexmedetomidine during shoulder surgery in the sitting position has not yet been established, the use of IV dexmedetomidine requires caution, and further studies are needed.

Various syncopal reactions, including HBEs, may be triggered by similar mechanisms and use the same efferent limb of the reflex [1,8]. HBEs often occur in response to an orthostatic stimulus (prolonged sitting position), other non-orthostatic stimuli (fear, emotional stress, pain), and a variety of activities (coughing, swallowing, and pressure on the carotid sinus) [15]. These stimuli cause a sudden transient failure of the autonomic nervous system, resulting in hypotension and bradycardia. This study revealed that lower baseline SBP and DBP (Table 4) were associated with the development of HBEs. We also found that older age, lower BMI, and the female sex were associated with the development of HBEs in univariable analysis. Sex differences in patients with HBEs in this study may be closely related with female predominance in neurally mediated syncope [9,16]. Women are more susceptible to orthostatic intolerance in warm environments. Recently, Meendering et al. [17] evaluated the influence of menstrual cycle and
sex on the hemodynamic responses to combined orthostatic and heat stress, and found that men had greater orthostatic tolerance than women during combined upright tilting and passive heating. Neurally mediated syncope is more common in younger people [9], but in this study, HBEs tended to occur more frequently in older people. In addition, this study showed that higher ASA physical status (Table 1) and a history of hypertension (Table 2) were risk factors for HBEs. Although syncope in the elderly is usually multifactorial, and often associated with orthostatic hypotension and carotid hypersensitivity [18–20], further research is needed to clarify the association between HBEs and these factors.

Recent studies have reported the effects of ISB on sympathetic activity, possibly by the extension of ISB to the stellate ganglions [21,22], and some studies have reported the possibility of a difference between the left and right sides [4,21]. A previous retrospective study [4] has reported that the ISB site (right versus left) may be considered a risk factor of HBEs, but this result may be underpowered owing to the small sample size.

However, our results did not identify the ISB site as a risk factor of HBEs (Table 1), and we consider them to be more reliable, because our study had a much larger sample size than the previous one. Additionally, we also examined the association between the total amount of local anesthetics and HBEs, without finding a significant result. Our results may suggest that HBEs cannot be separated from various other types of syncopal reaction. However, preoperative ISB was reported as one of the risk factors associated with HBEs in a recent study of open shoulder surgery [23]. Further studies are thus needed before a definite conclusion can be drawn about the impact of the ISB on HBEs.

The definition of HBEs may differ somewhat from that of neurally mediated syncope that is defined using the tilting test [9,24]. The definition of HBEs used in this study was based on the general guidelines for the administration of ephedrine or atropine upon changes in patient blood pressure or heart rate during shoulder arthroplasty. This specific definition might explain the high prevalence of HBEs assessed in this study. In addition, as a retrospective analysis of data from a single research center, this study inevitably has some limitations. One of the potential limitations is the long study period, chosen so as to include all cases operated in our institution without selection; in particular, regarding nerve stimulator-guided ISB, the period included in the study was 16 years long. Owing to such a long period, there were some changes in anesthesia and surgical procedures that could affect the results of the study. However, as previously described, only one surgeon and three anesthesiologists were involved in the surgeries in this study, and we tried to standardize the anesthesia process, so that the changes occurred during the study period might not present a major concern. Unfortunately, a large part of the data was taken before our institution adopted an electronic medical record system; thus, a significant portion of data about the amount and type of perioperative drugs was missing. This made it difficult to analyze the role of the amount and type of perioperative drugs. However, all patients were analyzed simultaneously, without selectivity. Therefore, our results are more reliable than those of other retrospective studies, thanks also to the comparatively large sample size and the controlled ISB procedure.

In conclusion, our findings indicate that the use of hydralazine, propofol, and dexmedetomidine before HBEs increases the susceptibility to HBEs during shoulder arthroscopic surgery in the sitting position under ISB.

**Conflicts of Interest**

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

**Author Contributions**

Taeha Ryu (Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft; Writing – review & editing)

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Seong Jun Woo (Data curation; Methodology; Resources; Visualization)

So Young Lee (Data curation; Resources; Software; Visualization; Writing – review & editing)

Jung A Lim (Resources; Software; Validation; Visualization; Writing – review & editing)

Sang Gyu Kwak (Data curation; Formal analysis; Methodology; Software; Validation; Visualization)

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References

Abdominal wall blocks rely on the spread of the local anesthetic within the musculo-fascial planes to anesthetize multiple small nerves or plexuses, rather than targeting specific nerve structures [1,2]. A novel approach for chest wall and upper abdominal analgesia, termed the rhomboid intercostal and subserratus plane (RISS) block, initially showed promising results [3]. It was reported for different abdominal surgeries, rib fractures, and chest tube-associated pain [3]. The clinical evaluation of the RISS block demonstrated consistent analgesia from the T5 to T8 dermatome [3]. In a cadaveric study, the injectate was observed spreading between the intercostal muscles and then deep into the rhomboids and serratus anterior muscles, and staining the lateral cutaneous branches of the intercostal nerves from T4 to T9 [2]. This emphasizes the role of chest wall blocks as an analgesic modality for the abdominal wall as it is innervated by intercostal nerves [4]. In this paper, we describe a retrospective case series of patients who received bilateral RISS blocks (either through single-shot injections or through catheter infusion) for analgesia after an abdominal surgery.

**Background:** The rhomboid intercostal and subserratus plane (RISS) block is a new interfascial block technique that has shown promising results for abdominal and thoracic surgeries. Our objective was to describe the improved analgesia and dermatomal coverage in patients who received bilateral RISS blocks after a major abdominal surgery.

**Case:** Twenty-one patients who underwent abdominal surgery received the rhomboid intercostal component of the block at the T5 to T6 levels, and the subserratus component block was performed at the T6 to T9 levels. The RISS blocks provided effective postoperative analgesia. There was a variation in the dermatomal coverage ranging from T3 to T12. Patients reported a high satisfaction rate from pain management.

**Conclusions:** The RISS block in abdominal surgery seems to have an important role in perioperative pain management, complementing the multimodal analgesic regimen. To determine the efficacy of the RISS block for abdominal surgery, we need further randomized control trials.

**Keywords:** Fascial plane block; Interventional ultrasonography; Pain; Pain management; Postoperative pain; Regional anesthesia.

Abdominal wall blocks rely on the spread of the local anesthetic within the musculofascial planes to anesthetize multiple small nerves or plexuses, rather than targeting specific nerve structures [1,2]. A novel approach for chest wall and upper abdominal analgesia, termed the rhomboid intercostal and subserratus plane (RISS) block, initially showed promising results [3]. It was reported for different abdominal surgeries, rib fractures, and chest tube-associated pain [3]. The clinical evaluation of the RISS block demonstrated consistent analgesia from the T5 to T8 dermatome [3]. In a cadaveric study, the injectate was observed spreading between the intercostal muscles and then deep into the rhomboids and serratus anterior muscles, and staining the lateral cutaneous branches of the intercostal nerves from T4 to T9 [2]. This emphasizes the role of chest wall blocks as an analgesic modality for the abdominal wall as it is innervated by intercostal nerves [4]. In this paper, we describe a retrospective case series of patients who received bilateral RISS blocks (either through single-shot injections or through catheter infusion) for analgesia after an abdominal surgery.

**Case Report**

The Cleveland Clinic Institutional Review Board approved the study (IRB #18-168) and waived the requirement for informed consent. All cases were conducted at the Cleveland Clinic.
land Clinic Main Campus during the period between April 2018 and January 2019. The reporting of this study adhered to the Preferred Reporting of Case Series in Surgery Guidelines [5]. The procedure was conducted on adult patients undergoing an elective major abdominal surgery.

The blocks were performed either preoperatively or postoperatively by one of the investigators (i.e., H.E.). Patients were positioned in the lateral decubitus position and were monitored according to the standard American Society of Anesthesiologists monitoring. The rhomboid intercostal injection was performed using a linear probe ultrasound transducer (6–12 MHz, X-Porte, SonoSite, USA). The transducer was placed in the sagittal plane medial to the medial border of the scapula and then rotated to produce an oblique sagittal view (paramedian sagittal oblique) approximately 1 to 2 cm medial to the medial scapular border. The tissue plane between the rhomboid major and the intercostal muscles was identified. A 17 gauge (G) Tuohy needle was advanced in plane from a superomedial to an inferolateral direction through the trapezius and rhomboid major muscles (Figs. 1 and 2). Five to 10 ml of the local anesthetic (0.5% ropivacaine or bupivacaine) was administered to the patients receiving a single-injection block on each side, or 5 to 10 ml of 0.2% ropivacaine to the patients receiving a catheter infusion. The rhomboid intercostal component of the block was performed as a single-shot injection at the T5 to T6 levels. The ultrasound probe was then moved caudally and laterally to identify the tissue plane between the serratus anterior and the external intercostal muscle for the subserratus block at the T6 to T9 levels (depending on the desired dermatomal coverage for the lower part of the incision) (Figs. 3 and 4). The needle was inserted into the same skin entry site as that used for the rhomboid intercostal injection but directed caudally and laterally beyond the inferior angle of the scapula. Fifteen to 20 ml of the local anesthetic was administered (0.5% ropivacaine or bupivacaine for the patients receiving single-shot blocks or 0.2% ropivacaine for the patients receiving a catheter infusion). The target landmark was the plane located superficial to the intercostal muscles. In subjects undergoing a continuous infusion, a 19 G, 40-cm catheter (Arrow®, Teleflex, USA) was then introduced into the subserratus plane and advanced 3 to 5 cm beyond the needle tip. The catheter tip position was confirmed with an injection of 5 ml of 0.2% ropivacaine under direct ultrasound visualization. The catheters were secured with sterile adhesive dressing. The patient was then repositioned, and the procedure was repeated on the opposite side. During the application of each block, the total local anesthetic dose used per patient was adjusted for the body weight (maximum dose of 3 mg/kg for ropivacaine and 2 mg/kg for bupivacaine).

For the catheter infusions, each catheter was connected to a patient-controlled infusion pump (Curlin PainSmart™ IOD infusion pump, Curlin Medical, Inc., USA) containing 0.2% ropivacaine at a basal rate of 6 ml/h which was started within 1 h after the operation, with an additional on-demand bolus of 6 ml every 60 min.
as needed. Moreover, as per clinical routine, all patients were provided with hydromorphone via an intravenous patient-controlled analgesia (PCA) pump. This PCA pump was started within 1 h from arrival to the post-anesthesia care unit. Pain-at-rest scores using the visual analog scale (VAS) were collected as per clinical routine, with a minimum frequency of once every 4 h. The mean and range of the VAS were reported as a time-weighted average over 24 h for the single-shot blocks and over the local anesthetic infusion duration for the catheter infusion. Outcome data were obtained from the electronic medical records including the overall opioid consumption over 24 h for the single-shot blocks and the RISS catheter infusion. The first evaluation of the patients’ dermatomal coverage was 15 min after the block application on the day of surgery. The extent of the sensory dermatomal block was determined by a diminished cold sensitivity to ice on the side of the trunk compared with that on the ipsilateral arm; it was assessed daily around 9 a.m. by the acute pain team. Additional data regarding the duration of analgesia and possible side effects from

Fig. 2. (A) The corresponding ultrasound image. (B) Schematic illustration showing the surrounding structures and needle position for performing the rhomboid intercostal injection at the T5 and T6 levels. IM: intercostal muscles, LA: local anesthetic, RM: rhomboid major muscle, Trap: trapezius muscle.

Fig. 3. (A) Ultrasound transducer position for performing the subserratus plane injection at the T7 and T8 levels. (B) Schematic illustration of an axial section at the T7 to T8 levels showing the surrounding muscle layers and local anesthetic spread. LD: latissimus dorsi muscle, RM: rhomboid major muscle, SA: serratus anterior muscle, Trap: trapezius muscle, ES: erector spinae muscle.
the procedure including bleeding, hematoma, hypotension, internal organ injury, catheter site infection, and local anesthetic toxicity were recorded. Data on patients’ satisfaction were obtained from the results of the pain control questionnaire with yes/no answers in the daily report of the acute pain team.

The intervention was administered to 21 opioid-naïve patients (16 males and 5 females; mean age: 59 years [range: 33 to 87 years]). Two patients who were expected to be discharged soon and who underwent less extensive surgery received single-shot blocks, and 19 patients received continuous catheter infusion. Indications were major abdominal surgeries, including exploratory laparotomy and bowel resection (7 patients), pancreateoduodenectomy (5 patients), hepatectomy (6 patients), gastric bypass (1 patient), ureteral reimplantation (1 patient), and radical nephrectomy (1 patient). A variation in the dermatomal sensory block with a range of coverage from T3 to T12 was achieved. The dermatomal coverage from T7 to T8 was consistent in all the cases (Table 1). However, we could not evaluate the midline dermatomal coverage owing to the dressing of the midline incision. Data for the mean and range of time-weighted average pain scores, opioid consumption, and duration of the catheter infusion are listed in Table 1. Most of the patients were satisfied except for 3 patients. There were no reported block-related adverse events or local anesthetic toxicity.

Discussion

In this paper, we report a retrospective case series of adult patients having a major abdominal surgery provided with bilateral RISS blocks for postoperative analgesia. The intervention was found to obtain a reproducible dermatomal sensory analgesic coverage from T7 to T8 bilaterally in all the 21 cases, irrespective of the level of needle application, which could be anywhere from approximately T5 to T6 for the rhomboid intercostal block and from T6 to T9 for the subserrate block. Moreover, we recorded a variation in the dermatomal coverage, which ranged from T3 to T12. The procedure was well tolerated by the patients, most of whom reported a high satisfaction rate from the pain management except for three patients. Because our case series consisted of a heterogeneous group of patients who underwent different types of abdominal surgery, it may serve as a pioneering example for other randomized clinical trials.

Since the original publication of the RISS block [6], several studies on patients undergoing different operations such as lung transplantation [7], back surgery [8], thoracotomy [9], transcatheter aortic valve implantation [10], breast reconstruction surgery [11], and modified radical mastectomy [12] with axillary curettage have shown that the RISS block may generate analgesia from the T2 to T9 dermatomes.

A previous cadaveric study provided an evidence that the tissue plane deep into the erector spinae muscle, rhomboid muscles, serratus anterior muscles, latissimus dorsi, and upper part of the external oblique muscle is continuous [3]. In the RISS block, the injectate is directed toward the tissue plane located between the rhomboid and the intercostal muscles, and then deep into the scapula and the serratus anterior muscle, which targets the lateral

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Elsharkawy et al. · Rhomboid intercostal–subserratus block

Table 1. Patient Demographics and Outcomes

<table>
<thead>
<tr>
<th>Patient age (yr)/sex</th>
<th>Operation</th>
<th>Range of dermatomal coverage</th>
<th>Pain scores mean (range)</th>
<th>Morphine equivalent opioid usage (mg)</th>
<th>Patients’ satisfaction</th>
<th>Duration of catheter infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) 33/F</td>
<td>Gastric bypass</td>
<td>Right: T4–T10</td>
<td>4.7 (3.9–5.8)</td>
<td>49</td>
<td>Satisfied</td>
<td>6 days</td>
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<tr>
<td></td>
<td></td>
<td>Left: T3–T11</td>
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<tr>
<td>2) 59/F</td>
<td>Exploratory laparotomy and bowel resection</td>
<td>Right: T7–T11</td>
<td>3.6 (2.8–4.8)</td>
<td>97.5</td>
<td>Satisfied</td>
<td>4 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left: T7–T11</td>
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</tr>
<tr>
<td>3) 73/M</td>
<td>Pancreaticoduodenectomy</td>
<td>Right: T7–T12</td>
<td>5.4 (3.8–7.1)</td>
<td>215.8</td>
<td>Not satisfied</td>
<td>6 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left: T7–T12</td>
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<tr>
<td>4) 31/M</td>
<td>Exploratory laparotomy and bowel resection</td>
<td>Right: T6–T12</td>
<td>3 (2–4.2)</td>
<td>88</td>
<td>satisfied</td>
<td>2 days</td>
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<tr>
<td></td>
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<td>Left: T6–T12</td>
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<tr>
<td>5) 80/M</td>
<td>Pancreaticoduodenectomy</td>
<td>Right: T5–T10</td>
<td>3.8 (1.5–6)</td>
<td>50</td>
<td>Satisfied</td>
<td>4 days</td>
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<td>Left: T5–T10</td>
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<tr>
<td>6) 65/M</td>
<td>Pancreaticoduodenectomy</td>
<td>Right: T6–T9</td>
<td>5.3 (2.5–6)</td>
<td>5.3</td>
<td>Not satisfied</td>
<td>Single shot</td>
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<tr>
<td></td>
<td></td>
<td>Left: T6–T9</td>
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<tr>
<td>7) 63/M</td>
<td>Pancreaticoduodenectomy</td>
<td>Right: T6–T10</td>
<td>2.5 (1–3)</td>
<td>189</td>
<td>Satisfied</td>
<td>4 days</td>
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<tr>
<td></td>
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<td>Left: T6–T10</td>
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<tr>
<td>8) 47/M</td>
<td>Pancreaticoduodenectomy</td>
<td>Right: T7–T10</td>
<td>5 (2–8)</td>
<td>280</td>
<td>Satisfied</td>
<td>4 days</td>
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<td>Left: T7–T10</td>
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<tr>
<td>9) 72/M</td>
<td>Exploratory laparotomy and bowel resection</td>
<td>Right: T7–T12</td>
<td>2.5 (1–3)</td>
<td>189</td>
<td>Satisfied</td>
<td>3 days</td>
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<tr>
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<td>Left: T7–T12</td>
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<tr>
<td>10) 51/M</td>
<td>Exploratory laparotomy and bowel resection</td>
<td>Right: T6–T8</td>
<td>2.8 (2.5–3)</td>
<td>0</td>
<td>Satisfied</td>
<td>2 days</td>
</tr>
<tr>
<td></td>
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<td>Left: T6–T8</td>
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<tr>
<td>11) 83/F</td>
<td>Hepatectomy</td>
<td>Right: T7–T10</td>
<td>5 (1–7)</td>
<td>4</td>
<td>Satisfied</td>
<td>Single shot</td>
</tr>
<tr>
<td></td>
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<td>Left: T6–T8</td>
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<tr>
<td>12) 28/M</td>
<td>Exploratory laparotomy and bowel resection</td>
<td>Right: T5–T8</td>
<td>6.4 (3.5–9)</td>
<td>88.1</td>
<td>Satisfied</td>
<td>4 days</td>
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<td>Left: T5–T9</td>
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<tr>
<td>13) 40/F</td>
<td>Hepatectomy</td>
<td>Right: T6–T12</td>
<td>4 (2–6)</td>
<td>108.6</td>
<td>Satisfied</td>
<td>3 days</td>
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<td>Left: T5–T11</td>
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<tr>
<td>14) 64/M</td>
<td>Exploratory laparotomy and bowel resection</td>
<td>Right: T5–T9</td>
<td>6.5 (6.1–6.9)</td>
<td>36.7</td>
<td>Satisfied</td>
<td>2 days</td>
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<td>Left: T6–T10</td>
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<tr>
<td>15) 77/M</td>
<td>Hepatectomy</td>
<td>Right: T7–T10</td>
<td>3 (2–4)</td>
<td>15.3</td>
<td>Satisfied</td>
<td>4 days</td>
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<td>Left: T7–T10</td>
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<tr>
<td>16) 57/F</td>
<td>Ureteral reimplantation</td>
<td>Right: T7–T11</td>
<td>6.4 (4.8–7.1)</td>
<td>78</td>
<td>Satisfied</td>
<td>3 days</td>
</tr>
<tr>
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<td>Left: T7–T11</td>
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<tr>
<td>17) 47/M</td>
<td>Exploratory laparotomy and bowel resection</td>
<td>Right: T6–T10</td>
<td>6.7 (6.3–7.2)</td>
<td>770.3</td>
<td>Not satisfied</td>
<td>2 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left: T8–T10</td>
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<tr>
<td>18) 87/M</td>
<td>Hepatectomy</td>
<td>Right: T6–T9</td>
<td>0.8 (0–1.2)</td>
<td>7.5</td>
<td>Satisfied</td>
<td>5 days</td>
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<tr>
<td>19) 41/M</td>
<td>Hepatectomy</td>
<td>Right: T3–T8</td>
<td>5.25 (5.2–5.3)</td>
<td>65</td>
<td>Satisfied</td>
<td>1 day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left: T4–T7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20) 62/M</td>
<td>Pancreaticoduodenectomy</td>
<td>Right: T5–T9</td>
<td>6 (5–7)</td>
<td>16.3</td>
<td>satisfied</td>
<td>1 day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left: T5–T9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21) 40/M</td>
<td>Radical nephrectomy</td>
<td>Right: T6–T10</td>
<td>4.1 (3.5–5)</td>
<td>114</td>
<td>Satisfied</td>
<td>2 days</td>
</tr>
</tbody>
</table>

Cutaneous branches of the ventral rami of the thoracic intercostal nerves [3]. The spread extends medially deep into the erector spinae tissue plane and superficial to the thoracic transverse processes at the point where the dorsal rami of the thoracic intercostal nerves emerge between the tips of the adjacent transverse processes from T3 to T9. Moreover, there are many factors that limit the cadaveric studies from exploring the extent of the dye injected. This is mainly because of the absence of the biomechanical prop-
erties in the cadaver tissues [2]. However, theoretically, as the local anesthetic spreads medially deep into the erector spinae muscle, it can penetrate deep into the paravertebral space and block other nerves including the anterior and motor branches of the ventral rami of the thoracic intercostal nerves.

Previous chest wall blocks such as the intercostal nerve [13] and thoracic paravertebral [14] blocks have been described for analgesia after upper abdominal surgeries. The RISS block offers an advantage over the transverse abdominus plane (TAP) block as the latter does not provide consistent coverage to the lower thoracic dermatome areas. Even the subcostal TAP does not cover the lateral supraumbilical area [15]. Moreover, the clinical advantage of the RISS block is that the point of injection is far from most surgical incisions, and a catheter is unlikely to interfere with the surgical field [3]. Moreover, compared with the erector spinae plane block, the RISS block is technically easier to administer in terms of patient positioning, defining the landmark (borders of the scapula), and spread of the local anesthetics between the interfascial planes of the rhomboid major or serrates anterior from one side and the external intercostal muscle from the other side. Moreover, it is less invasive than the epidural block and paravertebral blocks, which makes the RISS block theoretically less susceptible to hemodynamic instability, bleeding, local anesthetic systemic toxicity, or permanent nerve damage.

We recognize some limitations to the case series, the main one being that it is a retrospective review. Moreover, the different incisions and surgical procedures might have affected the variability of the results. Lastly, all the blocks were done by one investigator (i.e., H.E.).

The RISS technique was shown to be beneficial for patients in this case series; further randomized clinical trials are needed, particularly a comparison with neuraxial and interfascial plane blocks.

Conflicts of Interest

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

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The first case of coronavirus disease 2019 (COVID-19) in Singapore was confirmed on January 23, 2020. On February 7, 2020, Singapore raised the Disease Outbreak Response System Condition alert level to orange, indicating that the disease was severe and easily transmissible. Subsequently, a global pandemic was declared by the World Health Organization on March 11, 2020. Patients with COVID-19 are not only at a risk of developing acute hypoxemic respiratory failure, but also acute cardiac injury and multiorgan failure \[1\] requiring ventilation therapy and admission to intensive care unit. In addition to the stress of being in an emergency surgical condition, patients with concurrent COVID-19 infections are likely to present with severe physiological derangements.

COVID-19 is known to have high infectivity with an estimated reproduction number (Ro) of 2.2–3.6 \[2\]. Ro is a measure of the transmission potential of an epidemic, defined as the number of infections caused by an index case within a population with no pre-existing immunity \[3\]. In the past, the majority of Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) cases were associated with nosocomial transmission in hospitals as well as with aerosol-generating procedures \[4\]. In particular, intubation and surgery are associated with significant exposure of healthcare workers to patients’ bodily fluids \[4,5\]. The use of electrocautery, application of surgical energy devices \[6\], and evacuation of pneumoperitoneum during laparoscopic procedures \[7\] have been associated with bioaerosol generation. Laparoscopic procedures are
also associated with viral release under high pressure. Hence, careful execution of infection control measures is necessary to prevent nosocomial transmission to other patients and healthcare workers [8].

This paper describes the perioperative anesthetic and surgical considerations and hospital facility preparations for infection control undertaken to prepare for a potential surge in confirmed or suspected COVID-19 patients requiring surgery.

Case Report

We obtained written informed consent from the patient. A 66-year-old man with a history of Type II diabetes mellitus, hypertension, and hyperlipidemia, was presented to our hospital with a one-day history of acute shortness of breath, cough, and fever. Further, he had a recent travel history to Batam, Indonesia.

His vitals were as follows: temperature 38.0°C, blood pressure 130/70 mmHg, pulse 140 bpm, respiratory rate of 25 per minute. His oxygen saturation was 92% on room air, and he was promptly placed on a 40% Venturi mask. Physical examination revealed bilateral crepitations and a 20 × 20 cm back carbuncle.

Blood investigations revealed a white blood cell count of 31000/µl, a hemoglobin level of 11.5 g/dl, a lactate level of 5.92 mmol/L, and a pro-brain natriuretic peptide level of 731 pg/ml. Arterial blood gas in supplemental oxygen showed a pH level of 7.42, pCO₂ of 35.1 mmHg and pO₂ of 91.9 mmHg with a PaO₂/FiO₂ ratio of 230. A chest X-ray (CXR) revealed bilateral diffuse pulmonary infiltrates.

After discussion, the anesthesia and the surgical teams concluded that the patient required intubation of the carbuncle for sepsis control, and surgery could not be delayed till the COVID-19 swab results were revealed as the patient was acutely septic. Initially, our hospital conducted COVID-19 diagnostic tests only twice a day, and it would have taken another 6 hours to determine the results of this patient’s swab test. Since his recent travel history, infective symptoms, and CXR made him a possible COVID-19 suspect, additional infection control precautions had to be taken.

Prior to the transfer, a team huddle was performed to ensure that all members were aware of the sequences and their roles in the transportation of the patient to the operating theatre (OT). The patient was transported on a plastic-covered trolley while receiving supplemental oxygen through a face mask (Fig. 1A). Signages were posted to specify the transportation route, and security personnel were deployed to divert human traffic during patient transfer. Upon entering the OT, the plastic cover on the trolley was removed and discarded into a biohazard bag.

An airway trolley was placed in the OT, and a C-Mac video laryngoscope with disposable blade was chosen as the first-line airway equipment. Before the surgery was started, the anesthetist assembled all the drugs and equipment required for the procedure on a tray to minimize contact with the drug trolley during the surgery. Whenever additional drugs were required, hand cleansing and glove changing were performed before handling the drug trolley.

An adequate preoxygenation of 8 vital capacity over 1 minute, achieving an FiO₂ of 0.80, and modified rapid sequence induction was our preferred induction technique. Induction agents including 2–3 mg/kg of propofol, 1–2 mg/kg of succinylcholine, and 1–2 µg/kg fentanyl were administered, and mask ventilation was avoided. We ensured that sufficient muscle paralysis was achieved after loss of consciousness before intubation. Thereafter, the airway was secured by the most senior anesthetist using a video laryngoscope, as it was believed that this process had a higher probability of success in the first attempt. Moreover, it avoided repeated instrumentation of the airway. General anesthesia was maintained with desflurane, and mechanical ventilation with a tidal volume of 7 ml/kg was instituted as the patient’s lung compliance and oxygenation were normal. As the patient was in respiratory distress on presentation, we decided to keep him intubated to avoid re-intubation.

Fortunately, the patient was tested negative for COVID-19.

Discussion

During a global pandemic, the importance of minimizing nosocomial transmission cannot be overemphasized. Medical workers have accounted for 3.8% of the total number of COVID-19 cases in mainland China [8]. Anesthetists and other perioperative care providers are particularly at risk during airway management and other procedures performed on patients with COVID-19. Hence, it is crucial to design disease outbreak response measures in conjunction with the surgical, nursing, and allied health staff.

For confirmed or high suspicion cases, identified by the presence of symptoms with CXR changes, the minimum personal protective equipment (PPE) should be powered air-purifying respirator (PAPR). Personnel such as surgeons, anesthetists, and their assistants who are likely to be in contact with droplets, aerosol or bodily fluids, should wear an additional green cape to protect their neck and ears (Fig. 1B). For patients with low suspicion, i.e. asymptomatic but positive contact history, N95 respirators and face shields as well as disposable gowns, are necessary. Within the OT, the number of staff should be limited to a maximum of two senior anesthetists, two anesthesia unit nurses, two surgeons, and two scrub nurses.
Understanding the airflow within the OT is crucial in minimizing the risk of infection. As all our operating theatres were designed to only have a positive pressure, we designated an OT located at a separate bank that utilized a separate filter system from the rest of the OT complex. Access from the emergency department was possible via a dedicated route. The pressure in the scrub room was designed to be more positive than the OT and, the workflow was adapted to maintain human traffic in a single direction (Fig. 1C). For example, if a team member was to experience PAPR malfunction during the surgical procedure, he would go through Route 1 (Fig. 1C) to the doff and perform hand hygiene in the doffing room, before re-entering the donning room. Air exchange was increased from the default setting of 16–18 to a maximum of 20–23 air exchanges per hour.

Since COVID-19 can be spread by contact, surface cleansing of the anesthesia workplace is particularly important. In general, coronaviruses can survive on surfaces for up to nine days [9], but, is susceptible to killing by 62–71% alcohol, 0.5% hydrogen peroxide, or 0.1% sodium hypochlorite [9]. However, routine cleaning of surfaces and interior storage areas of anesthesia machines and carts is very challenging [9,10]. Hence, plastic covers were placed over 'high touch surfaces' such as the anesthesia machine, patient monitor, computer keyboard, mouse, and touch screens, as these have been shown to reduce the bioburden [11]. In addition, the same OT and anesthesia machine have been designated for use for confirmed/suspected COVID-19 cases throughout the pandemic. Each anesthesia circuit is equipped with a high-efficiency particulate air filter. Both the heat and moisture exchanger filters and soda-lime will be changed after each case. The anesthesia machine, patient monitor surfaces, and patient cart were thoroughly cleaned after use. Equipment that had been dedicated to the isolation OT were labeled to avoid inadvertent exchange and cross-contamination.

As the procedure entailed the complete saucerization of a large hyperemic area, the use of diathermy was inevitable. However, the generator was maintained at the lowest necessary setting in order to reduce the amount of plume generated. In addition, the scrub nurse provided close and constant suctioning using a smoke evacuation device to minimize contamination of the OT air. Given the size of the carbuncle, saucerization was performed in quadrants, starting with a cruciate incision across the center of the affected area. As the infected tissue in each quadrant was excised, hemostasis was maintained, and the operative area was packed with gauze. This reduced the aerosolization of the blood in contact with the heated diathermy. Similarly, additional precautions were undertaken during laparoscopic procedures as a part of our institution’s COVID-19 workflow; but did not pertain to this case of open surgery.

Aerosols produced during airway management are particularly hazardous to anesthesia providers [12,13]. A systematic review showed that compared to healthcare workers who did not perform aerosol-generating procedures, those who performed tracheal intubation were at a higher risk of contracting SARS (odds ratio: 6.6), as were those who performed non-invasive ventilation (odds ratio: 3.1), tracheotomy (odds ratio: 4.2), and manual ventilation before intubation (odds ratio: 2.8) [13]. In general, coughing and assisted mask ventilation can generate aerosols and hence, were avoided. A C-Mac video laryngoscope was chosen as it not only allows direct visualization like a direct laryngoscope but also...
allows the assistant to visualize the airway and facilitate the procedure. Adjuncts like these are useful because visibility is known to be reduced with PPE, and they are crucial to achieve success in intubation in the first attempt since most patients are already in acute hypoxemic respiratory failure with minimal to no respiratory reserve [14]. In addition, such equipment also allows more distance between the operator and the patient’s airway and reduces the risk of airborne transmission.

Since we anticipated further respiratory deterioration in the patient, he was kept intubated postoperatively to avoid the risks of re-intubation. The need for emergent intubation limits the time available for donning PPE and increases the likelihood of mistakes in the procedure in increased aerosol exposure. Patients who can be extubated are recovered in the OT till standard Post Anesthetic Discharge Scoring System discharge criteria are achieved. Subsequently, terminal cleaning of the OT is performed and then allowed to ventilate for at least an hour [15].

Since this was the first case experienced by the team, there were several challenges despite having well-designed protocols and processes. Hence, in our opinion all involved healthcare workers should attend briefings and simulations to familiarize themselves with the workflow and avoid inadvertent contamination.

Communication is difficult within PAPR, especially while using a telephone to communicate with people outside the OT. Thus, to circumvent the problem of handwriting misinterpretation, we instituted a ‘write and write back’ system, similar to the read-back system in a closed-loop communication. Hence, a writing board can be used to communicate with colleagues outside the OT to minimize contact and miscommunication.

In conclusion, organizing surgery for COVID-19 patients requires the involvement, and therefore potential exposure of various healthcare workers. Detailed planning and coordination between departments are required to minimize the risk of disease transmission. It is imperative for the containment measures to be effective yet practical, without hindering patient care, especially during a surgical emergency.

Conflicts of Interest

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

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The epidural space can be identified using various methods, with loss of resistance (LOR) to air and saline being the most common method. Air used in the LOR technique for identifying the epidural space can cause pneumocephalus; therefore, the use of saline, although less sensitive than the former technique, is being advocated. We report a case of unbearable and excruciating pain after passage of an accidental bolus of preservative-free sterile water through the epidural catheter.

A 45-year-old female patient with a weight of 56 kg and height of 160 cm (body mass index: 21.9 kg/m$^2$) was scheduled to undergo total abdominal hysterectomy for a fibroid uterus under general anesthesia with epidural analgesia. On arrival in the operation theater, following conformance with the surgical safety checklist, the monitors were connected to the patient, and the baseline values were recorded. Epidural catheter insertion was planned in the sitting position, and the insertion site was prepared. Under aseptic conditions, an 18 gauge epidural needle was inserted in the L3–L4 space after administering local anesthesia in the space. The epidural space was identified with the LOR-to-air (2 ml) technique followed by insertion of the epidural catheter. As the catheter was inadvertently flushed with 2 ml of sterile water (Aishwarya Lifesciences, Solan HP, India) by the anesthesia resident, considering it to be as innocuous as saline, the patient winced and arched her spine and complained of unbearable excruciating pain in the back. Pain was accompanied by sweating and resulted in a 25% increase in the heart rate and blood pressure from the baseline values. The catheter was immediately flushed with 2 ml of sterile water (Aishwarya Lifesciences, Solan HP, India) by the anesthesia resident, considering it to be as innocuous as saline, the patient winced and arched her spine and complained of unbearable excruciating pain in the back. Pain was accompanied by sweating and resulted in a 25% increase in the heart rate and blood pressure from the baseline values. The catheter was immediately flushed with the local anesthetic solution (3 ml of 2% of plain lignocaine), which relieved the pain gradually in > 2 minutes. The patient was then positioned supine after securing the catheter. The remaining intraoperative period was uneventful. The epidural catheter was removed on the second postoperative day, and the patient was discharged on the seventh postoperative day with no neurological sequelae.

The osmolarity of the fluid being used could account for the development of pain on injection of fluid in the epidural space. The development of pain after injection of sterile water could be explained by the stimulation of type C nociceptive fibers by hypo-osmolar fluid-like sterile water with zero osmolarity, resulting in severe burning sensation in the back [1]. Similar pain was observed during the infusion of the hypertonic saline used in the study for epidural adhesiolysis in cases of epidural fibrosis [2]. This observation reiterates the impact of the osmolarity of the fluid in invoking pain on injection in the epidural space.

Preservative-free sterile water, as described in literature by Lund, was used to identify the epidural space as it invoked pain and discomfort once it entered the epidural space. Mayhew [3] agreed with the findings of Lund and reported no neurological sequelae but dissuaded the use of sterile water as a solution for identifying epidural space, considering the patients’ comfort. Cohn and Levesque [4] observed that intense pain was experienced
when sterile water mixed with a steroid was injected in the epidural space; however, injection of the same steroid mixed with saline did not result in pain. A recent literature search for similar events yielded only one study where 4 ml of distilled water was accidentally injected in the epidural space for labor analgesia and generated severe pain in the lower back, which was relieved after injection of a local anesthetic solution, as was observed in our index case [5]. Following this incident, an immediate internal audit was performed in our department, and remedial measures were adopted to circumvent such errors in the future by issuing directives against the use of sterile water in any form in the operation theater.

To conclude, when saline is used for identifying the epidural space, extreme caution must be exercised to prevent inadvertent administration of sterile water, which can result in the development of unbearable pain in the patient and may potentially evoke dissatisfaction towards the anesthesia technique.

Conflicts of Interest

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

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We have read with great interest the article on rhomboid intercostal and subserratus block by Elsharkawy et al. [1]. They have reported that rhomboid intercostal and sub-serratus block helps effectively manage pain in patients after major abdominal surgeries. Herein, we would like to report that rhomboid intercostal block (RIB) may also provide effective pain relief in myofascial pain syndrome (MPS). MPS is a chronic disease that affects 21–30% of the population [2]. It originates in the painful trigger points of skeletal muscle, and patients suffer moderate to severe pain. Medications and ultrasound-guided injections at the trigger points may be used to treat MPS [2].

Thanks to the use of ultrasound, interfascial plane blocks have become very popular. RIB was first described by Elsharkawy et al. [3]. A local anesthetic solution is administered between the rhomboid muscle and intercostal muscles over the T5–T6 ribs 2–3 cm from the medial border of the scapula. By cadaveric examination, Elsharkawy et al. observed that injectate caudad and cephalad had spread into the deep tissues over the T2–T8 levels containing the posterior primary rami and the clavipectoral fascia of the axillary region (T2–T9). RIB targets the posterior rami and the lateral cutaneous branches of the thoracic nerves, and it provides analgesia for the hemithorax from T2 to T9 [3–5]. Here we report our experience of using RIB in a patient suffering from MPS.

We used a visual analog scale (VAS) to evaluate the patient’s pain before and after im-

#### Ultrasound-guided rhomboid intercostal block effectively manages myofascial pain

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We have read with great interest the article on rhomboid intercostal and subserratus block by Elsharkawy et al. [1]. They have reported that rhomboid intercostal and sub-serratus block helps effectively manage pain in patients after major abdominal surgeries. Herein, we would like to report that rhomboid intercostal block (RIB) may also provide effective pain relief in myofascial pain syndrome (MPS). MPS is a chronic disease that affects 21–30% of the population [2]. It originates in the painful trigger points of skeletal muscle, and patients suffer moderate to severe pain. Medications and ultrasound-guided injections at the trigger points may be used to treat MPS [2].

Thanks to the use of ultrasound, interfascial plane blocks have become very popular. RIB was first described by Elsharkawy et al. [3]. A local anesthetic solution is administered between the rhomboid muscle and intercostal muscles over the T5–T6 ribs 2–3 cm from the medial border of the scapula. By cadaveric examination, Elsharkawy et al. observed that injectate caudad and cephalad had spread into the deep tissues over the T2–T8 levels containing the posterior primary rami and the clavipectoral fascia of the axillary region (T2–T9). RIB targets the posterior rami and the lateral cutaneous branches of the thoracic nerves, and it provides analgesia for the hemithorax from T2 to T9 [3–5]. Here we report our experience of using RIB in a patient suffering from MPS.

Written informed consent was obtained from the patient at Istanbul Medipol University Hospital to perform the procedure and for the publication of this report. A 33-year-old male patient (height 175 cm, weight 88 kg) had been diagnosed with MPS 3 years earlier. He was not known to have had any other systemic disease. For the last 6 months, he had suffered from severe pain in the left dorsal hemithorax from T2 to T7. His pain was unresponsive to medications; trigger point injections, given on five previous occasions, had not provided pain relief.

While the patient was in a sitting position, he had placed his left hand over his right shoulder by moving his hand over his chest. This movement caused lateral movement of his scapula, and the cavity was opened; therefore, we opted for RIB. Under aseptic conditions, a linear high-frequency probe was medially placed in the sagittal plane on the medial border of the scapula at the T5–T6 level. The trapezius muscle, rhomboid major muscle, intercostal muscle, ribs, and pleura were visualized. We inserted a 22-gauge needle into the fascial plane between the rhomboid major and intercostal muscles in a craniocaudal direction and injected 20 ml of 0.25% bupivacaine with 8 mg of dexamethasone into the fascial plane.

We used a visual analog scale (VAS) to evaluate the patient’s pain before and after im-
implementing the block. Before the procedure, arm movement had been limited by pain, and the VAS had been 6/10 during rest and 9/10 during movement. Thirty minutes after RIB, the patient was able to move his arm easily, and he felt no pain in his arm (when moving and at rest). We followed his progress for 4 weeks. For 2 weeks, we prescribed 25 mg of oral dexketoprofen and 8 mg of thiocolchicoside bid. He felt no pain, and no other analgesia was administered to him.

Although the literature on RIB is limited, several cases now provide evidence that this novel interfascial plane block may be an effective addition to the multimodal analgesic regimen for managing pain in MPS. Further studies may be needed to improve our understanding of the mechanisms and analgesic efficacy of RIB.

Conflicts of Interest

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

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We carefully read the letter by Ekinci et al. [1] who replied to the detailed paper by Elsharkawy et al. [2] describing a case report on the use of rhomboid intercostal block (RIB) to manage myofascial pain syndrome (MPS).

We congratulate the authors for the clinical management of the patient and clear presentation of their results. The use of RIB for MPS is a new approach, and reports have been rising in the current literature to support the efficacy of RIB as part of the multimodal treatment [3,4].

We want to contribute to the discussion by focusing our attention not only on the benefits but also potential limitations of RIB to treat MPS.

It is crucial to obtain the correct diagnosis of MPS. MPS can be primary, which may be an overuse condition, such as lateral epicondylitis or piriformis syndrome, or secondary to other diseases or postural maladaptive changes. In secondary cases, if no therapeutic interventions are performed to treat the underlying cause, the results of fascial plane blocks as RIB are transient [5]. In the described case, Ekinci et al. [1] injected 20 ml of bupivacaine and dexamethasone which was a good idea, the authors had also performed hydrodissection of fascial planes in this way. This can provide outstanding and long-lasting results in case of fascial adhesion that is not easy to detect, but can contribute to MPS development [1,4].

The authors followed-up the patient for 4 weeks after the treatment. However, it would be interesting to have a longer follow-up, maybe 3 to 6 months, in order to establish if fascial plane blocks without any prevention strategy can ensure more consistent long-term results. In our experience, this is not as apparent, while the success of fascial plane blocks combined with physiotherapy has been reported [3–5].

**Conflicts of Interest**

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

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Ketamine use in the COVID-19 era: be cautious!

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Coronavirus disease 2019 (COVID-19) is a highly contagious disease, which is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It spreads mainly through coughing and sneezing, which generates aerosols and droplets of varying sizes, and direct human-to-human physical contact. The patient’s upper aerodigestive tract has a high viral load, and any procedure on the upper airway can increase the risk of infection transmission via droplets and aerosols. Frontline workers such as anesthesiologists are at high risk of contracting this disease. Prolonged preoxygenation, along with rapid sequence induction, has been recommended to decrease the coughing and aerosol generation [1]. The role of antisialagogues like glycopyrrolate has also been advocated by some experts during tracheal intubation to minimize oral secretions [2]. All these measures act as aerosol barriers, or they decrease the amount of generated aerosols by reducing the oral and bronchial secretions. On the other hand, commonly used anesthetic drugs such as ketamine, which causes bronchorrhea or hypersalivation, need to be used with caution during this COVID era.

Ketamine is frequently used alone or in combination for induction in pediatric and hemodynamically unstable patients and procedural sedation and analgesia. Recently, clinicians have recommended its use in COVID-19 patients, owing to its better hemodynamic stability [3]. One of its commonest side effects is increased oral and bronchial secretions, for which an anti-sialogogue has been advocated. In a meta-analysis by Shi et al. [4], it was observed that the addition of atropine to ketamine significantly reduces hypersalivation that results from ketamine premedication. However, hypersalivation and bronchorrhea may still be present in 12% of the patients receiving atropine. Moreover, administering an anticholinergic to each patient may not be possible, and it may be associated with side effects like arrhythmias.

Ketamine is an N-methyl D-aspartate receptor antagonist. It inhibits the catecholamine reuptake and increases the norepinephrine concentration at the postsynaptic receptors. This increased norepinephrine stimulates the sympathetic arm of the salivary glands, which results in hypersalivation [5]. We have found the following disadvantages of using ketamine in this COVID era: 1) Preserved gag and cough reflex during procedural sedation can increase the aerosol spread, 2) Increase in the amount of aerosol generated from saliva and bronchial secretions caused by leaks around the endotracheal tube cuff in a patient on positive pressure ventilation, 3) Increased need for repeated oral and bronchial suctioning increases the healthcare worker exposure, and repeated suctioning also carries an inherent risk of aerosolization of the virus particles, 4) Blurring of vision of videolaryngoscope.

The WHO and the United States Center for Disease Control and Prevention recommends the use of full personal protective equipment while providing care to COVID-19 patients; however, these methods have not been fool-proof. Often, the COVID-19 status of the patient is not known, or it may be falsely negative. There is an urgent need for ad-
ditional measures against this highly infectious disease. At our center, we have seen a significant increase in bronchial secretions and the need for airway suctioning after the use of ketamine in these patients. Therefore, we suggest a cautious use of ketamine for sedation and anesthesia in this COVID era. To conclude, the use of ketamine for sedation and anesthesia should be cautious in suspected or confirmed COVID-19 patients, and the benefits of its use must be weighed against its associated increased risk of COVID-19 infection spread.

Conflicts of Interest

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

Author Contributions

Aditi Suri (Conceptualization; Data curation; Writing – original draft; Writing – review & editing)
Gaurav Sindwani (Conceptualization; Data curation; Resources; Supervision; Writing – original draft; Writing – review & editing)

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References

Pregabalin-induced hypoglycemia in a dialysis patient

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We experienced a case of unexpected severe hypoglycemia in a patient in whom pregabalin was newly administered. Informed consent was obtained from the patient and officially saved. The acceptance of submission was obtained from the institute. A 73-year-old man (height: 164 cm, weight: 50 kg) with diabetes had received hemodialysis for diabetic nephropathy for 1 year. Dialysis was smoothly introduced and the course of diabetes was favorable. Recently, he complained of chest oppression and an emergency percutaneous coronary angioplasty was conducted through the right femoral artery. After the intervention, ischemic changes were observed on the right lower extremity. The ischemia was not ameliorated after the emergency endovascular femoral stenting and thus, right limb amputation was carried out. No further adverse complication was observed. The daily living activity of the patient was fully restored. Although fasting blood sugar (FBS) control level worsen during the event, he could freely eat after the wound was healed and the FBS level was steadily maintained around 170 mg/dl.

One month later, the patient complained of pain on the leg stump, and 75 mg pregabalin was administered. After 3 days of consecutive administration, the dose was doubled to 150 mg a day. Three days later, the patient visited the hemodialysis station and the routine regimen of dialysis was initiated, but the technician in charge noticed that the patient was drowsy. Immediately after the dialysis was started, an emergency laboratory examination revealed severe hypoglycemia (56 mg/dl) despite the use of dialysate containing 100 mg/dl glucose. The hemodialysis was promptly canceled. The patient was administered 20 g glucose and was transferred to the intensive care unit (ICU). Consciousness was rapidly regained, and hemodialysis was re-conducted at the ICU.

Pregabalin-induced hypoglycemia was strongly suspected because no other treatment was changed. The pain regimen was changed to opioids. After the cessation of pregabalin and hemodialysis in the ICU, the FBS level recovered to between 130 mg/dl and 220 mg/dl the next day, and he developed no hypoglycemic symptoms during the 3-day observation period before he was discharged from the hospital.

This is the first report describing the possibility of acute pregabalin-induced hypoglycemia in hemodialysis patients. One of the most common symptoms is dizziness [1]. Dizziness is one of the symptoms of hypoglycemia. Recently, few cases reported pregabalin-induced hypoglycemia after long-term treatment [2,3]. Pregabalin is mainly (> 90%) eliminated through the kidney and the pharmacokinetics depends on renal function [4]. The exact mechanism of hypoglycemia induced by pregabalin is still unknown [5].

Pregabalin is a well-known and effective drug against neuropathic pain including diabetic neuropathy and is administered to patients by many physicians [1]. Attention should be paid to this acute and critical adverse effect of this popular drug used in cases...
of chronic pain treatment, even in short-term medication.

**Conflicts of Interest**

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

**Author Contributions**

Hanayo Masaki (Conceptualization; Investigation; Writing – original draft; Writing – review & editing)
Takahiro Tamura (Conceptualization; Writing – original draft; Writing – review & editing)
Yushi Ueda Adachi (Conceptualization; Project administration; Writing – original draft; Writing – review & editing)
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**References**


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What is the proper way to apply the multiple comparison test?

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The article Lee S and Lee DK, "What is the proper way to apply the multiple comparison test?" contained an error in the first appeared equation on page 353.

Before correction:

μA ≠ μB ≠ μC or μA ≠ μB = μC or μA = μB ≠ μC or μA ≠ μC = μB

The correct information is found below:

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⁶Lee S and Lee DK. What is the proper way to apply the multiple comparison test? Korean J Anesthesiol 2018; 71: 353-60.
⁷The CONSORT statement, checklist, and flow diagram can be found at http://www.consort-statement.org.
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Use generic names. If a brand name must be used, insert it in parentheses after the generic name. Provide ® or ™ as a superscript and manufacturer’s name, and country.

· Ions
Ex) Na⁺ [O], Mg⁴⁺ [O], Mg²⁺ [X], Mg⁺² [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.

⑤ 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.

⑥ 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.

⑦ References

- 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.
- If necessary, the editorial board may request original documents of the references.
- Six authors can be listed. If more than 6 authors are listed, only list 6 names with ‘et al.’
- Provide the start and final page numbers of the cited reference.
- 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.
- Description format
A. Regular journal
Author name. Title of journal Name of journal published year; volume: start page-final page.
Ex) Hirota K, Lambert DG. Ketamine: its mechanism(s) of action and unusual clinical uses. Br J Anaesth 1996; 77:
Tables should be more than 4 rows and should not be over 1 page.

- Except for titles and first letters, all of the text in the tables should be written in small alphabetic letters.
- In demographic data, sex would be provided as M/F, and age in yr. Data of year, weight, height, and any other units would be provided with 1 decimal place.
- "±" sign in the upper column of table should be lined up with the lower column.
- Footnotes should be provided consecutively in order of the cited tables or statistics.
- Marks for footnote should be given in order of *, †, ‡, §, II, ¶, **, ††, ‡‡... When marks are used to explain items of the table, indicate them with superscripts.
- Define all abbreviations except those approved by the International System of Units. Define all abbreviations every time they are repeated.

C. Chapter


D. Electronic documents


E. Online journal article


F. Papers that have been submitted and accepted for publication should be included in the list, with the phrase ‘in press’ replacing volume and page number. Authors should be prepared to give the volume and page number at the time of proof correction.


10. Legends for figures and photographs

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

(3) Figures and illustrations

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

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

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

④ Photographs should be submitted individually. If 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.
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) 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. 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.
3) Reviews
Review articles synthesize previously published material into an integrated presentation of our current understanding of a topic. Review articles should describe aspects of a topic in which scientific consensus exists, as well as aspects that remain controversial and are the subject of ongoing scientific disagreement and research. Review articles should include unstructured abstracts 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 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.

4) Letters to the Editor
Letters to the Editor also should include brief constructive comments on the articles published in KJA and interesting cases. 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 IRB approval should be provided. 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.

5) Book Reviews and Announcements
Book reviews as well as News of Scientific Societies and scientific meeting dates in Korea or abroad can be included. Their formats will be same as Letter to the Editor.

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 November 2019 submissions.