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Aims and Scope

The Korean Journal of Anesthesiology (Korean J Anesthesiol; KJA) is an international, English-language, and Peer-reviewed journal for anesthesiology, critical care, and pain medicine. As an official journal of the Korean Society of Anesthesiologists, KJA was founded in 1968 and published monthly until 2014 and will now publish bimonthly in 2015.

KJA aims to publish high-quality clinical and scientific materials on all aspects of anesthesiology, critical care, and pain medicine. In addition to publishing original articles, KJA features reviews, editorials, case reports, and letters to the editor. The major consideration for publication includes clarity, uniqueness, and advancement in design, performance, and knowledge. KJA also features Statistical Round to provide educational fundamentals and practical implications for clinical and experimental statistics to its readers. Additionally, KJA gladly reviews and publishes negative results for which publication will benefit clinical practice and promote further research activity.

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Anesthetics or anesthetic techniques and cancer surgical outcomes: a possible link

Azeem Alam, Sanketh Rampes, Sonam Patel, Zac Hana, Daqing Ma

Division of Anesthetics, Pain Medicine and Intensive Care, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, Chelsea & Westminster Hospital, London, UK

2018년 현재 전 세계적으로 매년 960만 건의 사망이 암으로 인한 것이며, 인구 고령화와 함께 암 발생률은 계속해서 증가할 것으로 예상된다. 수술은 고형 장기 암에 있어 중요한 치료 방법이다. 악성 종양의 발달 과정이 여러 마취제의 작용 경로와 중첩될 수 있기 때문에, 마취제 유형이나 투여 방법이 암 환자의 수술 후 결과에 영향을 미칠 수도 있다는 점이 지적되어 왔다. 본 종설은 PubMed, EMBASE, Cochrane 등 여러 데이터베이스, 학술지, 서적에서 수집된 최신 증거들에 대한 문헌 고찰로서, 암 발생 및 진행의 병태생리적 과정과 마취제 작용 기전의 관계, 암과 마취제에 대한 임상적, 후향적 연구와 진행 중인 임상시험 등을 살펴보았다. 부위마취 대비 전신마취가 암 재발에 미치는 영향에 대한 연구 결과들은 전반적으로 상충되고 있지만, 흡입 마취제 대비 정맥 마취제에 대한 연구들에서는 정맥 마취제 프로포폴이 유익하다고 제시한 결과가 다수이다. 우리가 수술 염증 반응에 관련된 생체 변화를 연구하면, 암을 진행시키는 어떤 잠재적인 영향을 막을 수 있는 고유의 기회를 얻을 수 있다.

Keywords: Anesthesia; Anesthetics; Cancer; Neoplasms; Postoperative period; Surgery.
Interpretation of volume kinetics in terms of pharmacokinetic principles

Byung-Moon Choi

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수액 역학(volume kinetics)은 정주된 수액이 어떻게 분포되고 제거되는지에 관한 약동학이다. 일반적으로 약동학 모수는 약물의 농도를 측정하여 추정할 수 있다. 하지만 수액의 농도를 직접 측정하는 것은 거의 불가능하다. 따라서 수액 역학에서 수액의 배치(disposition)는 혈색소(hemoglobin)의 손실이 없다는 전제하에 혈색소 농도를 측정하여 간접적으로 정량화한다. 수액을 투여하면서 혈색소 농도를 반복적으로 측정하게 되면, 해당 측정 시점에 대한 혈장량의 상대적인 변화(희석)를 얻을 수 있다. 여기에서 희석은 수액 투여로 인한 혈장량의 확장 개념으로 해석할 수 있다. 구획 분석으로 약물의 배치를 정량화하는 방법이 수액 역학에도 동일하게 적용된다. 구획 간 수액의 이동은 일차 역학으로 설명되며, 수액은 중심 구획에서만 제거한다고 가정하였다. 집단 분석(population analysis)을 사용하게 되면 수액 동역학 모수의 개인 간 변이를 설명하는 공변량을 파악할 수 있다. 체중 및 평균 혈압은 수액 역학 모수의 대표적인 공변량이다. 정질액 및 교질액을 투여하였을 때 수액 공간의 확장 효과를 수액 역학 변수를 사용하여 더 효과적으로 이해할 수 있으며, 수액 요법을 적절하게 시행하는 데 도움이 된다. 물론 수액 역학에 한계점이 있기는 하지만 수액을 투여하는 임상의사에게 중요한 시사점을 제공해 줄 수 있을 것이다.

Keywords: Body fluids; Colloids; Crystalloid solutions; Hemoglobins; Pharmacokinetics; Statistical models.
A comparison of the breathing apparatus deadspace associated with a supraglottic airway and endotracheal tube using volumetric capnography in young children

Eduardo Javier Goenaga-Diaz¹, Lauren Daniela Smith², Shelly Harrell Pecorella³, Timothy Earl Smith¹, Gregory B Russell¹, Kathleen Nicole Johnson⁴, Martina Gomez Downard¹, Douglas Gordon Ririe¹, Dudley Elliott Hammon¹, Ashley Sloan Hodges¹, Thomas Wesley Templeton¹

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Keywords: Airway management; Capnography; Child; General anesthesia; Laryngeal mask airway; Positive pressure respiration; Ventilation.
Comparison between two different concentrations of a fixed dose of ropivacaine in interscalene brachial plexus block for pain management after arthroscopic shoulder surgery: a randomized clinical trial

Seung Cheol Lee, Joon Ho Jeong, Seong Yeop Jeong, Sung Wan Kim, Chan Jong Chung, So Ron Choi, Jeong Ho Kim, Sang Yoong Park

Department of Anesthesiology and Pain Medicine, Dong-A University College of Medicine, Busan, Korea

Keywords: Brachial plexus; Pain management; Patient-controlled analgesia; Postoperative pain; Shoulder pain; Ultrasonography.

Comparison between two different concentrations of a fixed dose of ropivacaine in interscalene brachial plexus block for pain management after arthroscopic shoulder surgery: a randomized clinical trial

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Endotracheal intubation in patients undergoing open abdominal surgery in the lateral position: a comparison between the intubating video stylet and fiberoptic intubating bronchoscopy

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Keywords: Airway management; Bronchoscope; Intratracheal intubation; Laparotomy; Patient positioning; Video stylet.

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Accepted: October 19, 2020

Background: Specialized case, the anesthesiologist and pain management in the lateral position, the patient may require intubation. As such, non-operative interventions are advocated. In this study, we aimed to compare the efficacy of video stylet intubation (VS) with fiberoptic intubation (FO) in patients undergoing open abdominal surgery in the lateral position.

Methods: A total of 50 patients were randomized into two groups: VS group and FO group. The intubation procedure was performed by a single experienced operator using a standardized technique. The primary outcomes were time to intubation and the occurrence of complications. The secondary outcomes included intubation success rates.

Results: The mean time to intubation in the VS group was significantly shorter than in the FO group (39.5 ± 10.0 s vs. 75.6 ± 16.2 s, P < 0.001). Intubation success rates were 88% in the VS group and 100% in the FO group (P < 0.05). The incidence of post-intubation sore throat was higher in the VS group (P = 0.002).

Conclusion: Video stylet intubation is a feasible technique in patients undergoing open abdominal surgery in the lateral position. However, it is associated with a higher risk of post-intubation sore throat compared to fiberoptic intubation.

Keywords: Airway management; Bronchoscope; Intratracheal intubation; Laparotomy; Patient positioning; Video stylet.
Preoperative high-sensitivity troponin I and B-type natriuretic peptide, alone and in combination, for risk stratification of mortality after liver transplantation

Young-Jin Moon, Hye-Mee Kwon, Kyeo-Woon Jung, Kyoung-Sun Kim, Won-Jung Shin, In-Gu Jun, Jun-Gol Song, Gyu-Sam Hwang

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Keywords: B-type natriuretic peptide; Liver transplantation; Mortality; Postoperative complication; Risk assessment; Troponin-I.
Patient barrier acceptance during airway management among anesthesiologists: a simulation pilot study

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Keywords: Aerosols; COVID-19; Healthcare acceptability; Infectious disease transmission; Intubation; Personal protective equipment; Protective device.

 배경: 의료인(healthcare providers, HCP)을 보호하는 것이 코로나19 (COVID-19) 팬데믹 중 환자 관리에 있어 심각한 도전이 되었다. 추가적인 물리적 장벽이 개인보호구(personal protective equipment, PPE)를 강화하는 데 사용되었다. 이 연구에서 2가지 새로운 장벽에 대한 사용자 수용도가 평가되었으며, PPE 단독 및 PPE와 추가 장벽 간 기도 관리 성능을 비교하였다.

방법: 공개된 2군 시뮬레이션 파일럿 연구가 수행되었다. 각 참여자는 백-마스크 환기 및 GlideScope를 사용한 기관내삽관을 (1) PPE 착용, 이후 (2) PPE 착용과 격리 챔버(IC) 또는 에어로졸 박스(AB) 추가 등 2가지 시나리오에서 수행하였다. 비디오 후두경을 사용한 기관내삽관 시간을 측정하였다. 참여자는 시뮬레이션 사전 및 사후 설문지를 작성하였다.

결과: 마취과 의사 29명이 시험에 포함되었다. 시뮬레이션 사전 및 사후 설문지에 대한 응답은 추가 장벽의 수용도를 뒷받침하였다. 군별로 삽관 시간에는 유의한 차이가 없었다 (PPE vs. IC 95% CI, 26.3–35.1; PPE vs. AB 95% CI, 25.9–35.5; IC vs. AB 95% CI, 23.6–39.1). IC 및 AB 간 시뮬레이션 사전 설문지 응답 비교에서 유의한 차이가 보이지 않았다. 참여자는 추가 장벽이 의사소통, 시각화, 작동에 있어 부정적인 영향을 미치지 않았다고 했다.

결론: 전반적으로 IC 및 AB는 비슷한 성능을 보였고, 실험 조건에서 성능에 대한 부정적 영향은 없었다. 실험에 따르면 마취과 의사의 기도 관리 중 추가적인 보호 장벽에 대한 긍정적인 수용도를 보였다.

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Endotracheal intubation using a three-dimensional printed airway model in a patient with Pierre Robin sequence and a history of tracheostomy -a case report-

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Keywords: Airway management; Computer simulation; Endotracheal intubation; Pierre Robin sequence; Pierre-Robin syndrome; 3D printing.
Refractory gram-negative septic shock complicated by extended purpura fulminans and multiple organ failure in a 23-year-old puerpera -a case report-

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Background: Maternal infections are the cause of 3rd leading cause of maternal deaths worldwide. The purpose of this report is to present a 23-year-old puerpera with septic shock complicated by disseminated intravascular coagulation and multiple organ failure.

Case Report:

A 23-year-old woman presented with septic shock, disseminated intravascular coagulation, and multiple organ failure. She was treated with antibiotics, fluid resuscitation, vasopressors, steroids, and apheresis. Despite all interventions, her condition did not improve, and she died on the 7th day of hospitalization.

Keywords: Disseminated intravascular coagulation; Hypercoagulability; Purpura fulminans; Septic shock; Therapeutic use; Vasoconstrictor agents.
Interscalene brachial plexus block (ISB) has been widely used to control postoperative pain in patients undergoing shoulder and arm surgeries. Continuous ISB with catheter insertion has been shown to be more effective than single-shot ISB for postoperative pain control. However, catheter-related complications, such as dislodgement and infection, should be considered when using continuous ISB with a catheter. When single-shot ISB is chosen for the fear or prevention of catheter-related complications, the duration of ISB is critical to achieve effective postoperative pain control. There are various determinants for the duration of nerve block. Local anesthetics, itself, have two determinants for the duration of nerve block, the concentration and volume, regardless of the characteristics of the local anesthetic used. Pippa et al. [1] reported that low concentration and high volume of local anesthetics for ISB covered more block areas and avoided complications, compared with high concentration and low volume of local anesthetics at the same dose. However, Zhai et al. [2] reported that ropivacaine 50 mg with 0.25, 0.5, or 0.75% with different volumes for ISB had similar block results, although 0.75% showed a faster onset.

The current issue of the Korean Journal of Anesthesiology deals with the effect of the concentration and volume of local anesthetics in single-shot ISB on the characteristics of the block. Lee et al. [3] compared 0.75% ropivacaine 10 ml and 0.375% ropivacaine 20 ml with a fixed dose of 75 mg in patients undergoing arthroscopic shoulder surgeries. They found that low concentration and high volume (0.375% ropivacaine 20 ml) was effective in reducing the postoperative opioid requirement within 24 h of the surgery, although it was associated with a longer onset and did not prolong the duration of the block. They also checked pulmonary function using a spirometer, before and after ISB. Similar changes in pulmonary function after ISB were observed with the use of 0.75% ropivacaine 10 ml and 0.375% ropivacaine 20 ml.

To achieve successful ISB without complications, the minimal effective concentration with minimal effective volume of the local anesthetic should be determined and used. This can only be achieved if the needle for ISB is positioned correctly. Although nerve stimulators and ultrasonography have been used for the success of ISB, it remains difficult to find the minimal effective concentration and minimal effective volume of the local anesthetic for individual patients.

There is controversy over the concentration and volume of local anesthetics to be prioritized in single-shot ISB to control postoperative pain in patients undergoing shoulder and arm surgeries. Considering that a higher concentration of local anesthetics with a longer duration is known to be associated with local anesthetic toxicities [4], a trial to reduce the concentration could be prioritized in single-shot ISB.
In conclusion, the study by Lee et al. [3] might be helpful in providing evidence that the use of ropivacaine at a lower concentration for ISB had a beneficial effect, compared with the higher concentration. However, further studies are needed to clarify the priority of the concentration and volume of local anesthetics to achieve a longer duration of ISB without complications.

Conflicts of Interest

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

References

As of 2018 cancer is responsible for almost 9.6 million deaths annually and, with an aging population, the incidence of cancer is expected to continue to rise. Surgery is an important treatment modality for patients with solid organ cancers. It has been postulated that, due to potentially overlapping processes underlying the development of malignancy and the therapeutic pathways of various anesthetic agents, the choice of anesthetic type and method of administration may affect post-operative outcomes in patients with cancer. This is a literature review of the most recent evidence extracted from various databases including PubMed, EMBASE, and the Cochrane, as well as journals and book reference lists. The review highlights the pathophysiological processes underpinning cancer development and the molecular actions of anesthetic agents, pre-clinical and retrospective studies investigating cancer and anesthetics, as well as ongoing clinical trials. Overall, there are conflicting results regarding the impact of regional vs. general anesthesia on cancer recurrence, whilst the majority of data suggest a benefit of the use of intravenous propofol over inhalational volatile anesthetics. The biological changes associated with the surgical inflammatory response offer a unique opportunity to intervene to counteract any potentially cancer-promoting effects.

**Keywords:** Anesthesia; Anesthetics; Cancer; Neoplasms; Postoperative period; Surgery.
attention over the past decade and has resulted in many retrospective studies and pre-clinical research into the area. An increasing body of pre-clinical laboratory data suggests that general anesthetic agents have the ability to influence key hallmarks of cancer involved in tumorigenesis and metastasis [6]. There are two key classes of general anesthetic agents used in clinical practice: intravenous propofol and inhalational volatile anesthetic agents such as sevoflurane. Inhalation anesthetics have been shown to enhance proliferation, migration, invasion, and angiogenesis across a range of cancer cell types, whereas propofol has been shown to antagonize these same pathways [6]. Several retrospective studies have demonstrated an association between inhalational anesthesia and reduced recurrence-free survival in cancer patients undergoing elective surgery compared to survival in cancer patients who receive propofol-based anesthesia [7,8]. However, there are smaller retrospective studies that show no association, highlighting the need for future prospective and randomized controlled trials.

In this literature review we present the most recent evidence extracted from various databases including PubMed, EMBASE, and the Cochrane, as well as journals and book reference lists.

Cancer development

Cancer results from the proliferation of a clonal population of cells—a multistage process termed carcinogenesis. A single cell undergoes a mutation in critical genes responsible for the control of cell division, cell death, and the maintenance of genetic integrity thereby rendering the cell susceptible to the acquisition of further mutations [9]. The tumor cell becomes refractory to regulatory biochemical cell signaling pathways, which results in the progressive loss of differentiation and in turn, uncontrolled cellular proliferation ensues [9]. The expanding pre-neoplastic cell clone outgrows the capacity of the host vasculature and subsequent tumor progression is dependent on angiogenesis for the supply of growth factors and oxygen [10]. Pro-angiogenic factors including vascular endothelial growth factor (VEGF), platelet-derived endothelial growth factor (PDGF), and fibroblast growth factor are released from the tumor, establishing a new capillary network that promotes tumor growth, local invasion, and metastasis [11].

Metastasis and tumor progression

The pathogenesis of cancer metastases is complex, of which a series of tumor-host interactions are outlined by the metastatic cascade. Tumor cells lose their cell polarity and cell-cell adhesion properties, allowing for a subclone of cells with metastatic potential to invade the surrounding stroma and dissociate from the primary tumor mass (invasion) [12]. The detached cells, known as circulating tumor cells (CTCs), enter the systemic circulation via the established blood vessel network formed through angiogenesis and the lymphatic system (invasion). During this process, most CTCs are rapidly destroyed by the immune system as a result of host immunosurveillance carried out by NK cells and CD8+ T cells, with only 0.1% of cells viable after 24 h [13]. The surviving tumor cells arrest in the capillary beds of a distant organ and adhere to capillary endothelial cells and thus penetrate the endothelium and basement membrane (extravasation). Consequently, proliferation within the secondary organ parenchyma achieves metastasis and the formation of a malignant tumor.

It is becoming increasingly recognized that various anesthetic agents used in the perioperative setting for primary cancer surgery have a role in cancer recurrence through postoperative metastasis [14]. In this narrative review, we aim to present the current state of evidence linking anesthetic techniques and cancer surgical outcomes.

Molecular actions of anesthetics and cancer

Inhalational anesthetics

Volatile anesthesia

Rapidly acting volatile anesthetic agents, such as sevoflurane and isoflurane, are commonly used for the maintenance of general anesthesia. It is well-established that these agents have pro-inflammatory and immune modulatory effects, and therefore, may have deleterious effects in cancer recurrence, although the exact molecular mechanisms are incompletely understood [6,15,16].

In particular, volatile anesthetics have been shown to suppress NK cell cytotoxicity and induce T-lymphocyte apoptosis, of which both cells have a vital role in immune surveillance and achieving anti-metastatic immunity after cancer surgery [17,18]. Thus, volatile agents may promote immunosuppression and the metastatic spread of residual cancer cells postoperatively.

Moreover, volatile anesthetics have a protective role against ischemia-reperfusion injury in various organs and tissues [19]. These cytoprotective features, however, are associated with the upregulation of hypoxia-inducible factor 1-alpha (HIF-1α) in tumor cells, causing increased transcription of genes encoding VEGF and PDGF [20] and thereby facilitate tumor angiogenesis, residual cell survival, and tumor cell migration.

Nitrous oxide

Nitrous oxide is an anesthetic gas used for the maintenance of anesthesia often in combination with more potent general anes-
thetic techniques for surgical anesthesia. This inhaled agent has been related to a number of immunosuppressive effects, primarily through impaired neutrophil chemotaxis and suppressed NK cell and macrophage function [21,22]. This is mediated by its interaction with vitamin B12, causing selective inactivation of methionine synthase, which is critical for DNA, purine, and thymidylate synthesis [23]. Consequently, there is impaired synthesis of hematopoietic cells involved in tumor surveillance.

**Intravenous anesthetics**

**Propofol**

Propofol is the most extensively used intravenous anesthetic agent for induction and maintenance of general anesthesia. It has been demonstrated to possess a range of antitumor properties and may seem to have protective effects against cancer cell dissemination and development of metastasis. This is achieved directly by regulating key cell signaling pathways implicated in tumorigenesis, such as the MAPK and NF-κB pathways [24], as well as regulating expression of miRNA and HIF-1α [24,25]. Indirectly, propofol has been shown to minimize perioperative immunosuppression by preserving NK cell and cytotoxic T cell function [26].

**Ketamine and thiopental**

Ketamine and thiopental are alternative suitable intravenous anesthetic agents indicated in emergency medicine and for patients with high intracranial pressure respectively. Both agents have exhibited immunomodulatory effects by suppressing NK cell activity and increasing tumor cell viability [27]. In particular, ketamine can upregulate anti-apoptotic proteins such as Bcl-2 enabling tumor cell proliferation and promotes production of pro-inflammatory cytokines such as IL-6 and TNFα [28,29].

**Local anesthesia**

Local anesthetics cause reversible, local inhibition of nociception, providing targeted anesthesia and analgesia. Local anesthetics have been shown to exert anti-tumor growth activity [30], although exact mechanisms are widely conflicted in studies. Possible mechanisms include their well-established inhibitory actions on voltage-gated sodium channels, which are expressed by cancer cells and correlate with tumor growth and metastatic formation [31]. Other evidence suggests these agents have protective effects on cell-mediated immunity and administration of lidocaine in particular can directly inhibit the epidermal growth factor receptor (EGFR) involved in cellular proliferation [30]. Intravenous infusions of lidocaine are a popular component of multimodal analgesia, particularly for major surgery, and therefore, are a feasible adjunct.

**Sedatives**

Common benzodiazepines, consisting of midazolam, lorazepam, and diazepam, are primarily used for preoperative sedation. The effect of benzodiazepines on tumor recurrence is disputed between studies. Early studies show that these sedatives, especially midazolam, have negative immunomodulatory effects and potentiate tumor occurrence [32]. Other studies report there is no association [33].

**Opioids**

Opioid analgesics are widely used in the perioperative period to supplement general anesthetic agents during induction and maintenance of anesthesia. Evidence from experimental studies investigating the role of opioids in tumor growth and metastasis is conflicting. Multiple animal studies have found that some opioids promote immunosuppression and in turn, tumor recurrence post-operatively, with the effects on immune function varying between the different types of opioids. In particular, morphine has largely been shown to suppress NK cell cytotoxicity and T-cell proliferation [34,35]; however, a small number of studies contradict these findings and instead propose the antitumor effects of morphine [36,37]. Likewise, fentanyl has been shown to inhibit NK cells and promote apoptosis of lymphocytes and macrophages in various laboratory studies [38,39]. Yet, a recent retrospective cohort study of 1,679 patients with stage I-III colorectal cancer showed no association between fentanyl and oncological outcomes/prognosis [40]. Alternatively, tramadol has been shown to have immune stimulatory properties by enhancing NK cell cytotoxicity [41].

There is also evidence that mu-opioid receptors (MORs) are overexpressed in certain cancers. Consequently, opioid binding at the MOR directly promotes cancer cell growth via growth-factor induced receptor signaling and potentiation of angiogenesis [42]. A study of lung samples from 34 patients with stage I-III colorectal cancer demonstrated there was a two-fold increase in MOR expression in patients with metastatic lung disease [43]. Clinical studies further support the role of MOR in cancer progression. In a retrospective study of 113 prostate cancer patients, overexpression of MOR was associated with reduced overall survival and progression-free survival, especially prominent in those with metastatic disease [44]. In keeping with these results, two randomized controlled trials have shown treatment with Methylnaltrexone (a MOR antagonist)
is associated with increased overall survival in end-stage cancer patients [45].

Overall, the role of opioids in facilitating tumor recurrence and metastasis are variable and conflicting with opioid type, dosage, and administration also influencing outcomes. Greater quality clinical evidence in the form of prospective randomized controlled trials is needed.

Pre-clinical in vitro and in vivo studies of cancer and anesthetics

The effects of anesthesia on various cancers have been extensively studied in vitro, although in vivo studies are limited in comparison. The molecular actions of anesthetic agents and lignocaine are summarized in Table 1. Understanding the underlying

Table 1. Summary of the Molecular Actions of Anesthetics Found in in vitro and in vivo Studies

<table>
<thead>
<tr>
<th>Anesthetics</th>
<th>Oncological effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevoflurane</td>
<td>Colon cancer cells:</td>
</tr>
<tr>
<td></td>
<td>Induces apoptosis</td>
</tr>
<tr>
<td></td>
<td>Inhibits proliferation and invasion as it inhibits Ras/Raf/MEK/ERK signaling pathway [46]</td>
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<tr>
<td></td>
<td>Ovarian cancer cells:</td>
</tr>
<tr>
<td></td>
<td>Inhibits migration and invasion ↓ MMP-9 and STC1 [48]</td>
</tr>
<tr>
<td></td>
<td>Inhibits proliferation via ↓ phosphorylation of JNK and p38 MAPK signaling pathways [49]</td>
</tr>
<tr>
<td></td>
<td>Potential enhanced cancer proliferation via ↑ VEGF-A, MMP-11, CXCR2, and TGF-β genes [50]</td>
</tr>
<tr>
<td></td>
<td>Cervical cancer cells:</td>
</tr>
<tr>
<td></td>
<td>Enhanced proliferation, migration, and invasion of cells via ↑ histone deacetylase 6 expression via the ERK1/2 and phosphatidylinositol 3-kinase/AKT signaling pathways [52]</td>
</tr>
<tr>
<td></td>
<td>Osteosarcoma cells:</td>
</tr>
<tr>
<td></td>
<td>Inhibits invasion and proliferation via ↓ miR-203/WNT2B/Wnt/β-catenin axis [53]</td>
</tr>
<tr>
<td></td>
<td>Leukemia cells:</td>
</tr>
<tr>
<td></td>
<td>Inhibits proliferation via ↓ Wnt/β-catenin [54]</td>
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<tr>
<td></td>
<td>Induces cognitive dysfunction via Wnt/β-catenin-Annexin A1 pathway [55]</td>
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<td></td>
<td>Lung cancer cells:</td>
</tr>
<tr>
<td></td>
<td>Promotes metastases via ↑ IL-6 [56]</td>
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<tr>
<td></td>
<td>Glioma cells:</td>
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<tr>
<td></td>
<td>Inhibits growth via ↓ MMP-2 migration and activity [57]</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>Hepatic carcinoma cells:</td>
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<tr>
<td></td>
<td>Inhibits growth via NF-κB and PI3K/Akt signaling pathways [58]</td>
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<tr>
<td></td>
<td>Glioblastoma cells:</td>
</tr>
<tr>
<td></td>
<td>Promotes tumor and migration [59]</td>
</tr>
<tr>
<td>Propofol</td>
<td>Human colon cancer cells:</td>
</tr>
<tr>
<td></td>
<td>Inhibits JAK2/STAT3 pathway</td>
</tr>
<tr>
<td></td>
<td>Inhibits proliferation, migration, and invasion [60]</td>
</tr>
<tr>
<td></td>
<td>Induces apoptosis via STAT3/HOTAIR by ↑ WIF-1 and ↓ Wnt pathway [61]</td>
</tr>
<tr>
<td></td>
<td>Adenocarcinoma alveolar basal epithelial cells:</td>
</tr>
<tr>
<td></td>
<td>Accelerates apoptosis via miR-21/PTEN/AKT pathway [62]</td>
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<tr>
<td></td>
<td>Pancreatic cancer cells:</td>
</tr>
<tr>
<td></td>
<td>Inhibits migration and induces apoptosis via miR-34a-mediated E-cadherin and LOC285194 signals [63] ↓ expression of ADAM8</td>
</tr>
<tr>
<td></td>
<td>Inhibits cell proliferation and migration via ↓ β1, ERK1/2, MMP2, and MMP9 [64]</td>
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<td></td>
<td>Human gastric cells:</td>
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<tr>
<td></td>
<td>Inhibition of EMT, migration, and invasion [65]</td>
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<td></td>
<td>Papillary thyroid cancer cells:</td>
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<tr>
<td></td>
<td>Inhibits proliferation and migration ↓ miR-320a and ↓ ANRIL ↓ Wnt/β-catenin and NF-κB [66]</td>
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<tr>
<td></td>
<td>Glioma cells:</td>
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<tr>
<td></td>
<td>Inhibits cell proliferation, invasion, and migration via mir-410-3p/TGFBR2 2 axis [67]</td>
</tr>
<tr>
<td></td>
<td>Cardia cancer cells:</td>
</tr>
<tr>
<td></td>
<td>Inhibits proliferation of cell growth</td>
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<tr>
<td></td>
<td>Induces apoptosis via inhibition of the MAPK/ERK signaling pathway [68]</td>
</tr>
</tbody>
</table>

(Continued to next page)
Sevoflurane

Literature studying the effects of volatile anesthetics on cancer proliferation, migration, apoptosis, and tumor aggression remains inconsistent. Yang et al. [46] incubated SW480 colon cells with different concentrations of sevoflurane (1.7%, 3.4% and 5.1%) for 6 h, and the results have shown sevoflurane's capacity to induce apoptosis and inhibit the proliferation and invasion of colon cancer cells by inactivating the Ras/Raf/MEK/ERK signaling pathway. However, research by Bundschzer et al. [47] had revealed sevoflurane's and desflurane's limited effect on SW480 colon cancer cells, albeit at lower concentrations of drug during incubation (1% or 2.5% sevoflurane).

Sevoflurane was also found to inhibit the viability of SKOV3 and OVCAR3 cells in a dose-dependent manner, by reducing the migration and invasion abilities of these cells. In addition, MMP-9 and stanniocalcin 1 (STC1) were also downregulated. These factors in combination have alluded to sevoflurane's involvement in inhibiting the progression of ovarian cancer (concentrations of sevoflurane ranging from 0.5% to 10%, depending on cell type) [48]. The effects of sevoflurane were corroborated in a study by Kang and Wang [49], which had also shown an inhibition of ovarian cancer proliferation (sevoflurane low concentration (1.7%), medium concentration (3.4%) and high concentration (5.1%) groups); however, this was through the repression of the phosphorylation of JNK and p38 MAPK signaling pathways. In contrast, a study that utilized higher concentrations of volatile anesthetics (sevoflurane 3.6%, isoflurane 2%, and desflurane 10.3%), but with a shorter incubation period, had revealed a significant increase in VEGF-A, MMP-11, CXCR2, and TGF-β genes, which collectively may enhance ovarian cancer proliferation [50]. Cervical cancer Caski and HeLa lines were incubated with sevoflurane (1–3%) for 2–4 h, which resulted in the proliferation, migration, and invasion of immortalized cervical cancer cells by increasing histone deacetylase 6 expression via the ERK1/2 and phosphatidylinositol 3-kinase/AKT signaling pathways [51,52].

Data from Chen et al. [53] has shown sevoflurane's inhibition of osteosarcoma cell invasion and proliferation through regulating miR-203/WNT2B/Wnt/β-catenin axis; cells were exposed to 0%, 1%, 2%, 5% and 10% sevoflurane. Further evidence of sevoflurane's involvement (0%, 2%, 4% or 8% sevoflurane) in the inhibition of Wnt/β-catenin is noted in the inhibition of leukemia cell proliferation [54], and involvement in cognitive dysfunction (3.6% sevoflurane) [55]. Furthermore, sevoflurane (0.2 mM) has been reported to promote lung metastases through the overexpression of IL-6 in pre-metastatic lung during the perioperative phase [56]. Results from Hurmath et al. [57] have highlighted that the inhibitory role of sevoflurane (2.5%), and different concentrations of thiopental, in glioma cells is dependent on regulating MMP-2 migration and activity. Another volatile anesthetic, isoflurane, has been shown to be involved in the inhibition of hepatic carcinoma aggression, as achieved through the regulation of NF-κB and PI3K/AKT signaling pathways [58], in addition to having detrimental effects in glioblastoma by promoting tumor and migration capacities (1.2% isoflurane) [59].

### Table 1. Continued

<table>
<thead>
<tr>
<th>Anesthetics</th>
<th>Cervical cancer cells:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine</td>
<td>Inhibits growth via modulation of IncRNA-MEG3/miR-421/BTG1 pathway [70]</td>
</tr>
<tr>
<td></td>
<td>Lung cancer cells:</td>
</tr>
<tr>
<td></td>
<td>Inhibits proliferation, migration, and invasion via ↓ TNFα, MMP-9 secretion, and ↓ GOLPH2 in NSCLC A549 cells [74]</td>
</tr>
<tr>
<td></td>
<td>Retinoblastoma cells:</td>
</tr>
<tr>
<td></td>
<td>Inhibits tumor growth via modulation of miR-520a-3p/EGFR axis [72]</td>
</tr>
<tr>
<td></td>
<td>Human gastric cancer cells:</td>
</tr>
<tr>
<td></td>
<td>Inhibits growth via altering MAPK pathway [73]</td>
</tr>
</tbody>
</table>

Propofol

A variety of mechanisms have been proposed to explain the role of propofol in cancer cells. Liang and Dong [60] incubated human colon cancer line SW480 with propofol (2, 4, and 8 μg/ml) and propofol with colicillin, which resulted in the inhibition of JAK2/STAT3 signaling pathway and the proliferation, migration, and invasion of human colon cancer cells. Similarly, Zhang et al. [61] incubated LOVO and SW480 cells with propofol (8 μg/ml), exerting an inhibition of cell invasion and induction of apoptosis through STAT3/HOTAIR by activation of Wnt-1 and the suppression of the Wnt pathway.

The A549 cancer line, which are adenocarcinoma alveolar basal epithelial cells, was incubated with propofol (0, 2, 5, and 10 μg/ml). Propofol demonstrated inhibition of A549 cell growth in a concentrated and time-dependent manner, by accelerating apoptosis via the miR-21/PTEN/AKT pathway [62]. Wang et al. [63] exposed pancreatic cancer PANC-1 cells to a relatively higher concentration of propofol (20 μg/ml). Consequently, propofol was seen to inhibit the migration and apoptosis induction of PANC-1 cells via miR-34a-mediated E-cadherin and LOC285194 signals.

In another study, PANC-1 cells were treated with 5 or 10 μg/ml of propofol, resulting in a reduced expression of ADAM8 and inhibition of cell proliferation and migration of PANC-1 via downregulation of β1, ERK1/2, MMP2, and MMP9 [64]. Human gastric cells, SGC-7901 and NCI-N87, were exposed to different concentrations of propofol (5, 10, 20 μM), in which inhibition of epithelial to mesenchymal transition, migration, and invasion of gastric cells were noted in a dose-dependent manner [65]. The inhibitory effects of propofol (5, 10, 20 mg/ml) on papillary thyroid cancer cells were reported, in which upregulation of miR-320a and downregulation of PTEN expression and repressed STAT3 signaling pathway and the proliferation, migration, and invasion of lung cancer cells, including the PI3K/AKT/mTOR signaling pathway [66]. This may provide us with potential clinical implications, we must be cautious in any interpretation as there are considerable discrepancies in the methodologies between studies. This can be ultimately reduced to different concentrations of propofol and varying length of incubation time.

Lidocaine

Lidocaine, a local anesthetic, has also been investigated for its role in cancer involvement. For instance, lidocaine (50, 100, 500 or 1000 μM) was shown to inhibit cervical cancer growth through the modulation of the IncRNA-MEG3/miR-421/PTG1 pathway [70]. The large-cell cancer line, 95D, was exposed to different concentrations of lidocaine (2, 5, and 10 μg/ml). In a dose-dependent manner, lidocaine demonstrated anti-tumor activity by inhibiting the PI3K/AKT/mTOR signaling pathway [71]. Lidocaine (50, 100, 500 or 1000 μM) has been shown to also inhibit the growth of retinoblastomas by modulation of the miR-520a-3p/EGFR axis [72] and human gastric cancers by alteration of the MAPK pathway [73].

Overall, current literature does indicate a possible association between anesthetics and anti-tumor properties [74]. Although this may provide us with potential clinical implications, we must be cautious in any interpretation as there are considerable discrepancies in the methodologies between studies. This can be ultimately reduced to different concentrations of anesthetic drugs and varying length of incubation time.

Retrospective studies

Numerous retrospective clinical studies have investigated the potential relationship between anesthetic technique and the outcomes of patients following oncological surgery. As surgical stress is thought to produce a pro-inflammatory response that favors tumor growth and metastasis, optimizing perioperative interventions, including anesthesia, may confer an improvement in long-term cancer outcomes. Furthermore, surgical resection in patients with solid tumors can lead to tumor cell release into the circulation [75,76].

There is a significant lack of prospective evidence regarding the putative relationship between anesthetic technique and post-operative outcomes in oncological surgery. The only such randomized controlled trial studied the efficacy of regional paravertebral anesthesia in combination with propofol-based total intravenous anesthesia (TIVA) vs. sevoflurane inhalational anesthesia plus opioid analgesia [77]. The study was conducted in thirteen countries and recruited 2,100 women due for primary breast cancer surgery. The authors found that propofol anesthesia with paravertebral block had no impact breast cancer recurrence compared...
with inhalational anesthesia and opioids (HR: 0.97, 95% CI: 0.74, 1.3; P = 0.84) [77]. As the first and potentially largest RCT of its kind, these findings are pivotal, particularly in the context of the significant amount of retrospective evidence purporting a relationship between the use of TIVA and an improvement in post-operative survival and disease recurrence compared to inhalational anesthesia.

Wigmore et al. [7] conducted the largest retrospective series of 7,030 patients over a 3-year period from one cancer center, with around half of the patients receiving TIVA with propofol and the remainder receiving volatile inhalational anesthesia.

The hazard ratio (HR) for death within the inhalational cohort compared to the TIVA cohort was 1.46 (95% CI: 1.29, 1.66; P < 0.001), after multivariable analysis of known confounders and a median follow-up of 2.6 years. Furthermore, within the inhalational cohort, 87.9% of patients survived at one year, compared to 94.1% in the TIVA cohort. The authors found that the decreased survival within the inhalational group was present regardless of American Society of Anesthesiologists grade, surgical severity, or the presence of metastases at the point of operation.

These findings are supported by similar studies. Using data from a Swedish database, a retrospective study of 2,838 patients who received surgery for colon, rectal, or breast cancer found that the survival rate for patients in the propofol group was 4.7% higher at one year and 5.6% higher at five years compared to patients receiving volatile inhalational anesthesia [78]. It is important to note that the differences in this study were not significant after adjustment for confounders. An additional retrospective observational study of 922 patients who underwent esophagectomy found the inhalational anesthesia cohort had reduced overall survival (HR: 1.58, 95% CI: 1.24, 2.01; P < 0.001) and recurrence-free survival (HR: 1.42, 95% CI: 1.12, 1.79; P = 0.003) after multivariate adjustment. Similar favorable long-term outcomes with propofol–TIVA have also been found in patients undergoing gastrectomy [79] and colectomy [80].

Overall, it seems unclear whether tumor type plays a critical role in this apparent correlation; evidence suggests that the degree of surgical stress is an important determining factor. This theory seems to be supported by a retrospective analysis of 383 patients receiving modified radical mastectomy, rather than commoner and less invasive breast-conserving procedures, which found a statistically significant decrease in cancer recurrence in the group that received propofol-based TIVA (HR: 0.550, 95% CI: 0.311, 0.973; P = 0.037) [81]. However, there was no difference in overall survival between the propofol-based TIVA group and the sevoflurane group, and the study did not directly compare the outcomes of patients receiving mastectomy compared to those having breast-conserving surgery [81].

Despite the various studies that seem to suggest improved outcomes in patients receiving TIVA, it is important to note that there is a limited amount of prospective evidence, whilst the only RCT conducted suggests no benefit in post-operative outcomes with TIVA [77]. Furthermore, other retrospective studies have also reported no benefit in overall survival in patients receiving intravenous anesthesia for breast [78,82,83], lung [84], and colorectal surgery [78].

With regards to regional anesthesia, early, predominantly retrospective studies suggest that the use of regional anesthesia is associated with an improvement in overall and disease-free survival for colorectal, prostate, breast, ovarian, and head and neck malignancies [85–88]. Furthermore, a randomized trial of 177 patients with colorectal cancer demonstrated a benefit associated with epidural analgesia, but this was limited to 1–5 years post-operatively [89]. A randomized study of 132 patients with cancer of abdominal organs treated with abdominal surgery receiving epidural analgesia showed a non-statistically significant improvement in recurrence-free survival, although the study was clinically underpowered [90]. Although the precise reasons for this benefit remain to be elucidated, it has been postulated it may be due to the avoidance of opioids, which have previously been shown to potentiate tumor cell survival and angiogenesis [7,91].

Despite this, post-hoc analyses of previous clinical studies, as well as randomized trials, suggest that there is limited benefit associated with regional anesthesia in the context of oncological surgery. Reanalysis of the MASTER trial is the first and largest post-hoc analysis of nearly 500 patients who had abdominal malignancy who were randomized to general anesthesia or epidural anesthesia. The study demonstrated no significant impact of epidural anesthesia on the recurrence of cancer [92]. Additionally a recent large multi-country randomized controlled trial investigating the impact of regional anesthesia–analgesia (paravertebral blocks and propofol) or general anesthesia (sevoflurane) and opioid analgesia on local or metastatic breast cancer recurrence in 2,132 women found no difference between the two groups (HR for regional anesthesia: 0.97, 95% CI: 0.74, 1.28; P = 0.84) [77].

In conclusion, studies investigating the relationship between regional anesthesia, cancer recurrence, and overall survival have yielded mixed results, with many studies suggesting no benefit [85,86]. The results of clinical studies investigating propofol-based TIVA versus inhalational anesthesia are summarized in Table 2. However, the heterogeneous, non-randomized, retrospective natures of the majority of these studies are key limiting factors.
As discussed previously, evidence regarding the effects of various anesthetic techniques on surgical outcomes in patients with cancer is almost exclusively from observational, retrospective studies. The single RCT that has been conducted suggests regional anesthesia is unlikely to impact recurrence after breast cancer surgery; other tumor types may show a difference based on anesthetic technique [77]. Furthermore, an interesting new pre-clinical development suggests that peri-operative systemically administered lidocaine decreases pulmonary metastases when combined with inhalational anesthesia, thus potentially heralding a new avenue for clinical trial development [93]

There are a several large, randomized controlled trials investigating the effect of inhalational anesthetic agents vs. propofol on cancer recurrence following surgery. Results from these trials are eagerly awaited and will be highly informative in providing high quality evidence to answer and provide greater certainty as to the impact of anesthetic choice on cancer recurrence (NCT01975064 [94], NCT02660411 [95], NCT03034096 [96], ACTRN12617001065381 [97], NCT02660411 [98]).

**Ongoing clinical trials**

As discussed previously, evidence regarding the effects of various anesthetic techniques on surgical outcomes in patients with cancer is almost exclusively from observational, retrospective studies. The single RCT that has been conducted suggests regional anesthesia is unlikely to impact recurrence after breast cancer surgery; other tumor types may show a difference based on anesthetic technique [77]. Furthermore, an interesting new pre-clinical development suggests that peri-operative systemically administered lidocaine decreases pulmonary metastases when combined with inhalational anesthesia, thus potentially heralding a new avenue for clinical trial development [93].

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**Implications and conclusions**

There is an increasing body of evidence investigating the impact of anesthesia and anesthetic techniques on cancer recurrence and survival in cancer patients. The impact of regional anesthesia vs. general anesthesia on cancer recurrence is also uncertain, with conflicting results from retrospective studies and small clinical trials. A recent large multi-country randomized controlled trial failed to show a benefit of regional anesthesia on either local or metastatic recurrence of breast cancer following surgery [77]. Further studies are required across a greater range of cancer types and more diverse patient populations to definitively prove any

---

### Table 2. Summary of the Clinical Studies Evaluating Relative Benefit of Propofol-based TIVA vs. Inhalational Anesthesia on Cancer Recurrence and Overall Survival

<table>
<thead>
<tr>
<th>Study type</th>
<th>Anesthesia</th>
<th>Cancer type</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized controlled trial [77]</td>
<td>Inhalational anesthesia plus opioids vs. propofol-based TIVA</td>
<td>Breast</td>
<td>Propofol-based TIVA had no impact on breast cancer recurrence compared with inhalational anesthesia and opioids: HR 0.97 (95% CI: 0.74, 1.3; P = 0.84)</td>
</tr>
<tr>
<td>Retrospective analysis [7]</td>
<td>Inhalational anesthesia vs. propofol-based TIVA</td>
<td>Solid organ</td>
<td>Inhalational anesthesia associated with greater HR of death: HR 1.46 (95% CI 1.29, 1.66; P &lt; 0.001)</td>
</tr>
<tr>
<td>Retrospective analysis [78]</td>
<td>Inhalational anesthesia vs. propofol-based TIVA</td>
<td>Breast, colorectal</td>
<td>Differences in overall one- and five-year survival rates for all three sites combined were 4.7% (P = 0.004) and 5.6% (P &lt; 0.001), respectively, in favor of propofol.</td>
</tr>
<tr>
<td>Retrospective analysis [79]</td>
<td>Inhalational anesthesia vs. propofol-based TIVA</td>
<td>Gastric</td>
<td>TIVA was associated with a HR of 0.67 (95% CI: 0.58, 0.77) for death in univariate analysis and 0.65 (95% CI: 0.56, 0.75) after a multivariate analysis of known confounders in the matched group.</td>
</tr>
<tr>
<td>Retrospective analysis [80]</td>
<td>Inhalational anesthesia vs. propofol-based TIVA</td>
<td>Colon</td>
<td>(HR: 0.22, 95% CI: 0.11, 0.42; P &lt; 0.001) or higher tumor-node-metastasis stage (HR: 0.42, 95% CI: 0.32, 0.55; P &lt; 0.001) and presence of metastases (HR: 0.67, 95% CI: 0.51, 0.86; P = 0.002) or absence of metastases (HR: 0.08, 95% CI: 0.01, 0.62; P = 0.016)</td>
</tr>
<tr>
<td>Retrospective analysis [81]</td>
<td>Inhalational anesthesia vs. propofol-based TIVA</td>
<td>Breast</td>
<td>Propofol group showed a lower rate of cancer recurrence (P = 0.037), with an estimated HR of 0.550 (95% CI: 0.311, 0.973).</td>
</tr>
<tr>
<td>Retrospective analysis [82]</td>
<td>Inhalational anesthesia vs. propofol-based TIVA</td>
<td>Breast</td>
<td>No association found using Cox regression analyses and propensity matching.</td>
</tr>
<tr>
<td>Retrospective analysis [83]</td>
<td>Inhalational anesthesia vs. propofol-based TIVA</td>
<td>Breast</td>
<td>Kaplan-Meier survival curves showed no significant difference in recurrence-free or overall survival between the two groups.</td>
</tr>
<tr>
<td>Retrospective analysis [84]</td>
<td>Inhalational anesthesia vs. propofol-based TIVA</td>
<td>Lung</td>
<td>No significant difference in HR for recurrence (P = 0.233) or HR for death (P = 0.551) between the two groups.</td>
</tr>
</tbody>
</table>

TIVA: total intravenous anesthesia, HR: hazard ratio.
The majority of evidence thus far suggests a benefit of the use of intravenous propofol over inhalational volatile anesthetics such as sevoflurane. This evidence is mainly pre-clinical and retrospective in nature. A recent meta-analysis that examined the effect of propofol vs. volatile anesthesia on cancer recurrence and survival found the use of propofol-based TIVA was associated with improved recurrence-free survival in all cancer types (pooled HR: 0.78, 95% CI: 0.65, 0.94; P < 0.01) and improved overall survival (pooled HR: 0.76, 95% CI: 0.63, 0.92; P < 0.01) [99]. Although this provides support that propofol is superior to volatile anesthesia in reducing cancer recurrence, the meta-analysis has several limitations. Notably nine of the ten studies included were observational studies, and heterogeneity in studies included in terms of study population, the stages of cancer and differences in use of regional anesthesia. Therefore, the results of four large randomized controlled trials investigating this question will be eagerly anticipated and will provide more definitive results as to whether propofol is superior to volatile anesthesia.

The perioperative period is characterized by physiological changes induced by surgery and perioperative interventions. These biological changes associated with the surgical inflammatory response, and the pharmacological actions of anesthetic drugs, may promote the recurrence of cancer in postoperative cancer patients. This highlights an opportunity to intervene to counteract any potentially cancer-promoting effects. Anesthesia, anesthetic technique, and other strategies such as the use of anti-adrenergic, anti-inflammatory, and anti-thrombotic therapies (which haven’t been discussed in this review) offer the potential to promote recurrence-free survival of postoperative cancer patients [6,100].

Conflicts of Interest

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

Author Contributions

Azeem Alam (Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Supervision; Writing – original draft; Writing – review & editing)
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Introduction

Maintenance of stable vital signs is crucial during surgery. In this context, anesthesiologists typically attempt to select an appropriate fluid type and administer the necessary amount to the patient. The quantification disposition of fluids administered to the body facilitates an efficient fluid administration. This process is similar to that used to describe the pharmacokinetics of intravenous drugs. Pharmacokinetic parameters can be estimated by measuring the concentration of a drug. However, it is almost impossible to directly measure the concentration of fluids. Therefore, in volume kinetics, the disposition of fluids is indirectly quantified by measuring the hemoglobin concentration under the premise of no hemoglobin loss. If the hemoglobin concentration is repeatedly measured while administering the fluids, the dilution (relative change of the plasma volume) for each corresponding hemoglobin concentration can be obtained. The dilution is based on the concept of plasma volume expansion. The method of quantifying the drugs disposition with compartmental analysis has been equally applied to volume kinetics. The transfer of fluids between compartments is explained by first-order kinetics, and it is assumed that fluid is only removed from the central compartment. Population analysis can be used to identify covariates that can account for inter-individual variability in volume kinetic parameters. Body weight and mean blood pressure are well-known representative covariates of kinetic volume parameters. Using volume kinetic parameters, the volume expansion effects of crystalloid and colloid solutions can be understood more effectively, thereby facilitating appropriate fluid therapy. Although limitations exist in volume kinetics, its implications are important for clinicians when administering fluids.

Keywords: Body fluids; Colloids; Crystalloid solutions; Hemoglobins; Pharmacokinetics; Statistical models.
Pharmacokinetic principles for understanding volume kinetics

Because general anesthesia is performed using various hypnotics and analgesics, anesthetic pharmacology can be considered as a basic subject for anesthesiologists. The basis for understanding pharmacology is the pharmacokinetic equation. The pharmacokinetic equation quantitatively evaluates drug transfer in the body and can be easily induced based on a few principles. In mammillary compartmental models, the kinetics of drug transfer between compartments were initially determined. Subsequently, linear differential equations were constructed based on kinetics. The Laplace transforms of these differential equations can be used to derive functions to calculate drug amounts in the central or peripheral compartments. In addition, the inverse Laplace transforms of these functions are used to obtain the pharmacokinetic equations in the time domain.

Kinetics of drugs

Pharmacokinetics is typically referred to as the ADME of a drug, which is acronym for absorption, distribution, metabolism, and excretion. Metabolism and excretion are known as elimination, and distribution and elimination are known as disposition. Kinetics refers to the process by which drugs are transferred to the body. Depending on the type of kinetics involved during absorption, distribution, and elimination, the differential equation describing the change in drug amount in the pharmacokinetic compartment varies, as well as the pharmacokinetic equation derived from it. Drug kinetics can be categorized into zero- and first-order kinetics. Zero-order kinetics are described when a fixed amount of a drug is consistently eliminated per time unit. Suppose that 100 mg of a drug exists in the body of an individual, and this drug follows the zero-order kinetics but its amount reduces by 10 mg per hour. Therefore, 90 mg of the drug will remain in the body of the individual after 1 h, 80 mg after 2 h, and 70 mg after 3 h (Fig. 1A). Conversely, if the drug is introduced, then the sign will be positive. For instance, assume that 100 mg of a drug exists in the body of an individual, and 20% of the drug is lost per hour. After 1 h, 80 (= 100 − 100 × 0.2) mg of the drug will remain in the body, 64 (= 80 − 80 × 0.2) mg after 2 h, and 51.2 (= 64 − 64 × 0.2) mg after 3 h. This can be illustrated by an exponential curve, as shown in Fig. 1B. A mathematical understanding of the exponential decrease in first-order kinetics is important. The loss of drugs following first-order kinetics can be expressed as a differential equation as follows:

\[
\frac{dX(t)}{dt} = -kX(t) \quad \text{(Equation 1)}
\]

Applying the Laplace transform to this equation yields

\[
sX(s) - X(0) = -kX(s)
\]

\[
X(s) = \frac{X(0)}{s + k} \quad \text{(Equation 2)}
\]

The inverse Laplace transformation of this equation yields a drug amount function over time, as follows:

\[
X(t) = X_0 - kt
\]

\[
X(t) = X_0 e^{-kt}
\]

Fig. 1. Zero-order (A) and first-order (B) kinetics. X: amount of drug, t: time in h, X_0 = 100 mg, k: elimination rate constant (mg/h for zero-order kinetics and 1/h for first-order kinetics).
where \( e^{-kt} \) refers to the fraction of the initial amount \( X(0) \) of the drug remaining in the body after the drug was removed by first-order kinetics during time \( t \), and has a value between 0 and 1. Additionally, the disposition of fluids in the body can be explained by first-order kinetics.

**Mammillary compartmental model**

Compartmental analysis is an analysis method that partitions the body into several compartments and quantifies the transfer of drugs between compartments. Among the compartmental models, the mammillary model is primarily used to estimate the pharmacokinetic parameters of drugs. In the mammillary compartmental model, the central compartment is related to all other peripheral compartments, but no relationship exists among the latter. In addition, it is assumed that the transfer of drugs between the central and peripheral compartments is based on first-order kinetics. Furthermore, it is assumed that the drug is only removed from the central compartment. For example, a two-compartment mammillary pharmacokinetic model can be expressed as shown in Fig. 2. The differential equation for the change in drug amount by compartment is as follows:

\[
\frac{dA_i}{dt} = A_i(t) k_{i2} - A_i(t) (k_{10} + k_{12})
\]

\[
\frac{dA_2}{dt} = A_1(t) k_{12} - A_2(t) k_{21} \quad \text{(Equation 4)}
\]

These differential equations are used in the same structural model to estimate the volume kinetic parameters. In Fig. 2, the pharmacokinetic parameters are expressed in the micro-rate constant domain \((V_i, k_{10}, k_{12}, k_{21})\). However, they can be expressed in terms of volume and clearance domain \((V_i, \text{volume of distribution in the central compartment}; V_j, \text{volume of distribution in the peripheral compartment}; Cl, \text{metabolic clearance}; \text{Q, inter-compartmental clearance})\). The relationship between the two domains can be described as follows:

\[
Cl = V_i \times k_{10} \quad Q = V_i \times k_{12} = V_2 \times k_{21} \quad \text{(Equation 5)}
\]

In other words, if the pharmacokinetic parameters of one domain are estimated from the time-concentration curve, they can be converted to those of the other domain.

**Population analysis**

It is typically observed that different effects are exhibited in different individuals, even when the same weight-based dose was administered. This is owing to variabilities in pharmacokinetics and pharmacodynamics from one person to another. These variabilities may be due to a person's specific characteristics (covariates). For example, these variabilities can occur because of weight, height, age, sex, race, and genetic variations. Population analysis is a method that can explain the inter-individual variability in pharmacokinetics and pharmacodynamics by mathematically connecting patient-specific covariates for each pharmacokinetic and pharmacodynamic parameter [2]. Unlike the standard two-stage method, which analyzes individual time–concentration curves separately, all individuals are analyzed at once to identify the characteristics that can be associated with the pharmacokinetic and pharmacodynamic parameters. Several software programs can be used to perform population analysis; however, the first and most representative is nonlinear mixed-effects modeling (NONMEM), created by Lewis B. Sheiner (physician) and Stuart L. Beal (statistician) of the University of San Francisco [3]. NONMEM is also the name of a standard software (ICON Development Solutions, Ireland) for population analysis. Fig. 3 shows the basic concept of population pharmacokinetic and pharmacodynamic analyses using NONMEM. In the mixed-effects model, a pharmacokinetic parameter is estimated by dividing mixed-effects by a fixed-effect parameter that does not change from person to person \((\theta \text{ in NONMEM})\) and a random-effect parameter between individuals \((\eta \text{ in NONMEM})\). Herein, the random-effect parameter between subjects describes the random inter-individual variability of the pharmacokinetic parameters. This random variability between
individuals exhibits a normal distribution with a mean of 0 and a variance of $\omega^2$, and it is a biologically natural phenomenon. In the population analysis, the part that can be explained by the patient's characteristics (covariate) among the random inter-individual variability of the pharmacokinetic parameter is mathematically linked to the fixed-effect parameter. This is the essence of population analysis. Hence, the control stream of NONMEM is written as follows, using $V_1$ (volume of distribution in the central compartment) as an example.

$$TV_1 = \text{THETA}(1)$$
$$V_1 = TV_1 \times \text{EXP(ETA}(1)))$$

where TV1 is a representative value of $V_1$ (typical value, a typical human or population average value with zero variation between random individuals), and in this case, THETA(1). ETA(1) is the random effect parameter between individuals in $V_1$. In other words, THETA(1) is connected by an exponential function with ETA(1). Additionally, they can be connected by multiplication or addition, and the one that best describes the data will be selected. Suppose that part of ETA(1) is described by the patient's weight; in this case, the NONMEM control stream can be changed as follows:

$$TV_1 = \text{THETA}(1) + \text{THETA}(2) \times \text{WT}$$
$$\text{WT} = \text{weight}$$

When a pharmacokinetic model involving the equation above is incorporated into the target-controlled infusion system, the dose can vary based on weight [4,5]. Previously, in the field of volume kinetics, parameters were primarily estimated using MATLAB (Mathworks, Inc., USA), but population analysis has been primarily used since 2016 [6–9].

Calculation of plasma volume expansion caused by fluid administration using hemoglobin

If blood volume is defined as the volume of hemoglobin distribution, then hemoglobin can be used as an endogenous tracer to analyze the volume expansion of a fluid space. In this regard, the following two assumptions should be applied: (i) no loss of red blood cells; (ii) the hemoglobin concentration decreases as the plasma volume expands. Dr. Robert G. Hahn introduced a new method to calculate plasma volume expansion using hemoglobin in 1997 [1], and the effectiveness of this method was confirmed in clinical trials participated by healthy volunteers [10,11]. The plasma volume ($V_p$) at any time t after the start of intravenous infusion can be expressed as follows, based on the hematocrit (Hct).

$$V_p(t) = V_b(t) \times (1 - Hct(t)) \text{ (Equation 6)}$$

where $V_b(t)$ is the blood volume at any time t. Assuming that the volume of erythrocytes is constant during the observation time, then the volume of erythrocytes at $t = 0$ before intravenous infusion is equivalent to the volume of erythrocytes at any time t after intravenous infusion.

$$Hct(0) \times V_e(0) = Hct(t) \times V_e(t) \text{ (Equation 7)}$$

However, if bleeding occurs, Equation 7 does not hold. In other words, the amount of hemoglobin at $t = 0$ before intravenous infusion and the amount of hemoglobin at any time t after intravenous infusion will be the same. The hemoglobin level is calculated by multiplying the hemoglobin concentration and blood volume as follows:
Using Equations 6 and 8, the following equation can be derived.

\[
V_p(t) = \frac{C_r h(0) \times V_r(0)}{C_r h(t)} = \frac{C_r h(0) \times V_r(0)}{C_r h(t) \times (1 - Hct(t))} \quad \text{(Equation 9)}
\]

If the amount of administered fluid is set as \(A_p\), then \(A_p(t)\), during an intravenous infusion can be described as follows:

\[
A_p(t) = V_p(t) - V_p(0) \quad \text{(Equation 10)}
\]

The relative change in the plasma volume induced by fluid infusion can be expressed as shown in Equation 11.

\[
D_p(t) = \frac{A_p(t)}{V_p(0)} \quad \text{(Equation 11)}
\]

where \(D_p\) is dimensionless and is referred to as plasma dilution. Substituting Equation (10) into Equation 11 yields

\[
D_p(t) = \frac{V_p(t) - V_p(0)}{V_p(0)} \quad \text{(Equation 12)}
\]

The longer the administration of the fluid, the greater are \(V_p(t)\) and \(D_p(t)\), and this is equivalent to an increase in plasma volume due to the fluid administered. Substituting Equation (6) into Equation 12 yields

\[
D_p(t) = \frac{V_p(t) \times (1 - Hct(t)) - V_p(0)}{V_p(0)} \quad \text{(Equation 13)}
\]

Substituting Equation 9 into Equation 13 yields

\[
D_p(t) = \frac{\frac{C_r h(0) \times V_r(0)}{C_r h(t)} \times (1 - Hct(t)) - V_r(0)}{V_r(0)} = \frac{\frac{C_r h(0) \times (1 - Hct(t))}{C_r h(t)}}{\frac{C_r h(0)}{C_r h(t)}} - 1 \quad \text{(Equation 14)}
\]

Combining Equations 7 and 8 yield the following:

\[
Hct(t) = \frac{Hct(0) \times V_r(0)}{C_r h(0) \times V_r(0)} = \frac{Hct(0) \times C_r h(t)}{C_r h(0)} \quad \text{(Equation 15)}
\]

Substituting Equation 15 into Equation 14 yields

\[
D_p(t) = \frac{C_r h(0) \times \left(1 - \frac{Hct(0) \times C_r h(t)}{C_r h(0)}\right)}{C_r h(t) \times (1 - Hct(0))} - 1
\]

If the hemoglobin concentration is repeatedly measured while administering the fluids, the degree of plasma volume dilution for each corresponding hemoglobin concentration can be obtained (Fig. 4). The degree of plasma volume dilution is the same as that of plasma volume expansion.

**Structure model for volume kinetics**

In volume kinetics, a mammillary compartment model is used to quantify fluid disposition. Table 1 shows a comparison of the similarities and differences between traditional pharmacokinetic and volume kinetic expressions.

**One-volume model**

The one-compartment model is suitable for quantifying the disposition of fluids that are predominantly distributed in blood vessels, such as colloids [12,13]. When the last hemoglobin measurement time is insufficient to capture the elimination phase, then crystalloids can be explained using the one-volume model. A schematic diagram of the one-volume model is shown in Fig. 5. Based on this figure, the differential equation in the one-volume model can be described as follows:

\[
\frac{d}{dt} \left(\frac{V_r(t) - V_r(0)}{V_r(0)}\right) = k_1 - k_2 - k_e \times \left(\frac{V_r(t) - V_r(0)}{V_r(0)}\right) \quad \text{(Equation 17)}
\]

In this study, basal elimination (\(k_e\)) was not estimated and was set as a fixed value. In general, \(k_e\) is 0.5–1.5 ml/min in adults [14]. Robert G. Hahn often set it to 0.8 or 1.0 ml/min for modeling [10,11]. If the data are fitted to the model, then the estimated value of renal clearance (\(k_2\)) will exceed 100 ml/min; therefore, even if \(k_e\) is fixed to a specific value in the range of 0.5–1.5 ml/min, the
Changes in hemoglobin (A) and plasma dilution (B) caused by fluid administration. Male volunteer received 40 ml/kg Ringer’s lactate solution over 1 h. Dilution was calculated as follows:

\[
D_p(t) = \frac{C_{\text{Hb}}(0) - t}{1 - Hct(0)},
\]

where \(C_{\text{Hb}}(0)\) and \(Hct(0)\) are the hemoglobin concentration and hematocrit measured prior to the administration of Ringer’s lactate solution, respectively; \(C_{\text{Hb}}(t)\) is the hemoglobin concentration measured at any time \(t\).

### Table 1. Basic Similarities and Differences between Traditional Pharmacokinetic and Volume Kinetic Expressions

<table>
<thead>
<tr>
<th>Administration substance</th>
<th>Observation</th>
<th>Pharmacokinetics</th>
<th>Volume kinetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug, mg</td>
<td>Concentration (mg/ml)</td>
<td>Fluid, ml</td>
<td>Dilution (no unit)</td>
</tr>
</tbody>
</table>

\[
\frac{dA}{dt} = k_i - k_b - k_r \times D_p(t)
\]

\[
\frac{dX}{dt} = \text{Rate} - k_{so} \times A(t)
\]

**Parameters**

- One-compartment: \(V_p, Cl\)
- Two-compartment: \(V_p, V_s, Cl, Q\)
- Clearance: \(Cl\)

\(D_p(t)\): plasma dilution at any time \(t\) during intravenous infusion, \(C_{\text{Hb}}(0)\): hemoglobin concentration at \(t = 0\) before intravenous infusion (g/dl), \(C_{\text{Hb}}(t)\): hemoglobin concentration at any time \(t\) after intravenous infusion (g/dl), \(Hct(0)\): hematocrit at \(t = 0\) before intravenous infusion, \(V_p(0)\): plasma volume at \(t = 0\) before intravenous infusion (ml), \(V_p(t)\): plasma volume at any time \(t\) after intravenous infusion (ml), Rate: infusion rate of the drug (mg/min), \(k_{so}\): elimination rate constant (1/min), \(A(t)\): drug amount at any time \(t\) (mg), \(V_p\): volume of distribution in the central compartment (ml), \(Cl\): clearance (ml/min), \(V_s\): volume of distribution in the peripheral compartment (ml), \(Q\): inter-compartmental clearance (ml/min), \(k_i\): infusion rate of fluid (ml/min), \(k_b\): basal elimination reflecting ongoing losses of water due to respiration, sweating, and basal renal filtration (ml/min), \(k_r\): renal clearance (ml/min), \(k_d\): distributional clearance (ml/min).

The actual estimated value will not be affected significantly.

### Two-volume model

The two-volume model is widely used in volume kinetics, and it can be used to effectively explain the plasma dilution-time data observed when crystalloids are administered [6,15]. A schematic diagram of the structural two-volume model is shown in Fig. 6. Based on this figure, the differential equation for the two-volume model can be written as follows:

\[
k_i \quad V_p(0)\]

\[
k_b \quad k_r \quad \frac{V_p(t) - V_p(0)}{V_p(0)}\]

\[
k_d \quad k_r \quad V_s\]

Fig. 5. One-volume model. \(k_i\): infusion rate of the fluid (ml/min), \(k_b\): basal elimination reflecting ongoing losses of water due to respiration, sweating, and basal renal filtration (ml/min), \(k_r\): renal clearance (ml/min), \(V_p(t)\): plasma volume at any time \(t\) after intravenous infusion (ml).
Byung-Moon Choi · Volume kinetics

\[
\frac{d(V_1(t) - V_r(0))}{dt} = k_i - k_b \times \left( \frac{V_1(t) - V_r(0)}{V_1(0)} \right) - k_r \times \left( \frac{V_1(t) - V_r(0)}{V_r(0)} \right) + k_r \times \left( \frac{V_2(t) - V_r(0)}{V_r(0)} \right)
\]

(Equation 18)

In pharmacokinetics, the transfer of drugs between the central and peripheral compartments is classified into \(k_{12}\) and \(k_{21}\); however, in volume kinetics, it is estimated as \(k_b\). This can be understood by recalling that the observed value in volume kinetics is the plasma dilution measured based on the hemoglobin concentration. Because hemoglobin exists only in blood vessels, it cannot move to the peripheral compartment, and it may be impossible to estimate the rate at which fluid propagates from the peripheral compartment to the central compartment or is cleared through the lymphatic system. In addition, owing to the nature of crystalloids, the rate of transfer between the central and peripheral compartments will not differ significantly. Moreover, it is beneficial to reduce the number of parameters to be estimated to ensure model stability (parsimonious). In some studies, \(k_{12}\) and \(k_{21}\) were estimated separately using the two-volume model [6–9]. The objective function value of a model can be reduced significantly by distinguishing the two parameters; however, this often causes model instability. Considering these characteristics of volume kinetics, it is almost impossible to explain the plasma dilution-time data of crystalloids using a three-volume model. The NONMEM control streams for one- and two-volume models are presented in the Appendix 1.

Calculation of renal clearance using urine volume

The fluid administered was primarily removed by renal clearance (\(k_r\)). Because renal clearance is proportional to the plasma volume expansion, the following differential equation can be established:

\[
\frac{dU(t)}{dt} = k_r \times D_p(t) + k_b \quad \text{(Equation 19)}
\]

where \(U(t)\) is the urine volume at time \(t\). If the total urine volume \((U_{TOT})\) is known during the entire observation time \(T\), then \(k_b\) and \(k_r\) can be calculated as follows:

\[
\int_0^T \frac{dU(t)}{dt} dt = U_{TOT} = k_b \int_0^T D_p(t) dt + k_r \int_0^T \cdot \text{AUC}(D_p) + k_b \cdot T
\]

(Equation 20)

As previously mentioned, \(k_b\) is typically 0.5–1.5 ml/min in adults [14]. Herein, \(k_r \cdot \text{AUC}(D_p)\) refers to the urine volume produced by intravenous infusion, and \(k_b \cdot T\) the urine volume induced by basal elimination. However, in reality, renal clearance is controlled by a complex mechanism that involves various hormones such as antidiuretic hormone, renin-angiotensin, atriopeptin, aldosterone, and angiotensin II [14]. Moreover, specific cell receptors are involved, including baroreceptors and osmoreceptors that regulate salt and water homeostasis [14]. Renal clearance can be obtained via two methods. The first is an estimation method from the structural model of volume kinetics, and the second is a calculation method based on the area under the time-dilution curve for the central compartment divided by the observed total urinary output [15]. The more accurate method is yet to be determined. However, it is reasonable to estimate \(k_r\) from the same dataset with other volume kinetic parameters.

Covariates describing inter-individual variabilities of volume kinetic parameters

In pharmacokinetics, the inter-individual variability in the distribution volume is well explained by body weight, and the clearance is primarily explained by body weight or age [5,16,17]. Similar results have been reported in previous studies pertaining to the volume kinetics (Table 2). Body weight is a significant covariate for the distribution volume in the central compartment [7,15]; furthermore, it is physiologically reasonable that the greater the weight, the larger is the plasma volume. Renal clearance deteriorates with age [7], i.e., a natural aging process. An interesting fact is that the mean blood pressure is a significant covariate in renal clearance [7,15]. A positive correlation exists between mean blood pressure and renal clearance; this implies that the lower the mean blood pressure is clinically, the more severe is fluid retention in
the body. This can be observed more clearly when simulated using a volume kinetics model [15]. The simulated volume expansion of the central and peripheral compartments in a hypothetical patient who was administered 10 ml/kg of Ringer’s lactate solution over 15 min followed by a rate of 8 ml/kg/h for 165 min is presented in Fig. 7. In patients of the same weight, it was observed that the lower the average blood pressure, the greater was the fluid retention in the interstitium. In clinical practice, fluid is generally administered in consideration of body weight, but relatively rarely in consideration of mean blood pressure. When blood pressure decreases, more fluids are typically administered. In this case, if the blood pressure does not recover as expected, the fluids administered will continue to accumulate in the interstitium.

**Clinical application of volume kinetics**

Understanding volume kinetics enables the distribution of fluids administered to the body to be described quantitatively. In a recent study, 12 male volunteers were randomly assigned to four groups, and each group received four fluid solutions in specified sequences, separated by 1-week intervals to avoid any carryover effects [13]. The volunteers received 1,000 ml of 6% tetrastarch (hydroxyethyl starch, HES 130/0.4; VOLULYTE, Fresenius Kabi AG, Germany), 1,000 ml of 10% pentastarch (HES 250/0.45; PENTASPN, Jeil Pharmaceutical CO., Ltd., Korea), 40 ml/kg of Ringer’s lactate solution (JW Pharmaceutical Co., Ltd., Korea), and 20 ml/kg of 5% dextrose water (JW Pharmaceutical Co., Ltd., Korea) for 60 min. Changes in plasma dilution induced by the administration of crystalloids and colloids were described effectively using two- and one-volume models, respectively [13]. Volume expansion effects can be easily understood by performing simulations based on the fluid dynamics parameters of these crystalloids and colloids (Fig. 8) [13]. When the same volume was administered, the volume expansion effects of colloids were approximately four times higher than those of crystalloids by the time when the infusion was terminated. This can be interpreted as a validation of volume kinetics, in that a suggested theory (a crystalloid solution should have 1/4th the volume-expanding capacity of the colloid solution [18]) was proven through a scientific method. In addition, in the case of Ringer’s lactate solution, the simulation results show that only approximately 20% of the administered volume was present in the blood vessel at the end of the fluid administration, whereas approximately 70% propagated to the interstitium. Some studies indicated results that differed slightly from the simulation results [9,19,20]. However, the abovementioned approach may be beneficial in maintaining euvolemia to maintain stable hemodynamics during general anesthesia. The concentration and molecular weight of HES affect the volume expansion effect [21].

In the simulation study, 10% pentastarch demonstrated a long-lasting volume expansion compared with 6% tetrastarch [13]. This is because the renal clearance of 6% tetrastarch was greater than that of 10% pentastarch. Similarly, a previous study showed that 6% HES indicated a greater renal clearance than 10% HES solution [22]. As such, using volume kinetics enables the effect of volume expansion between HESs to be compared indirect-

---

**Table 2. Representative Covariates Reflecting Inter-individual Variabilities of Volume Kinetic Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Covariate</th>
<th>Correlation between parameter and covariate</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_1$</td>
<td>Body weight</td>
<td>Positive</td>
<td>[7,15]</td>
</tr>
<tr>
<td>$k_r$</td>
<td>MAP</td>
<td>Positive</td>
<td>[7,15]</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>Negative</td>
<td>[7]</td>
</tr>
</tbody>
</table>

$V_1$: volume of distribution in central compartment (ml), $k_r$: renal clearance (ml/min), MAP: mean arterial pressure.
by without directly measuring the plasma volume.

**Limitations of fluid kinetics**

Although fluid kinetics is a favorable methodology for quantifying the disposition of fluids, it has some limitations. First, it cannot explain the hemoconcentration observed in clinical practice. Hemoconcentration can be observed in patients undergoing restrictive fluid management [15]. This is because fluid is administered at the minimum amount required, and the urine output is relatively high. When hemoconcentration occurs, the value of plasma dilution is negative (Fig. 9A) [15]. The structural model of volume kinetics evaluates the volume expansion induced by fluid administration compared with the baseline, and the reduction from the initial volume is structurally unpredictable [15]. Therefore, even for the observed value with a negative dilution, the model will predict a positive value (Fig. 9B) [15]. Second, it fails to account for the transfer of fluids through the lymphatic system in the interstitium. As mentioned earlier, because the increase in plasma volume due to the administration of fluids is indirectly quantified by measuring the hemoglobin concentration, the transfer of fluids in the interstitium without hemoglobin cannot be structurally explained. Hence, it is difficult to estimate the elimination clearance ($k_{e}$) removed from the peripheral compartment without passing through the central compartment. In this regard, a previous study that explained the disposition of Ringer’s lactate solution based on a three-volume model is difficult to understand [23].

**Conclusion**

Volume kinetics is an effective method for quantitatively explaining the distribution and elimination of fluids administered to the body. The quantification of the disposition of drugs via compartmental analysis was applied to volume kinetics. The transfer of fluids between compartments was explained via first-order kinetics, and it was assumed that fluid was removed only in the central compartment. Volume expansion induced by the administration of fluids was indirectly evaluated by measuring the decrease in hemoglobin concentration. Using the volume kinetic parameters, the volume expansion effects of crystalloid and colloid solutions can be understood more effectively, thereby facilitating fluid therapy. Dr. Hahn’s research team has been conducting extensive
research pertaining to volume kinetics. Nonetheless, further research can be pursued. Owing to the limitations of the structural model of fluid kinetics, it cannot reflect the clinical situation of all patients. However, even if the current method is used, it can provide reasonably meaningful implications to clinicians when administering fluids. Researchers should consider the patient group, type of infusion solution to be selected, and type of covariate to be added to achieve clinical significance. It is hoped that this review will facilitate research pertaining to volume kinetics.

Acknowledgements

I am deeply grateful to Dr. Robert G. Hahn for pioneering the quantification of the disposition of crystalloid and colloid solutions using a methodology known as volume kinetics. This work was supported by the Korea Medical Device Development Fund grant funded by the Korea government (the Ministry of Science and ICT, the Ministry of Trade, Industry and Energy, the Ministry of Health & Welfare, the Ministry of Food and Drug Safety) (Project Number: KMDF_PR_20200901_0031, 202011B25-01).

Conflicts of Interest

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

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Appendix 1. NONMEM control streams of one- and two-volume kinetic models.

< One-volume model >

$PROB RUN# 100 (One-volume kinetic model)
$INPUT ID OID TIME DUR RATE AMT DV MDV EVENT HB HCT SEX AGE WT HT BSA LBM IBW BMI CO CI SVV SV SVI HR SBP DBP MBP
; DV (dilution, unitless) = (BHB/HB-1)/(1-BHCT) = (expandable plasma volume - baseline plasma volume)/(baseline plasma volume) = (V(t) - BV)/BV
$DATA 05_06_NONMEM_data_OID_ID25.csv IGNORE = #
$SUBROUTINE ADV AN13 TRANS = 1 TOL = 6
$MODEL COMP (VOLUME)
$PK
    TH1 = THETA(1)
    TH2 = THETA(2)
    TH3 = THETA(3)

    KB = TH1 ; basal elimination rate (ml/min, 0.8 at Anesthesiology 1997; 87: 204-12)
    KR = TH2 ; renal clearance (ml/min)
    V0 = TH3 ; baseline plasma volume (ml)

    KB = TH1*EXP(ETA(1))
    KR = TH2*EXP(ETA(2))
    V0 = TH3*EXP(ETA(3))

$DES
    DADT(1) = RATE - KB - KR*(A(1)/V0)
    ; A: volume expansion (V(t) - V0); V(t) and V0 mean plasma volume at any time and at baseline, respectively.

$ERROR
    A1 = A(1)
    TA = A1/V0

    IPRED = TA
    W = 1
    IRES = DV - IPRED
    IWRES = IRES / W
    Y = IPRED + W * EPS(1)

$THETA ; #2
    0.8 FIX ; KB
    (0 200) ; KR
    (0, 3000) ; V0

$OMEGA ; #2
    0 FIX ; IIV_KB
    0.3 ; IIV_KR
<Two-volume model>

$PROB RUN# 200 (Two-volume kinetic model)

$INPUT ID OID TIME DUR RATE AMT DV MDV EVENT HB HCT SEX AGE WT BSA LBM IBW BMI CO CI SVV SV SVI HR SBP DBP MBP

; DV (dilution, unitless) = (BHB/HB-1)/(1-BHCT) = (expandable plasma volume - baseline plasma volume)/(baseline plasma volume) = (V(t) - BV)/BV

$DATA 05_06_NONMEM_data_OID_ID25.csv IGNORE = #

$SUBROUTINE ADV AN13 TRANS = 1 TOL = 6

$MODEL COMP (VOLUME1) COMP (VOLUME2)

$PK

TH1 = THETA(1)
TH2 = THETA(2)
TH3 = THETA(3)
TH4 = THETA(4)
TH5 = THETA(5)

KB = TH1; basal elimination rate (ml/min, 0.8 at Anesthesiology 1997; 87: 204-12)
KR = TH2; renal clearance (ml/min)
VC0 = TH3; baseline plasma volume (ml)
VT0 = TH4; baseline interstitial volume (ml)
KT = TH5; distributional clearance (ml/min)

KB = TH1*EXP(ETA(1))
KR = TH2*EXP(ETA(2))
VC0 = TH3*EXP(ETA(3))
VT0 = TH4*EXP(ETA(4))
KT = TH5*EXP(ETA(5))

$DES

DADT(1) = RATE - KB - KR*(A(1)/VC0) - KT*(A(1)/VC0) + KT*(A(2)/VT0)
DADT(2) = KT*(A(1)/VC0) - KT*(A(2)/VT0)

; A1: plasma volume expansion at central compartment (VC(t) - VC0); VC(t) and VC0 mean plasma volume at any time and at baseline, respectively.
; A2: interstitial volume expansion at tissue compartment (VT(t) - VT0); VT(t) and VT0 mean interstitial volume at any time and at baseline tissue compartment, respectively.

$ERROR

A1 = A(1)
A2 = A(2)
TA = A1/VC0
TB = A2/VT0

IPRED = TA
W = 1
IRES = DV - IPRED
IWRES = IRES / W
Y = IPRED + W * EPS(1)

$\theta$ ; #4
0.8 FIX ; KB
(0, 100) ; KR
(0, 2000) ; VC0
(0, 3000) ; VT0
(0, 100) ; KT

$\omega$ ; #4
0 FIX ; IIV_KB
0.2 ; IIV_KR
0.2 ; IIV_VC0
0.2 ; IIV_VT0
0.2 ; IIV_KT

$\sigma$ ; #1
0.01

$\text{ESTIMATION NOTBT NOOBT NOSBT MAXEVA}=9999 \text{ SIGL}=6 \text{ NSIG}=2 \text{ PRINT}=5 \text{ METHOD}=1 \text{ INTER NOABORT MSFO}=200.0 \text{ MSF COVAR OPTION E}$
A comparison of the breathing apparatus deadspace associated with a supraglottic airway and endotracheal tube using volumetric capnography in young children

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Background: Supraglottic airway (SGA) devices including the air-Q® are being used with increasing frequency for anesthesia in infants and younger pediatric patients. To date, there is minimal research documenting the potentially significant airway deadspace these devices may contribute to the ventilation circuit when compared to an endotracheal tube (ETT). The aim of this study was to evaluate the airway apparatus deadspace associated with an air-Q® versus an ETT in young children.

Methods: In a prospective cohort study, 59 patients between 3 months and 6 years of age, weighing between 5 and 20 kg, scheduled for outpatient urologic or general surgery procedures were recruited. An air-Q® or ETT was inserted at the discretion of the attending anesthesiologist, and tidal volume, positive end expiratory pressure, respiratory rate, and end-tidal CO₂ were controlled according to protocol. Airway deadspace was recorded using volumetric capnography every 2 min for 10 min.

Results: Groups were similar in demographics. There was a significant difference in weight-adjusted deadspace volume between the air-Q® and ETT groups, 4.1 ± 0.8 ml/kg versus 3.0 ± 0.7 ml/kg, respectively (P < 0.001). Weight-adjusted deadspace volume (ml/kg) increased significantly with decreasing weight for both the air-Q® and ETT groups.

Conclusions: In healthy children undergoing positive pressure ventilation for elective surgery, the air-Q® SGA introduces significantly greater airway deadspace than an ETT. Additionally, airway deadspace, and minute ventilation required to maintain normocarbia, appear to increase with decreasing patient weight irrespective of whether a SGA or ETT is used.

Keywords: Airway management; Capnography; Child; General anesthesia; Laryngeal mask airway; Positive pressure respiration; Ventilation.

Introduction

Supraglottic airway (SGA) devices including the air-Q® (Cookgas, USA) are being...
used with increasing frequency for elective anesthesia in infants and younger pediatric patients [1,2]. Although SGAs are presumed to contribute greater deadspace volume to the ventilation circuit when compared to endotracheal tubes (ETT), there has been minimal research that quantifies that difference. This information is relevant in very young patients breathing spontaneously through these devices, who may be unable to generate sufficient tidal volumes to compensate for this added deadspace over time, and in those undergoing positive pressure ventilation who may require increasing levels of support to maintain adequate levels of ventilation [3,4].

Volumetric capnography is a technique that can be used to accurately evaluate airway deadspace by monitoring the concentration of exhaled carbon dioxide (CO$_2$) over the course of a respiratory cycle [5]. Exhaled CO$_2$ is plotted against exhaled volume, and from the resulting waveforms, alveolar partial pressure of carbon dioxide (PaCO$_2$) and mean exhaled partial pressure of carbon dioxide can be calculated and used to determine airway deadspace [6]. Compared to prior methods that require use of a Douglas bag or calorimetry, volumetric capnography is faster, less cumbersome, and more easily applied clinically [7]. With this technology, it is thus possible to measure the apparatus and airway deadspace noninvasively and in real time.

The primary aim of this study was to compare the magnitude of the airway and apparatus deadspace associated with the use of an ETT or air-Q® SGA using volumetric capnography in young children undergoing general anesthesia and surgery. Additionally, our primary hypothesis was that airway and apparatus deadspace, normalized by weight, is significantly higher in young infants and children when using an air-Q® SGA when compared to the airway and apparatus deadspace associated with an ETT. Our null hypothesis was that there is no difference in deadspace volume between devices.

**Materials and Methods**

**Patient selection**

This study was approved by the Institutional Review Board at the Wake Forest University Health Sciences (IRB00055260) and was registered on ClinicalTrials.gov prior to beginning recruitment (NCT03785977; 12/24/2018; PI-Templeton TW). Written informed consent from a parent/legal guardian was obtained for participation in this study. This manuscript adheres to the applicable Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) guidelines. Further, this clinical study was performed in accordance with Ethical Principles for Medical Research involving Human Subjects, outlined in the Helsinki Declaration of 1975 (revised 2013).

Pediatric patients between the ages of 3 months and 6 years, weighing between 5 and 20 kg, and scheduled for outpatient urologic or general surgery procedures, were identified for participation in the preoperative holding area. All procedures were performed in the pediatric operating room at Brenner Children’s Hospital, Wake Forest Baptist Medical Center from March 2019 to August 2019. Exclusion criteria included: patients with a history of difficult airway/intubation (defined as greater than two attempts at intubation or having required any unanticipated or secondary intubating technique other than direct or elective video laryngoscopy in the past) or those suspected to have a difficult airway; morbid obesity (body mass index > 39 kg/m$^2$); history of prematurity; asthma or second-hand smoke exposure; patients with upper respiratory infection symptoms such as nasal drainage, cough, or fever within 7 days of the date of surgery; American Society of Anesthesiologists physical status ≥ 3; and emergency case status. The attending anesthesiologist responsible for the care of the patient was consulted to ensure the patient met none of the aforementioned exclusion criteria, and that the chosen airway management strategy was consistent with deficits in the respective size groups to avoid over-recruiting for a given group. Neither the patient care team nor the research team was blinded to the study group.

**Intraoperative management**

Patients were taken to the operating room, where standard monitors were applied, including pulse oximetry, electrocardiogram, blood pressure, temperature, capnography, and end-tidal gas analysis. Induction of anesthesia was carried out with sevoflurane in oxygen or oxygen/nitrous oxide. Intravenous access was obtained. Each patient was administered a standardized relaxant dose of 0.7 mg/kg rocuronium. Airway management and selection of airway device were at the discretion of the patient’s clinical care team and had been determined prior to consent for participation.

In the case of patients who received an ETT, the airway was secured and the patient was subsequently placed on the anesthesia ventilator (Avance CS2®, GE Healthcare, USA) using pressure control ventilation to deliver a tidal volume of 10 ml/kg at a rate of 20 breaths/min. Positive end-expiratory pressure (PEEP) was set to 5 cmH$_2$O. The ventilator rate was adjusted as necessary to maintain end-tidal carbon dioxide (ETCO$_2$) in the range of 38 to 45 mmHg, and the inspiratory pressure was adjusted to maintain tidal volume of 10 ml/kg. Cuffed ETT size was determined using
the Duracher formula (ETT internal diameter = Age in years / 4 + 3.5) [8]. Absence of leak around the ETT was confirmed with auscultation. ETT cuff pressure was not measured.

For the SGA device arm of the study, an air-Q® Masked Laryngeal Airway device was used, and a similar procedure was followed. Initial device size was determined according to the manufacturer’s recommendations based on weight. Following placement of the air-Q® the presence of an adequate airway seal, defined as a sealing pressure > 16 cmH₂O, was checked by manually increasing the airway pressure and noting the pressure at which a leak was audible. The patient was then placed on the anesthesia ventilator in pressure control mode with initial settings of inspiratory pressure of 17 cmH₂O with PEEP of 5 cmH₂O and a rate of 20 breaths/min. As in the ETT group, the inspiratory pressure was then adjusted to maintain a tidal volume of 10 ml/kg, and the respiratory rate (RR) was adjusted to maintain ETCO₂ in the range of 38 to 45 mmHg. Additionally, the leak fraction (defined as the ratio of exhaled tidal volume [Vₑ] to inspired tidal volume) was observed. A ratio of < 0.9 was considered to be excessive and the patient was either excluded or had the air-Q® exchanged for the next size up and these parameters were reassessed. The rate was then adjusted as necessary to maintain ETCO₂ in a similar range to the ETT group.

Following ETT or air-Q® placement a disposable optical detector attached to the Respironics NM3® monitor (Philips North America, USA) was then inserted into the anesthesia circuit for all patients, in between the airway device and the circuit Y-piece. The time at which the detector was inserted was considered time zero. After 2 min, the Vₑ, inspiratory pressure, PEEP, RR, and oxygen saturation were recorded from the standard anesthesia monitor, and the airway deadspace (VDaw, the sum of anatomic and device deadspace), ETCO₂, volume of carbon dioxide (VCO₂), airway resistance (Rₑ), and dynamic compliance (Cₑ) were recorded from the NM3 monitor. This was repeated at 2 min intervals for 10 min. All measurements were recorded at each time point.

Following the fifth measurement in each patient, the disposable optical detector was removed from the anesthesia circuit and care was deferred to the clinical team caring for the patient. At this time the patient’s participation in the study was considered to be complete. Any adverse events associated with ongoing management of the case as well as any events at the time of emergence were recorded.

Statistical analysis

Initial pilot data in 10 patients (five ETT and five air-Q®) revealed that the airway and apparatus deadspace associated with an ETT was 3.2 ml/kg compared to a volume of 5.1 ml/kg associated with the air-Q® with a standard deviation of 1.9 ml. Using this information, sample size calculations were created; this revealed that with a power of 90% and an alpha of 0.05, a minimal sample size of 20 patients per group would provide the ability to detect at least a difference of 2 ml/kg in the primary outcome of airway deadspace between groups. Further, a priori, we decided to recruit 10 patients for each of the three weight ranges (5.0–9.9 kg, 10.0–14.9 kg, and 15.0–20.0 kg) to obtain a more evenly distributed sample across a range of weights for both the ETT tube and the air-Q® group. Thus, the study aimed for 60 total subjects (30 ETT and 30 air-Q®). This would also allow for a possible attrition and still maintain an adequate sample size.

Outcome measurements were recorded every 2 min for 10 min total, and the five data points were averaged for analysis. Descriptive statistics, including medians and interquartile ranges for demographic data not normally distributed and means and standard deviation for continuous measures and frequencies and proportions for categorical data, were calculated. Mann-Whitney test for non-parametric data, independent t-tests for normally-distributed continuous measures, and Fisher’s Exact Tests for categorical variables were used to test for differences between the two device groups. Spearman correlation coefficients were used to assess the strength of association between continuous variables. Analysis of variance (ANOVA) regression models were created to analyze the relationship between outcome measures and independent predictors which included weight, device, and device size. P values < 0.05 were assumed to be significant. SAS (version 9.4, USA) was used for all analyses.

Results

A total of 70 patients were approached for the study (Fig. 1). Sixty-two patients were consented for participation. Two patients were excluded after consent and did not participate in the study: one patient’s weight range had already been filled, and another patient was excluded because the surgeon requested the team caring for the patient not to use muscle relaxant for the case. A total of 60 patients were enrolled, 30 in each group. One patient from the air-Q® group was excluded from analysis due to incomplete data as a result of monitor malfunction. All patients had leak fractions greater than 0.9 except one who had a SGA initially; the device was exchanged for an ETT and this patient was secondarily assigned to the ETT group. Demographics for both device groups are summarized in Table 1. There were no significant differences between groups. No significantly morbid events were noted in any patient during the entire surgical or anesthetic epoch up to and
including discharge from the post anesthesia care unit.

There was no statistically significant difference between the air-Q® and ETT groups in V̇e, ETCO2, or total minute ventilation although minute ventilation in the air-Q® group did trend higher. These results are summarized in Table 2. There was a significant difference in weight-adjusted deadspace volume (the sum of airway deadspace and device deadspace) between the air-Q® and ETT 4.1 ± 0.8 ml/kg versus 3.0 ± 0.7 ml/kg, respectively (P < 0.001). Weight-adjusted deadspace volume (ml/kg) increased significantly with decreasing weight for both the air-Q® and ETT groups (Fig. 2).

Weight-adjusted deadspace volume varied more significantly from one size of ETT to another (P < 0.001) but did not vary with weight for each specific size. Conversely, for the air-Q® group, weight-adjusted deadspace volume did not vary significantly between sizes (P = 0.07), but retained an inverse relationship with weight for each specific size. This is summarized in Fig. 3.

### Discussion

The primary finding of this study is that use of an air-Q® SGA is associated with significantly more apparatus and anatomic deadspace when compared to an ETT. Further, while this difference is intuitive, the actual magnitude of weight-adjusted deadspace, especially in very young children, exceeds reasonable expectations of tidal volume during spontaneous ventilation in young children undergoing anesthesia [3]. Additionally, this deadspace will have to be compensated for when selecting mechanical ventilator settings to maintain CO2 homeostasis calling into question the wisdom of smaller tidal volume, lung protective ventilation strategies in very young children even in some cases when an ETT is present. While some might argue that although the result is statistically significant, the overall difference in deadspace/kg between the devices is less clinically significant. In assessing this though it is important to note that the difference enclosed by the 95% CI may actually be significantly higher, especi-
cially in very young children. These findings are clinically important because they may inform airway device selection for a given patient, as well as guide the clinician’s approach to determining the length of time they allow a patient to breathe spontaneously through a SGA.

Overall, there were no adverse events in our study group, and mild hypercarbia is generally well tolerated in healthy children, but for select patients increased airway deadspace may be clinically relevant. For example, children with pulmonary hypertension or certain types of congenital heart disease may deteriorate with hypercapnia and respiratory acidosis [9]. In these more fragile populations, the clinician may want to use an ETT instead of a SGA and/or the clinician may simply need to compensate with more aggressive mechanical ventilation or reduce periods of spontaneous ventilation [3].

Another interesting finding was that the weight-adjusted deadspace increases with decreasing patient size for both devices—not just the air-Q®. The inverse variation of weight-adjusted deadspace with both devices highlights the fact that, just because smaller devices are available for pediatric patients, non-linear scaling in physiologic processes and anatomy in smaller patients may require additional compensation strategies that may not at first glance be apparent. This is consistent with prior work in which the in vitro device volumes of several SGA devices were measured, including those for the air-Q® [10]. When the air-Q® device volume is normalized to the manufacturer’s recommended

<table>
<thead>
<tr>
<th></th>
<th>air-Q® (n = 29)</th>
<th>ETT (n = 30)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ETCO₂ (mmHg)</td>
<td>41.6 ± 5.0</td>
<td>41.2 ± 4.6</td>
<td>0.75</td>
</tr>
<tr>
<td>VCO₂ (ml/min)</td>
<td>64.6 ± 18.1</td>
<td>63.4 ± 22.9</td>
<td>0.82</td>
</tr>
<tr>
<td>Vₜ (ml)</td>
<td>116.8 ± 35.4</td>
<td>117.5 ± 40.6</td>
<td>0.95</td>
</tr>
<tr>
<td>Vₜ by weight (ml/kg)</td>
<td>9.3 ± 1.0</td>
<td>9.5 ± 1.7</td>
<td>0.61</td>
</tr>
<tr>
<td>Mean deadspace difference (ml)</td>
<td>15.0 (11.5, 18.5)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Mean deadspace by weight difference (ml/kg)</td>
<td>1.1 (0.7, 1.5)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Minute ventilation by weight difference (ml/kg/min)</td>
<td>8.5 (~11.6, 28.4)</td>
<td>0.40</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or mean difference (95% CI). ETT: endotracheal tube, ETCO₂: end-tidal CO₂, VCO₂: volume of carbon dioxide, Vₜ: exhaled tidal volume.

Fig. 2. Weight-adjusted deadspace volume (WADSV) for each device versus patient weight. Best-fit model (R² = 0.930) is WADSV = 0.0164 w² – 0.597 w + 1.172 d + 7.604 where: w is the child’s weight; d is the airway device: equals 0 for endotracheal tube (ETT), 1 for air-Q®.
weight ranges, per kilogram device volume increases with decreasing device size: 0.66–1.17 ml/kg for air-Q® 2.0, 0.84–2.0 ml/kg for air-Q® 1.5, 1.4–2.5 ml/kg for air-Q® 1.0, and up to 3.3 ml/kg for air-Q® 0.5.

Another interesting finding of our study is that there appears to be a significant difference in the in vivo weight-adjusted deadspace from one size ETT to another, but not from one size air-Q® to another. This is likely related to a combination of two factors. First, there is a greater increase in apparatus volume as air-Q® size increases (up to 51%) as compared to ETTs (up to 25%) for the sizes used in the study. Second, a greater fraction of anatomic deadspace is inherent when using a SGA as compared to an ETT that excludes anatomic deadspace above the cuff. Practically speaking then, up- or down-sizing an ETT may make a significant difference in deadspace for a specific patient, but less so for a SGA that sometimes are up sized because of an inadequate sealing pressure.

Finally, it is important to note that despite significantly larger total deadspace in the air-Q® group, there was no statistically significant difference in ETCO_2, V_{aw}, and minute ventilation between groups as one would expect. While the study was not necessarily powered to detect a difference in these parameters, one would expect to see a difference in ETCO_2 if the minute ventilation is the same with a larger proportion of the minute ventilation being from deadspace ventilation. As additional apparatus deadspace is introduced into the circuit, a smaller percentage of the delivered tidal volume ventilates the alveoli, and exhaled CO_2-saturated gas is diluted by inhaled volume that did not exchange gas. In these cases, an increase in deadspace may actually lead to an increase in the A-a gradient. Over time, increasing PaCO_2 will lead to an increase in ETCO_2 despite the increased deadspace. However, ETCO_2 due to the increased A-a gradient, may remain an underestimate of PaCO_2, in proportion to the deadspace. It is likely that in our study, a measurement of PaCO_2 in all children would have shown that the higher deadspace air-Q® group had higher PaCO_2 values, and thus they were relatively hypoventilated, compared to the ETT group, despite similar ETCO_2 between the groups. This also raises the possibility that during patient care a similar situation arises, whereby the clinician using a large deadspace airway device derives a false sense of security from a ‘normal’ ETCO_2, when the patient is actually hypoventilated and hypercarbic. This may be of particular importance in smaller children in which the ratio of deadspace to tidal volumes is larger and therefore the gradient may be larger leading to a greater relative underestimate of ventilation adequacy using minute ventilation and ETCO_2.

The results of this study are consistent with the work of Chhibber et al. [11,12] who compared the ETCO_2 and arteriolar carbon dioxide (PaCO_2) levels in infants and children undergoing ventilation with an LMA Classic® or ETT using a crossover design. In both studies, the authors found that patients had higher ETCO_2 and PaCO_2 values, as well as an increased ETCO_2-PaCO_2 difference with the LMA versus an ETT using similar ventilator settings. The disproportionate effects of apparatus deadspace on smaller children have also been alluded to in prior studies by Kwon [13] and Chau et al. [14] who measured increased levels of ETCO_2 when adding heat and moisture exchanger to the ventila-

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**Fig. 3.** Boxplot of weight-adjusted deadspace volume (WADSV) for endotracheal tube (ETT) and air-Q® as a function of device size. Box upper and lower borders denote 75th and 25th percentile values, respectively, and enclosed line denotes median value. Whiskers denote range. Note significant difference in WADSV when comparing sizes for ETT. WADSV for air-Q® follows a similar trend but is not statistically significant.
tion circuit under similar ventilator settings. Finally, in a mathematical modeling study, Pearsall and Feldman [15] derived equations to evaluate \( \text{PaCO}_2 \) and RR as a function of weight and deadspace. They found that the relationship between both \( \text{PaCO}_2 \) as well as minute ventilation as a function of apparatus deadspace is exponential, and stressed the importance of patient weight since the ratio of deadspace volume to tidal volume \( (V_d/V_t)\) increases more rapidly for smaller patients as deadspace increases.

This study has several limitations. First, the sample size is small and the study was not powered to evaluate differences in secondary outcomes including minute ventilation, so while there was a trend toward increased minute ventilation to maintain similar \( 
\text{ETCO}_2 \) in the air-Q® group, it was not found to be statistically significant. Second, these results apply strictly to the air-Q® SGA, and while we suspect other SGAs will add varying amounts of deadspace based on their different designs, we did not specifically evaluate other devices and further study is warranted in that regard [10]. Additionally, group selection was determined prior to enrollment in the study according to the preference of the attending anesthesiologist assigned to a given case, not randomized. This may be a source of selection bias, although both groups had similar baseline demographics with similar underlying patient characteristics.

In healthy children undergoing positive pressure ventilation for elective surgery, the air-Q® SGA introduces significantly greater airway deadspace than an ETT. Additionally, airway deadspace, and minute ventilation required to maintain normocarbia, appear to increase with decreasing patient weight irrespective of whether a SGA or ETT is used. More study is necessary to evaluate the ventilation consequences of these differences in even younger patients and whether these differences will persist with other SGA devices.

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**Conflicts of Interest**

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

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2. Drake-Brockman TF, Ramgolam A, Zhang G, Hall GL, von Ungern-Sternberg BS. The effect of endotracheal tubes versus la-


Comparison between two different concentrations of a fixed dose of ropivacaine in interscalene brachial plexus block for pain management after arthroscopic shoulder surgery: a randomized clinical trial

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Background: Only a few studies have evaluated the differences between varying concentrations of a fixed dose of local anesthetics. This study was conducted to compare the effects of two different concentrations of a fixed dose of ropivacaine used in ultrasound-guided interscalene brachial plexus block.

Methods: This prospective, randomized, double-blind study included 62 patients who underwent arthroscopic surgery under general anesthesia. The patients were randomly assigned to receive ultrasound-guided interscalene block with 75 mg of ropivacaine at one of two concentrations: 0.75% (10 ml; Group C) or 0.375% (20 ml; Group V). Time to onset of sensory blockade, degree of blockade, pulmonary function changes, analgesic duration of the interscalene block, postoperative opioid requirement within 24 h, postoperative pain scores, satisfaction, and incidence of complications were recorded.

Results: Although the time to onset of sensory blockade was shorter for Group C (P = 0.015), successful blockade was achieved at 30 min after the interscalene block in both groups. The analgesic duration of the interscalene block was not significantly different between the groups. The amount of opioid used within 24 h after surgery was significantly reduced for Group V compared with Group C (P = 0.016). The rest of the parameters did not show any significant differences between the two groups.

Conclusions: Compared with 10 ml of 0.75% ropivacaine, interscalene block with 20 ml of 0.375% ropivacaine could be effective for the reduction of postoperative opioid requirement within 24 h after surgery despite it might not prolong the analgesic duration.

Keywords: Brachial plexus; Pain management; Patient-controlled analgesia; Postoperative pain; Shoulder pain; Ultrasonography.

Introduction

Shoulder arthroscopy is a common orthopedic procedure that presents substantial postoperative pain control challenges to the surgeon and the anesthesiologist [1]. Interscalene brachial plexus block (ISB) has been shown effective and is accepted because of its postoperative analgesic and opioid-sparing effects. ISB is therefore central to multi-
modal postoperative analgesic strategies for these patients [2,3].

Continuous ISB with a catheter insertion may extend the benefits described above. However, routine use of catheters for less invasive shoulder surgeries is impractical and unrealistic and may not be possible in all cases because of the lack of expertise and logistics. In addition, there are risks of catheter dislodgement and infection [3–5]. When single-shot ISB is used, the block duration can be an important indicator of clinical efficacy. The duration of ultrasound (US)-guided ISB is reported to be related to the volume and concentration of the local anesthetic (LA) [6]. However, only a few studies have evaluated the differences between varying concentrations of a fixed dose of LA [7,8].

Accordingly, this study was conducted to compare two different concentrations of a fixed dose of ropivacaine when US-guided ISB was performed for pain control after arthroscopic shoulder surgery. This study compared 20 ml of 0.375% ropivacaine, recommended by Fredrickson et al. [9], with 10 ml of 0.75% ropivacaine. It was hypothesized that 75 mg of ropivacaine provided in two different concentration-volume ratios for US-guided ISB would produce different effects for the analgesic duration of ISB.

Materials and Methods

After Institutional Review Board approval (IRB No. DAUHIRB-19-012, Approved 2019-01-23), this prospective, randomized, double-blind study was registered in cris.nih.go.kr (KCT0003785) on April 15, 2019, prior to patient recruitment. This clinical research was done following the ethical principles for medical research involving human subjects in accordance with the Helsinki Declaration 2013. All patients signed a written consent form before their participation in the study that was conducted from April 18, 2019, to April 23, 2020. Patients aged 18–70 years (American Society of Anesthesiologists physical status of I, II, or III) who were scheduled to undergo arthroscopic shoulder surgery under general anesthesia and had agreed to receive an ISB were enrolled. The exclusion criteria were infection at the ISB site, chronic opioid dependence, morbid obesity (body mass index > 35 kg/m²), pre-existing neurological deficit, chronic obstructive pulmonary disease, coagulopathy, allergy to ropivacaine, uncontrolled diabetes mellitus and/or psychosis, pregnancy or lactation, and refusal to participate. A computer-generated sequence of random numbers and a sealed envelope technique were used to randomize the patients to receive ISB with a fixed dose but different concentrations of ropivacaine as follows: 10 ml of 0.75% ropivacaine (Group C) or 20 ml of 0.375% ropivacaine (Group V).

Intravenous routes were secured for the patients in each ward. Routine monitors (electrocardiogram, non-invasive blood pressure measurement, and pulse oximetry) were attached on arrival of the patient in the operating room. A bedside baseline spirometry was performed for all patients. For bedside spirometry, the patient was placed upright at an angle of 45° on a hospital stretcher, and a Micro handheld spirometer with a disposable mouthpiece (CareFusion, USA) was used. The patient was informed about the procedure, and the forced expiratory volume in one second (FEV₁) and forced vital capacity (FVC) were measured three times; the highest measurement was recorded. All measurements were reassessed 30 min after the ISB to record any changes.

Subsequently, the patient was placed in the lateral decubitus position with the operative shoulder nondependent and the neck extended to facilitate probe positioning. The skin was prepped in a typical sterile fashion, and US-guided ISB was performed using the CX50 device (Philips Ultrasound; USA) with a 12–13 MHz, 38-mm linear array transducer (L12-3; Philips). Transverse scanning was performed at the level of the interscalene groove, with the long axis of the probe parallel to the clavicle. The transducer was then moved slightly caudally until the brachial plexus roots were identified. Following confirmation of the transducer’s position, 2% lidocaine was injected into the skin to achieve a wheal. Then, a 25-gauge (G), 1.5-inch beveled needle was inserted into the lateral side of the transducer and entered using a lateral-to-medial, in-plane technique. The target position of the needle was the posterior space between the C5 and C6 roots. The position of the needle was confirmed, and 10 ml of 0.75% ropivacaine or 20 ml of 0.375% ropivacaine was slowly injected with intermittent aspiration. When intraneural injection was suspected because of strong resistance during injection or a complaint of paresthesia or pain by the patient, the injection was stopped and the needle was withdrawn and redirected. All ISBs were performed under US guidance alone by a single expert anesthesiologist with experience in the performance of ≥ 200 blocks.

Block assessment

Neural blockade was evaluated by a clinician who was blinded to the volume and concentration of the injected ropivacaine. Sensory blockade and motor blockade were checked every 3 min for up to 30 min after ISB. Sensory blockade was tested via pinpricks on the C4 (top of the shoulder), C5 (deltoid area), C6 (first fingertip), C7 (middle fingertip), and C8 (little fingertip) dermatomes. The sensory blockade was evaluated using a 3-point verbal rating scale, in which 2, 1, and 0 indicated normal sensation, dull sensation, and absence of sensation, respectively. Motor blockade was evaluated by shoulder abduction (deltoid sign) and forearm flexion, using the modified Bromage scale as follows; 4: full power, 3:
red had the ability to lift the arm against resistance, 2: able to move the muscle group against gravity but unable to lift the arm against resistance, 1: perceptible muscle contraction, but unable to move on purpose, and 0: unable to move the relevant muscle group.

The onset time for a sensory block was defined as the time that elapsed between the end of the ISB procedure and the moment when the pinprick test of the deltoid area yielded a score of 0. Successful blockade was defined as an adequate motor blockade with a score of ≤ 2 for shoulder abduction and the absence of sensation with pinpricks of the deltoid area. Block failure was considered if shoulder abduction was possible after 30 min or if the pinpricks were felt in the deltoid area; these patients were excluded from the study.

Perioperative period

General anesthesia was induced according to the standardized protocol that included intravenous administration of propofol 2–2.5 mg/kg and fentanyl 1 μg/kg with rocuronium 0.6 mg/kg. Anesthesia was maintained with sevoflurane, and the bispectral index was monitored and maintained between 40 and 60. The patient was maintained in a sitting position during surgery. For a hypotensive bradycardic event, defined as intraoperative bradycardia (sitting heart rate [HR] decrease within 5 min by > 30 beats/min compared to the baseline HR, or a decrease to < 50 beats/min at any time) and/or hypotension (sitting systolic blood pressure decrease within 5 min by ≥ 30 mmHg compared to the baseline pressure, or a decrease to < 90 mmHg at any time), phenylephrine or ephedrine was used by the anesthesiologist, who was blinded to which solution had been injected for ISB. At the end of surgery, remnant neuromuscular blockade was reversed with sugammadex 1–4 mg/kg following confirmation of the patient’s train-of-four.

Upon extubation, the patient was transferred to the post-anesthesia care unit (PACU). Once the patient was stable and oriented after emergence in the PACU, and a modified Aldrete scale score of > 9 was confirmed, a blinded observer confirmed the pain intensity, measured using the numeric rating scale (NRS; 0 = no pain, 10 = worst possible pain), and the occurrence of Horner syndrome, hoarseness, respiratory distress, postoperative nausea and vomiting (PONV), pneumothorax, dizziness, or paresthesia. After the patient left the PACU, the pain score (at 1, 2, 3, 6, 12, and 24 h) and satisfaction score associated with pain control (at 24 h; 0–100) were recorded via a predefined questionnaire. Any complications that occurred within 24 h were also recorded.

After surgery, all patients received ibuprofen (400 mg every 8 h) and acetaminophen (1,000 mg every 8 h) intravenously. Intravenous patient-controlled analgesia (IVPCA) was prepared at a total volume of 100 ml by adding fentanyl 20 μg/kg and ramosetron 0.6 mg to normal saline. The baseline infusion rate, bolus demand dose, and lock-out time were 1 ml/h, 1 ml, and 10 min, respectively. The IVPCA was initially clamped and first used when the patient complained of pain with an NRS score of ≥ 4; the time of IVPCA initiation was recorded. The analgesic duration of the ISB was defined as the time between the end of LA injection for the ISB and the postoperative initiation of IVPCA. At 24 h after surgery, the remaining IVPCA volume was assessed, and the fentanyl dosage used until that time was calculated; this marked the end of the study.

Sample size estimation

The primary outcome was the ISB analgesic duration. A pilot study (n = 10) revealed that the analgesic duration after US-guided ISB with 10 ml of 0.75% ropivacaine in patients who underwent arthroscopic shoulder surgery had a mean ± SD of 10 ± 3.8 h. It was hypothesized that a higher volume would result in prolonged analgesic duration of the ISB, and a 20% of time difference was considered clinically important. Considering a type I error of 0.05 and a type 2 error of 0.2, 28 patients were considered necessary for each group. Estimating a 10% dropout rate, 31 patients were recruited for each group.

Statistical analysis

Data were presented as mean ± SD, median (Q1, Q3), or numbers of patients (%). Quantitative variables were analyzed using the Student’s t test or Mann–Whitney U test, and qualitative variables with the chi-square test or Fisher’s exact test. The time to the first infusion of IVPCA was analyzed by Kaplan–Meier survival analysis with a comparison between groups using the log-rank test. Survival time was defined as the time from the end of the ISB to the first infusion of IVPCA. All data were analyzed using SPSS® software, version 26.0 (SPSS, Inc., USA). Survival curves were plotted using Prism 7.0 for Windows (GraphPad Software, Inc., USA). P < 0.05 was considered statistically significant.

Results

Out of 72 patients assessed for eligibility, seven patients did not meet the inclusion criteria and three patients declined to participate. Sixty-two patients participated in the study; the CONSORT flowchart is shown in Fig. 1. There were no significant between-group differences in the demographic and operative data (Table 1).
The onset of sensory blockade was faster in Group C (8.0 ± 2.9 min) compared with Group V (10.0 ± 3.1 min) (P = 0.015). Successful blockade was achieved at 30 min after ISB in all patients. There were no differences between the groups in sensory blockade or motor blockade 30 min after ISB (Table 2). Pulmonary function change assessed by FEV\(_1\) and FVC did not differ between the groups (Table 3).

There was no significant difference between the groups for the number of patients who did not require IVPCA analgesia within 24 h after surgery (Fig. 2). The ISB analgesic duration was not significantly different between the groups (Group C: 12.1 ± 5.4 h vs. Group V: 13.7 ± 4.7 h; P = 0.214). The total amount of fentanyl used within 24 h after surgery was significantly reduced for Group V (248.3 ± 112.2 μg) compared with Group C (331.3 ± 149.9 μg) (P = 0.016). Group V exhibited a reduction in the cumulative dose of the baseline infusion and the bolus demand for fentanyl within 24 h (Table 3).

The postoperative pain scores at each time point did not differ between the groups (Table 4). There were no differences between the groups for the incidence of complications or the satisfaction score associated with pain control for 24 h (Table 3).

**Discussion**

To our knowledge, this is the first study to compare the use of two different concentrations of a fixed dose of ropivacaine (75 mg) for US-guided ISB. The results showed no difference in pulmonary function change between the two groups, while the onset of sensory blockade was faster in Group C. There was no difference in analgesic duration of the ISB between the two groups. However, postoperative opioid requirement within 24 h was reduced in Group V.

A previous study comparing 1.0 ml/kg of 0.225% and 1.5 ml/kg of 0.15% ropivacaine for caudal analgesia for pediatric orchiopexy reported that the latter formulation produced a higher level of block and provided better quality and longer duration of analgesia [10]. However, 20 ml of 0.375% ropivacaine did not result in longer analgesic duration compared with 10 ml of 0.75% ropivacaine in our study. The most important possible factor for this differ-
higher nonneural-neural tissue ratio [11]. These characteristics may produce a more complicated relationship between the volume of LA and analgesic duration of the ISB compared with caudal analgesia. Another dose-finding study reported a reduced ED(dose)95 when a constant volume was set, and the concentration was lowered, than when a constant concentration was set and the volume was lowered [9]. Just as individual patients may respond differently to the same dose of the same drug delivered in exactly the same location in relation to the target nerves, the accuracy with which the LA drug can be deposited might differ between patients. It was expected that volume rather than concentration would have an advantage to prolong the analgesic duration that was not found in our study. The concept of the mean effective volume (MEV) and minimum effective anesthetic concentration (MEAC) may be more important than the ideal combination of volume and concentration in terms of analgesic efficacy of peripheral nerve block. If a well-experienced clinician uses the doses of the MEV and MEAC, then the accuracy of the LA deposit in relation to volume would no longer be significant.

Zhai et al. [7] evaluated US-guided ISB performed with different volumes of a 50 mg dose of ropivacaine and found that a higher concentration of ropivacaine was associated with faster onset of sensory blockade, as observed in this study. Although our study did not confirm the length of stay in the operating room and PACU, the results suggest that the higher concentration may be preferable to facilitate the surgery and reduce the overall processing time. However, this trend could not be verified, because our study compared only two groups that received one fixed dose. Further studies are necessary to verify the maintenance of this trend.

Table 2. Sensory and Motor Block Assessment after 30 min after Interscalene Block

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group C (n = 31)</th>
<th>Group V (n = 31)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance time (min)</td>
<td>9.0 ± 1.8</td>
<td>9.0 ± 1.9</td>
<td>&gt; 0.999</td>
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<td>Time to onset of a sensory block (min)</td>
<td>8.0 ± 2.9</td>
<td>10.0 ± 3.1</td>
<td>0.015</td>
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<td></td>
</tr>
<tr>
<td>C4</td>
<td>12/15/4</td>
<td>11/16/4</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>C5</td>
<td>31/0/0</td>
<td>31/0/0</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>C6</td>
<td>22/9/0</td>
<td>21/10/0</td>
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</tr>
<tr>
<td>C7</td>
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<td>0.310</td>
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<tr>
<td>C8</td>
<td>0/19/12</td>
<td>0/16/15</td>
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<td>Motor block (0/1/2/3/4)†</td>
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<td></td>
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<td>Shoulder abduction</td>
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<td>20/11/0/0/0</td>
<td>0.793</td>
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<tr>
<td>Forearm flexion</td>
<td>17/14/0/0/0</td>
<td>12/17/2/0/0</td>
<td>0.217</td>
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</tbody>
</table>

Values are presented as mean ± SD or number. Group C: 10 ml of 0.75% ropivacaine, Group V: 20 ml of 0.375% ropivacaine. *Sensory block: 2, normal sensation; 1, dull sensation; and 0, absence of sensation. †Motor block: 4, full power; 3, reduced power but able to lift arm against resistance; 2, moves muscle group against gravity but unable to lift arm against resistance; 1, perceptible muscle contraction, but unable to move purposely; and 0, no movement in relevant muscle group.
Although the difference in analgesic duration of the ISB between groups was not statistically significant, it could have influenced the postoperative opioid requirement within 24 h, in which the pain relief regimen primarily comprised single-shot ISB and IVPCA, reflected by the lower baseline-infused fentanyl dose in Group V. Bolus demand was greater in Group C compared with Group V. Nerve injury or neurotoxicity is one of the possible factors for rebound pain after peripheral nerve block; therefore, reducing the concentration of LA would be beneficial\[12,13\]. Reducing the concentration of ropivacaine rather than lowering volume could be associated with less rebound pain. To summarize, our results could be clinically significant for a postoperative pain control regimen centered on single-shot ISB and IVPCA within 24 h, during which the patients experienced the most severe pain.

ISB is associated with decreased pulmonary function due to ipsilateral phrenic nerve palsy\[14,15\]. Compared with previously published low-dose studies, our study used a relatively high dose; therefore, we expected to find a nearly 100% incidence of decreased pulmonary function in our study\[14–17\]. Only two patients in Group C and one in Group V showed no reduction in FEV1 and FVC. These patients might not have had phrenic nerve palsy, although this could not be confirmed, because direct US evaluation was not performed. In the pilot study, evaluation of diaphragmatic movements was attempted by the use of US. Because of the difficulties encountered with the use of the spleen as a window to identify the left diaphragm, this factor was excluded from analysis\[18\]. Even so, our study showed a similar probability of reduced pulmonary function as previous studies.

A previous study showed that a high volume/low concentration combination of LA for ISB could avoid major complications\[8\]; however, the evidence seemed weak because the study used a conventional LA dose and a multi-injection technique with nerve

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group C (n = 31)</th>
<th>Group V (n = 31)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV1 change 30 min after block (%)</td>
<td>-27.8 ± 11.4</td>
<td>-28.2 ± 7.9</td>
<td>0.864</td>
</tr>
<tr>
<td>FVC change 30 min after block (%)</td>
<td>-29.6 ± 12.2</td>
<td>-28.4 ± 7.4</td>
<td>0.647</td>
</tr>
<tr>
<td>Fentanyl baseline infusion dose (μg)</td>
<td>205.3 ± 92.4</td>
<td>163.0 ± 70.6</td>
<td>0.047</td>
</tr>
<tr>
<td>Fentanyl bolus dose (μg)</td>
<td>126.0 ± 77.8</td>
<td>85.3 ± 51.2</td>
<td>0.018</td>
</tr>
<tr>
<td>Fentanyl total dose (μg)</td>
<td>331.3 ± 149.9</td>
<td>248.3 ± 112.2</td>
<td>0.016</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horner syndrome</td>
<td>7 (22.6)</td>
<td>3 (9.7)</td>
<td>0.167</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>3 (9.7)</td>
<td>2 (6.5)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>3 (9.7)</td>
<td>1 (3.2)</td>
<td>0.612</td>
</tr>
<tr>
<td>PONV</td>
<td>3 (9.7)</td>
<td>3 (9.7)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>HBE</td>
<td>9 (29.0)</td>
<td>6 (19.4)</td>
<td>0.374</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3 (9.7)</td>
<td>4 (12.9)</td>
<td>&gt; 0.999</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>3 (9.7)</td>
<td>1 (3.2)</td>
<td>0.612</td>
</tr>
<tr>
<td>Satisfaction score at 24 h (0–100 scale)</td>
<td>60.0 (20.0, 80.0)</td>
<td>70.0 (50.0, 90.0)</td>
<td>0.162</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD or median (Q1, Q3) or number (%). Group C: 10 ml of 0.75% ropivacaine, Group V: 20 ml of 0.375% ropivacaine. FEV1: forced expiratory volume in one second, FVC: forced vital capacity, PONV: postoperative nausea and vomiting, HBE: hypotensive bradycardic event.

Table 4. Postoperative Pain Scores by Time Period

<table>
<thead>
<tr>
<th>Postoperative time period</th>
<th>Group C (n = 31)</th>
<th>Group V (n = 31)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At PACU</td>
<td>0.0 (0.0, 2.0)</td>
<td>0.0 (0.0, 1.0)</td>
<td>0.845</td>
</tr>
<tr>
<td>1 h</td>
<td>0.0 (0.0, 2.0)</td>
<td>1.0 (0.0, 2.0)</td>
<td>1.000</td>
</tr>
<tr>
<td>2 h</td>
<td>0.0 (0.0, 2.0)</td>
<td>1.0 (0.0, 2.0)</td>
<td>0.672</td>
</tr>
<tr>
<td>3 h</td>
<td>2.0 (0.0, 3.0)</td>
<td>1.0 (0.0, 2.0)</td>
<td>0.659</td>
</tr>
<tr>
<td>6 h</td>
<td>3.0 (0.0, 7.0)</td>
<td>3.0 (0.0, 4.0)</td>
<td>0.082</td>
</tr>
<tr>
<td>12 h</td>
<td>6.0 (4.0, 7.0)</td>
<td>4.0 (3.0, 6.0)</td>
<td>0.121</td>
</tr>
<tr>
<td>24 h</td>
<td>4.0 (2.0, 7.0)</td>
<td>4.0 (3.0, 6.0)</td>
<td>0.716</td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3). Group C: 10 ml of 0.75% ropivacaine, Group V: 20 ml of 0.375% ropivacaine, PACU: post anesthesia care unit.
stimulation. Thus, the LA volume variation was not an isolated independent factor. There was no significant between-group difference for the incidence of complications in our study. Previous studies showed that doses as low as 5 ml could lead to a reduction of ISB-associated complications [16,17]. Because ISB complications are related to the surrounding anatomy (e.g., Horner’s syndrome – stellate ganglion, hemidiaphragmatic paralysis – phrenic nerve, hoarseness – recurrent laryngeal nerve), the incidence of block-related complications can be expected to decrease only when the dose is low enough to prevent hemidiaphragmatic paralysis.

This study has several limitations. First, because the anesthesiologist who performed the procedure used a different volume of ropivacaine, correction of maldistribution of the injected LA might have been more ideal for Group V. However, considering that the US-guided ISB was performed by a single expert anesthesiologist, the need for repositioning of the needle was reduced. Second, sensory and motor blockades after surgery were not assessed that could affect the patient’s satisfaction score. However, the surgeon at the hospital wanted the shoulders and arms of the patients kept immobile in the early postoperative stage. Consequently, accurate evaluation was almost impossible because of the dressing or abduction brace. Third, the incidence of PONV was likely to be influenced by both the ISB and IVPCA, and not by ISB alone. However, the frequency was the same in both groups; therefore, it was unlikely to have a significant influence on the overall result.

In conclusion, compared with 10 ml of 0.75% ropivacaine, 20 ml of 0.375% ropivacaine did not prolong analgesic duration of the ISB. Nevertheless, it might be effective to reduce the postoperative opioid requirement within 24 h when combined with IVPCA for analgesia after arthroscopic shoulder surgery.

Acknowledgements

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Conflicts of Interest

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

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Sung Wan Kim (Data curation)
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References


Endotracheal intubation in patients undergoing open abdominal surgery in the lateral position: a comparison between the intubating video stylet and fiberoptic intubating bronchoscopy

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Department of Anesthesia, Surgical ICU and Pain Management, ¹Faculty of Medicine, Cairo University, ²Theodor Bilharz Research Institute, Cairo, Egypt

Background: Some situations compel anesthetists to execute endotracheal intubation in the lateral position. We compared elective endotracheal intubation in the lateral decubitus position using the video stylet (VS) device with the fiberoptic (FO) bronchoscope device in patients undergoing abdominal surgery.

Methods: Overall, 50 patients were enrolled in this prospective, randomized study. They were randomly classified into the VS intubation or FO intubating bronchoscope group. After anesthesia induction, patients were placed in the lateral decubitus position, and a single investigator well-versed with the use of the VS and FO bronchoscope performed the intubation. The primary outcome was the time taken for intubation. Secondary outcomes included the intubation success rate, hemodynamic response at specific time points and perioperative complications.

Results: The average time taken for intubation was significantly lesser in the VS group than in the FO group, with values of 39.5 ± 10.0 and 75.6 ± 16.2 s, respectively (P < 0.001). Incidences of a successful first attempt of intubation in the VS and FO groups were 88% and 100%, respectively, showing no significant difference. There was a negligible difference in complications between the groups, except sore throat, which showed a higher incidence in the VS group than in the FO group (P = 0.002).

Conclusions: In laterally positioned patients, elective endotracheal intubation with VS provides less intubation time; however, its use is accompanied by a significant increase in the hemodynamic response after intubation and an increased incidence of sore throat.

Keywords: Airway management; Bronchoscope; Intratracheal intubation; Laparotomy; Patient positioning; Video stylet.

Introduction

A difficult task confronting an anesthetist is airway management, which is also a main cause of morbidity related to anesthesia [1]. Accordingly, it is crucial for any anesthetist to acquire skills to handle challenges encountered in the operating theater [2]. One of them...
is intubation in uncommon positions, such as the lateral position, when it is problematic to put the patient in the supine position, such as in cases of accidental loss of the endotracheal tube (ETT) in the middle of operation, patients with trauma, inefficient regional anesthesia, and neoplasms of the back, occiput, or sacral region [3,4]. Recently, placing the ETT in the lateral position has been a huge concern for many anesthetists; moreover, several studies have been performed to determine the best method for lateral position intubation by using direct laryngoscopy, laryngeal mask airway, intubating the laryngeal mask airway with and without the aid of a lightwand, and intubation with the lightwand [5,6]. Unfortunately, these techniques have drawbacks of being time-consuming and putting the anesthetist in an ergonomically challenging position [7]. As a result, it was considered important to discover more ways that are both safe and successful. The fiberoptic (FO) bronchoscope was believed to achieve the sought goals [8,9]. However, it is a costly apparatus that requires thorough training. Therefore, current studies are investigating the pros of using the video rigid intubation stylet. It is a novel device with several advantages, including easy mobility with a clear display screen for vocal cord visualization, easy to clean, lightweight, chargeable, reusable, durable, and less expensive. It has a red-light source that is located at the far end of the stylet. Therefore, it is considered to be a more affordable choice than the FO bronchoscope in developing countries [10].

The aim of the present study was to compare the video stylet (VS) with the FO bronchoscope in laterally positioned patients undergoing laparotomy abdominal surgery.

Materials and Methods

This study was performed as a prospective randomized study at the Theodor Bilharz Research Institute Hospitals and Cairo University Hospital, after receiving approval from the Institutional Research Ethics Committee of the Faculty of Medicine, Cairo University (MD-53-2019) and Theodor Bilharz Research Institute Hospitals (No: 194471), with registration at ClinicalTrials.gov (NCT 04183959). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Written consent was obtained from each patient before enrollment in this study, which was designed to recruit 50 patients, including both men and women, between 18 and 60 years of age with the American Society of Anesthesiologists (ASA) physical status I or II, Mallampati class I or II, scheduled endotracheal intubation in the lateral decubitus position under general anesthesia for open abdominal surgery.

Exclusion criteria were pre-existing clinically significant cardio-vascular or hypertensive disorders, age under 18 or over 60 years, ASA physical status class > II, difficult intubation, Mallampati class > II, limited neck mobility due to cervical spine pathology, dental abnormalities, obesity (body mass index [BMI] ≥ 40 kg/m²), and a high risk of pulmonary aspiration. Before the start of the study, enrolled patients were randomly allocated into 2 equal groups, using a computer-generated table of random numbers with an opaque and sealed envelope prepared by a research assistant not otherwise participating in the study, according to the device used in intubation, into VS intubation and FO bronchoscope intubating groups.

One day before surgery, patients visited the anesthesia outpatient clinic for history-taking and assessment, including electrocardiogram, complete blood count, and coagulation profile. The study protocol was explained to them, and they were informed that they could drop out any time they desired. All patients fasted for 6 h before the procedure. After demographic data had been recorded, intravenous access was established with a 20 gauge (G) intravenous (IV) cannula over the forearm on arrival at the operating theater. Simultaneously, standard monitoring devices were attached, including the electrocardiograph, noninvasive blood pressure monitor, and pulse oximeter.

All patients were premedicated IV with ondansetron 4 mg and pantoprazole 40 mg. The anesthetic protocol was standardized in all the study groups. After pre-oxygenation for 5 min, anesthesia induction was commenced using propofol (1–2 mg/kg) with IV fentanyl (1–2 µg/kg) until loss of verbal communication occurred. Subsequently, muscle relaxation was maintained by an initial loading IV dose of cisatracurium (0.15 mg/kg). After adequate oxygenation and muscle relaxation, patients were placed in the lateral position and an inflatable beanbag was used to achieve the anterior and posterior support needed. The dependent lower limb of the patient was flexed, and a pillow was placed between both lower limbs to cushion the knees' bony protrusions. Moreover, the upper limbs were protected using pillows to support the non-dependent upper limb, while the dependent one was rested on an arm board. Furthermore, an axillary roll was used to prevent axillary vessels and brachial plexus injuries by positioning between the operating table and the patient's chest wall. The head and neck were kept in the neutral position through support using a firm 6-cm high pillow comprising 2 separate parts: one made of foam and another made of a synthetic gel substance in the horseshoe shape placed on top to help fixate the head in a proper and correct way, with attention paid to the dependent eye and ear to avoid pressure and ischemia [5]. Subsequently, patients were randomly allocated to the 2 groups, with 25 patients in each.

VS group: The trachea was intubated using a laryngoscopic-as-
sisted VS (Red-Light Directive Video Rigid Intubation stylet [BD-SL-A]; Shenzhen Besdata Technology Co., Ltd., China) by the consultant anesthesiologist expert with the use of the VS. Subsequently, an ETT was placed over the device and introduced into the mouth, and on visualizing the first 1 or 2 tracheal rings, the tube was slid into the airway.

FO group: Intubation was performed using an FO bronchoscope (RBS, Series Portable Fiber Intubation Scope, Pentax FI-16BS 5.2 mm, Pentax, USA) by the anesthesiologist expert with the use of the FO bronchoscope. For the FO bronchoscope, the scope was inserted carrying the ETT until the carina was visualized, and the tracheal tube was slid into the airway. In both groups, a trained assistant was present to help perform the maneuvers, such as lingual traction and anterior mandibular advancement to clear the airway. Each maneuver alone proved beneficial; nevertheless, they were more effective when performed together. The intubation process was thought to be a failure when not completed within either of the 2 trials or the patient’s oxygen saturation (SpO₂) reached < 90%. In cases of intubation failure, the patient was turned to the supine position and intubated with the conventional technique. After confirmation of successful intubation by capnography and chest auscultation, the patient was placed on mechanical ventilation with isoflurane 2% to maintain anesthesia. End-tidal CO₂ was maintained between 35 and 40 mmHg. Muscle relaxation was maintained with 0.03 mg/kg IV of cisatracurium every 20 min, and surgery was continued in the required position (supine or lateral). Upon completion of the procedure, the inspired anesthetic was then stopped and neostigmine 0.05 mg/kg combined with atropine 0.02 mg/kg were used to reverse the effect of the muscle relaxant. Subsequently, extubation was performed after fulfilling the criteria of extubation. Finally, the patient was taken to the post-anesthesia care unit, and duration of surgery was recorded.

The primary outcome of the current study was the time required to intubate (defined as the time from the instrument’s introduction into the subject’s mouth until its removal following confirmation of the ETT correct placement by witnessing the optimal waveform on capnography). The secondary outcome was the success of intubation. The anesthesiologist who performed the intubation was asked to score the ease of use on a 4-point scale (1 = difficult; 2 = moderately difficult; 3 = fairly easy; and 4 = very easy), vital signs based on systolic arterial blood pressure (SBP), mean arterial blood pressure (MBP), diastolic arterial blood pressure (DBP), heart rate (HR), and SpO₂. The latter was measured at baseline before anesthesia induction (BA), immediately after induction (AA), after induction of anesthesia but before intubation (T1), and after successful ETT placement (T2). The occurrence of side effects, including mucosal injuries, i.e., blood detected on the device, lip or dental trauma, postoperative nausea or vomiting, and desaturation (SpO₂ < 92%) were recorded.

Statistical analysis

Sample size was calculated by comparing the intubation time between using the VS and FO maneuver in the lateral position of open abdominal surgery cases, as previously reported [10]. The mean time of intubation was approximately 19.7 ± 2.8 s in the VS group and approximately 38.2 ± 6.9 s in the FO maneuver group (Standard deviation was calculated from the given 95% CI). Thus, the minimum proper sample size was calculated to be 22 participants in each group to enable detecting a real difference of 6 s (15% of the control group) with 80% power at the α = 0.05 level when using Student’s t-test for independent samples. Sample-size calculation was performed using Stats Direct statistical software version 2.7.2 for MS Windows (Stats Direct Ltd., UK). The number was increased to 50 patients (25 per group) to compensate for possible dropouts. Normally distributed continuous data are expressed as mean ± standard deviation. Non-normally distributed continuous and ordinal data are expressed as median (Q1, Q3). Categorical data are expressed as number of patients and incidence. The unpaired t-test was used to compare continuous data in the 2 groups. Repeated-measures analyses of variance with post-hoc Dunnett’s test was used to compare changes in continuous variables in relation to the baseline preoperative values, e.g., HR, SBP, MAP, and DBP within each study group. The chi-square or Fisher’s exact test was used to compare categorical data. For all statistical comparisons, a P value < 0.05 was considered significant. All data analyses and graphical demonstrations were dose-dependent and performed with the Statistical Package for Social Sciences SPSS ver. 25.0 software for Windows (IBM Corp., USA).

Results

Fifty-three patients were assessed for eligibility, of whom 3 were excluded based on the exclusion criteria. Thus, 50 patients were included in the study (Fig. 1).

There were no statistically significant differences in patient characteristics or airway parameters among groups (patient age, BMI, or Mallampati score). Intubation was successful at the first attempt in 22 (88%) patients of the VS group and in 25 (100%) patients of the FO group, showing no significant differences. However, the average time required for intubation was remarkably lower (P < 0.001) in the VS group than in the FO group at
39.5 ± 10.0 and 75.6 ± 16.2 s, respectively. At the end of intubation, we asked the anesthesiologists about their satisfaction with the ease of using this technique of intubation. The result showed that anesthesiologists were satisfied when using the VS for intubation compared to the FO bronchoscope (Table 1).

Hemodynamically, both groups were comparable regarding changes in SBP, MBP, DBP, HR, and SpO\textsubscript{2}, showing no statistically significant differences in BA, AA, or T1. However, immediately after successful intubation, T2 showed significant increases in SBP, MAP, DBP, and HR in the VS group compared to the FO group. Moreover, the mean SpO\textsubscript{2} showed significant reduction in the FO group compared to the VS group (Figs. 2 and 3).

Complications detected in the VS group included 11 cases (44%) of sore throat, 5 cases (20%) of mucosal trauma, 2 cases (8%) of nausea, 1 case (4%) of vomiting, and no case of desaturation and those detected in the FO group included 1 case (4%) of sore throat, 1 case (4%) of mucosal trauma, 2 case (8%) of nausea, 1 case (4%) of desaturation, and no case of vomiting. There was insignificant difference between groups in complications, except for the incidence of sore throat, which was significantly higher in the VS group than in the FO group (P = 0.002; Table 2).

**Discussion**

Intubation is considered a fundamental step in the management of airway, particularly when it is done in an unconventional position, such as the lateral position, or in patients with a restricted mouth opening or a restricted range of neck movement, as any deficiency in the airway management in these patients can lead to fatal outcomes. Recently, many researchers have developed methods, including the FO bronchoscope and rigid VS, for airway management in unusual positions. The rigid VS had many advantages in these extreme cases of preventing blind traumatic intubation and providing easy maneuver. Moreover, it is easy to master and adaptable to shape for better adjustment in patients with a distorted anatomy. Unfortunately, it has limitations of the inability to be used for nasal intubation in addition to not having a suction channel or oxygen delivery port. Finally, it affords only a limited

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**Table 1.** Demographics, Clinical Characteristics, and Intubation Profile

<table>
<thead>
<tr>
<th></th>
<th>VS group</th>
<th>FO group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>37.1 ± 10.5</td>
<td>34.6 ± 8.2</td>
<td>0.365</td>
</tr>
<tr>
<td>BMI (kg/m\textsuperscript{2})</td>
<td>25.7 ± 3.9</td>
<td>26.1 ± 4.8</td>
<td>0.773</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>9 (36)</td>
<td>13 (52)</td>
<td>0.393</td>
</tr>
<tr>
<td>F</td>
<td>16 (64)</td>
<td>12 (48)</td>
<td></td>
</tr>
<tr>
<td>Mallampati grades</td>
<td></td>
<td></td>
<td>0.778</td>
</tr>
<tr>
<td>I</td>
<td>11 (44)</td>
<td>13 (52)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>14 (56)</td>
<td>12 (48)</td>
<td></td>
</tr>
<tr>
<td>Intubation time (s)</td>
<td>39.5 ± 10.0*</td>
<td>75.6 ± 16.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Cases of a first</td>
<td>22 (88)</td>
<td>25 (100)</td>
<td>0.235</td>
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<tr>
<td>attempt of intubation</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Anesthesiologist</td>
<td></td>
<td></td>
<td>0.040</td>
</tr>
<tr>
<td>satisfaction</td>
<td>4 (3, 4)*</td>
<td>3 (2, 3)</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, number (%), and median (Q1, Q3). VS group: video stylet intubation group, FO group: fiberoptic bronchoscope group. BMI: body mass index. Anesthesiologist satisfaction scale: 1 = difficult, 2 = moderately difficult, 3 = fairly easy, and 4 = very easy. *P < 0.05
Fig. 2. Comparison of the systolic, mean, and diastolic blood pressures and mean heart rate. Values are presented as mean ± SD. VS: video stylet intubation group, FO: fiberoptic bronchoscope group, BA: before induction of anesthesia at baseline, AA: immediately after induction of anesthesia, T1: after induction of anesthesia but before tracheal intubation, T2: immediately after successful intubation, SBP: systolic blood pressure, MBP: mean blood pressure, DBP: diastolic blood pressure, HR: heart rate. *P < 0.05.

Fig. 3. Comparison of the mean oxygen saturation (SpO₂) of the 2 studied groups. Values are presented as mean ± SD. VS: video stylet intubation group, FO: fiberoptic bronchoscope group, BA: before induction of anesthesia at baseline, AA: immediately after induction of anesthesia, T1: after induction of anesthesia but before tracheal intubation, T2: immediately after successful intubation. *P < 0.05.

view, as it can be seen only as far as the proximal trachea [11,12].

The current study concluded that the outcome of using the VS to intubate patients in the lateral position undergoing laparotomy abdominal surgery appeared to be faster, showing more than a 36 s difference between the 2 devices, which can be explained by the more time required to slide the ETT along the longer FO bron-
Moreover, no statistically significant differences were found in he-
groups with a greater delay when using the FO bronchoscope.
the FO bronchoscope, showing an 18.5 s difference between the
paring both groups in terms of complications.
there was a statistically insignificant difference when com-
s delay when using FO bronchoscopy compared to the VS. How-
intubation and complication incidence. The study showed a 36.4-
bination resulting from jaw thrust performed during intubation using
the latter group. This could be explained by sympathetic stimula-
ral factors, including difficulty in shaping its stylet after mouth in-
experienced higher failure rates, which could be attributed to sev-
rates had average BMI scores and normal airways; therefore, our
results may not be generalizable for difficult intubation cases. Sec-
ond, the VS does not have suction or oxygen supplementation
ets might be considered as drawbacks when secretions or blood accumulates in the nasopharynx or oropharynx. Finally,
in the current study, the instruments were used by an expert anes-
coholic stylet. Furthermore, the need for advancement of the FO
bronchoscope up to the carina and that of an assistant to uplift the
patient's chin when using the FO bronchoscope can be considered
as reasons for such delay. Using the VS was also shown to yield a
more favorable intubation condition compared to using the FO la-
ryngoscope. However, despite almost similar success rates, as suc-
cessful intubation at the first attempt using the VS was shown to be
88% compared to the 100% found in the FO laryngoscope, the VS
experienced higher failure rates, which could be attributed to sev-
eral factors, including difficulty in shaping its stylet after mouth in-
insertion, poor image quality, and lack of a suctioning port [13,14].
Concerning the incidence of complications, despite the higher
rates of hypoxia shown in the FO bronchoscope group mainly due
to the longer time needed for intubation, higher increases in he-
modynamic parameters, including BP and HR, were measured in
the latter group. This could be explained by sympathetic stimula-
tion resulting from jaw thrust performed during intubation using
the VS; moreover, more manipulations required to centralize the
vocal cords could lead to a catecholamine surge [15]. However,
there was an insignificant difference in the occurrence of compli-
cations between the groups, except for sore throat. This appeared
to be higher when using the VS compared to the FO broncho-
scope, which can be explained by the rigidity of its stylet.
Lee et al. [11] conducted a study involving 80 patients undergo-
ing nasotracheal intubation to compare the use of the flexible FO
bronchoscope with the VS with regards to the time required for
intubation and complication incidence. The study showed a 36.4-
s delay when using FO bronchoscopy compared to the VS. How-
ever, there was a statistically insignificant difference when com-
paring both groups in terms of complications.
Another study was performed involving 60 patients undergoing
elective procedures in the supine position with the normal airway
to compare the time required for intubation between the VS and
the FO bronchoscope, showing an 18.5 s difference between the
groups with a greater delay when using the FO bronchoscope.
Moreover, no statistically significant differences were found in he-

Table 2. Comparison of Complications

<table>
<thead>
<tr>
<th></th>
<th>VS group</th>
<th>FO group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>2 (8)</td>
<td>2 (8)</td>
<td>1.000</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>1.000</td>
</tr>
<tr>
<td>Sore throat</td>
<td>11 (44)*</td>
<td>1 (4)</td>
<td>0.002</td>
</tr>
<tr>
<td>Mucosal trauma</td>
<td>5 (20)</td>
<td>1 (4)</td>
<td>0.189</td>
</tr>
<tr>
<td>Desaturation</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Values are presented as number (%). VS group: video stylet intubation
group, FO group: fiberoptic bronchoscope group. Desaturation: decrease
in SpO₂ < 92% after successful intubation. *P < 0.05.

In conclusion, in laterally positioned patients, elective endotra-
cheal intubation with VS provides less intubation time; however,
its use is accompanied by a significant increase in the hemody-
namic response after intubation and an increased incidence of
sore throat. Nevertheless, more studies using a larger sample size
are required to decide its use in patients with a difficult airway
and the incidence of complications.

Acknowledgements

Our sincere thanks and gratitude to all those who participated
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Conflicts of Interest

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

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Preoperative high-sensitivity troponin I and B-type natriuretic peptide, alone and in combination, for risk stratification of mortality after liver transplantation

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Background: Given the severe shortage of donor liver grafts, coupled with growing proportion of cardiovascular death after liver transplantation (LT), precise cardiovascular risk assessment is pivotal for selecting recipients who gain the greatest survival benefit from LT surgery. We aimed to determine the prognostic value of pre-LT combined measurement of B-type natriuretic peptide (BNP) and high-sensitivity troponin I (hsTnI) in predicting early post-LT mortality.

Methods: We retrospectively evaluated 2,490 consecutive adult LT patients between 2010 and 2018. Cut-off values of BNP and hsTnI for predicting post-LT 90-day mortality were calculated. According to the derived cut-off values of two cardiac biomarkers, alone and in combination, adjusted hazard ratios (aHR) of post-LT 90-day mortality were determined using multivariate Cox regression analysis.

Results: Mortality rate after 90 days was 2.9% (72/2,490). Rounded cut-off values for post-LT 90-day mortality were 400 pg/ml for BNP (aHR 2.02 [1.15, 3.52], P = 0.014) and 60 ng/L for hsTnI (aHR 2.65 [1.48, 4.74], P = 0.001), respectively. Among 273 patients with BNP ≥ 400 pg/ml, 50.9% of patients were further stratified into having hsTnI ≥ 60 ng/L. Combined use of pre-LT cardiac biomarkers predicted post-LT 90-day mortality rate; both non-elevated: 1.0% (21/2,084), either one is elevated: 9.0% (24/267), and both elevated: 19.4% (27/139, log-rank P < 0.001; aHR vs non-elevated 4.23 [1.98, 9.03], P < 0.001).

Conclusions: Concomitant elevation of both cardiac biomarkers posed significantly higher risk of 90-day mortality after LT. Pre-LT assessment cardiac strain and myocardial injury, represented by BNP and hsTnI values, would contribute to prioritization of LT candidates and help administer target therapies that could modify early mortality.

Keywords: B-type natriuretic peptide; Liver transplantation; Mortality; Postoperative complication; Risk assessment; Troponin-I.

Introduction

Given the severe shortage of donor liver grafts, the role of precise preoperative risk stratification is crucial to select a recipient who gains the greatest survival benefit from liver transplantation (LT) surgery. With improved surgical techniques and anesthetic management, cardiovascular disease is now the leading cause of early mortality following...
LT [1]. As a consequence, there is an increasing need for exact tools to evaluate cardiovascular risk in LT candidates [2,3]. However, the current model for end-stage liver disease (MELD) scoring system does not reflect any cardiovascular markers in its calculation. Since the era of MELD scores started in 2002, it allowed more objective prediction of 90-day mortality and improved prioritization of LT candidates [4], but it has remained barely unchanged for the last 20 years despite the ongoing need for revision [5]. Moreover, current noninvasive tests, such as dobutamine stress echocardiography and myocardial perfusion scan, which are mainly for detecting subclinical coronary and myocardial disease, do not have satisfactory performance in predicting postoperative outcomes [6].

Cardiac biomarkers, including B-type natriuretic peptide (BNP) and cardiac troponins, have been recognized for their powerful prognostic ability [7–9]. Guidelines on preoperative cardiovascular risk assessment recommend measuring BNP and cardiac troponin in patients scheduled for high-risk non-cardiac surgeries [10,11]. Troponin and BNP are reported to be correlated with severity liver disease [12], and a few studies have demonstrated the relevance of pre- and intraoperative elevated levels of these biomarkers in predicting LT outcome. Nevertheless, comprehensive combined interpretation of these two biomarkers and optimal cut-off values for LT candidates are still not established. For example, several studies employ just the 99th percentile upper reference limit (URL) of high-sensitivity troponin I (hsTnI), which has been used for healthy reference population [13,14], without consideration of particular cardiovascular characteristics such as a hyperdynamic circulation and the severity of illness in LT candidates.

Thus, we conducted this study to investigate whether elevation of cardiac strain indicated by a high BNP and accompanying subclinical myocardial injury assessed by hsTnI predict early mortality after LT. If so, the combined use of two cardiac biomarkers would help to improve preoperative risk stratification of LT candidates.

The objectives of the current study are (1) to determine any association between preoperative cardiac troponin and BNP in LT candidates, and (2) to define preoperative threshold of each biomarker that could predict short-term (90-day) mortality to assess the prognostic usefulness of these biomarkers, alone and in combination, in LT recipients.

Materials and Methods

Study Population

This retrospective study was approved by the Institutional Re-

view Board of Asan Medical Center (2019-0824). A total of 2,949 consecutive patients who underwent adult LT from January 2010 to January 2018 were reviewed. Of these, we excluded patients whose preoperative troponin I and BNP were not measured within a week before LT (n = 374) and those who underwent re-transplantation or multi-organ transplantation (n = 85). We included patients with a previous history of coronary artery disease (CAD), treated with percutaneous coronary intervention or coronary artery bypass surgery, to determine whether preoperative ischemic heart disease is a prerequisite for hsTnI release and portends a poorer survival rate during the early post-LT period.

Measurement of Troponin I and brain natriuretic peptide

Both cardiac markers, hsTnI and BNP, were routinely measured preoperatively as part of the institution’s routine protocol since 2010. Cardiac hsTnI was measured using ADVIA Centaur® XP TnI-Ultra (Siemens Healthcare Diagnostics, USA; the 99th percentile URL = 40 ng/L, lower limit = 6 ng/L). Plasma level of BNP was measured using ADVIA Centaur® CP Immunoassay System (Siemens Healthcare Diagnostics, USA). We only approved cardiac biomarkers that were measured within a week before LT or just before induction of anesthesia for LT. If there were multiple measurements of cardiac biomarkers, the latest sample before LT was used for analysis.

Data collection and definition of outcomes

Data collection was performed using a fully computerized Asan Medical Center research information system (ABLE, Asan Biomedical R-esearch) after approval from the local research ethics committee (protocol number 2019-0881), which waived the requirement for written informed consent. This included patient demographics, medical history, MELD score of liver cirrhosis severity, laboratory variables, comorbidities of liver cirrhosis, and mortality. Patient survival time was defined as the number of days between the day of surgery starting in January 2010 and ending on March 31, 2018 or the date of death (completed). Mortality data were obtained from patients’ electronic medical records and the Asan LT registry, which is regularly updated by the Asan Organ Transplantation Center. The primary end point was the cumulative 90-day all-cause mortality and secondary outcomes included cumulative overall mortality during the entire follow-up period.

Statistical analysis

Variables are expressed as numbers (percentages), mean ±
standard deviation, or median (Q1, Q3) as appropriate. Analyses between groups were performed using Student’s t-test, Mann–Whitney U test, analysis of variance, or Kruskal–Wallis test for continuous variables and χ² test or Fisher’s exact test for categorical variables, as appropriate. Distribution of BNP and hsTnI were evaluated with a histogram and a density plot according to patient survival. To assess the relationship between preoperative hsTnI and BNP values, they were log-transformed and depicted on a scatter plot and analysis of covariance was performed to evaluate the association between the two cardiac biomarkers and patient mortality.

Optimal cut-off points of each cardiac biomarker for 90-day mortality and overall mortality were calculated using the ‘maxstat’ package of R (version 3.3.1, R foundation for statistical Computing, Austria). Briefly, using maximally selected rank statistics, the prognostic cut-off point was determined by evaluating every possible cut-off point, classifying all patients into two groups according to their level, and selecting the most discriminating threshold for death, corresponding to the minimum P value according to the log-rank test [15,16]. The main difference of maximally selected rank statistics from classic receiver operating characteristic curve analysis is that there is no need to change a time-dependent endpoint (survival) into a classification variable [16]. In receiver operating curve analysis, investigators have to transform the time-dependent end point (survival) into a binary end point that is clinically relevant (e.g., survival at certain time point). Using the ‘maxstat’ package of R, maximally selected rank analysis for finding cut-off values that discriminate survival curves (time-dependent endpoint) can be done easily. Following this analysis, patients were dichotomized using these cut-off values and then patients were further divided into three groups using a combination of both cut-off values: both decreased, either one elevated, and both elevated. The three groups were evaluated by Kaplan-Meier analysis with log-rank test (Mantel-Cox), and its independent prognostic role was evaluated with the Cox regression model. The derived hazard ratios (HR) were adjusted by established risk factors reported from previous studies. Those factors included age [17], sex [18], deceased brain death donor or living donor LT [19,20], hepatic encephalopathy [21], massive transfusion (intraoperative transfusion of packed red blood cells > 10 units) [22], renal replacement therapy [23], MELD score, and C-reactive protein [24]. Donor age and height, cold/warm ischemic time, and graft-to-recipiennt body weight ratio were also included as covariates for donor risk factors [17,25–27]. We further performed a subgroup analysis by MELD score of 15. Kaplan-Meier curves were further stratified using a MELD score of 15 to observe the effect of liver disease severity.

Cubic spline interpolation was performed to represent the continuous changes in risk of 90-day all-cause death according to BNP and hsTnI values; three knots were considered. The BNP for which hazard ratio was equal to unity was chosen at the optimal cut-off value of BNP.

P values < 0.05 were considered statistically significant. All statistical analyses were performed using R software version 3.3.1.

**Results**

**Baseline characteristics**

Of the 2,490 included patients of aged 20–78 years, 2,122 (85.2%) underwent living donor and 368 (14.8%) underwent deceased brain death donor LT (Table 1). The patient population consisted of 1,843 (74.0%) men and 647 (26%) women, of median age 54 years (48–59) and a median MELD score of 14 (9–24). The primary causes of liver disease were hepatitis B or C virus-related liver cirrhosis (LC, 62.9%), alcoholic LC (21.8%), and others (15.3%).

During a median follow-up of 2.9 years (1.3, 4.9), 221 (8.9%) patients died after LT, including 72 (2.9%) who died during the first 90 days. Cardiovascular-related death comprised 24.9% (55/221) and 30.6% (22/72) of overall and 90-day mortality causes, respectively. Baseline characteristics of all patients are depicted in Table 1.

**Preoperative BNP concentrations**

The BNP histogram of the 2,490 enrolled patients is shown in Fig. 1. The median level of preoperative BNP was 80 pg/ml (39–178) and 1,044 (42%) had BNP > 100 pg/ml [28,29]. Patients who died within 90 days had significantly higher BNP values compared with those who survived for at least 90 days (median, 455.5 vs. 77.0 pg/ml, P < 0.001). With maximally selected rank statistic for the prediction of 90-day and overall mortality during the entire follow-up period, best cut-off values of BNP were 325 pg/ml and 442 pg/ml, respectively; therefore, we rounded them off to 400 pg/ml, which is an already well-known cut-off value associated with mortality risk [30]. When dichotomized with these cut-off values, patients with BNP ≥ 400 pg/ml (n = 273, 11%) had higher MELD scores (median, 34 vs. 13, P < 0.001). The 90-day mortality rate differed using a cut-off value of BNP of 400 pg/ml (1.6% vs. 13.6%, P < 0.001), with corresponding crude HR of 9.14 (95% CI, 5.75, 14.50, P < 0.001) and adjusted HR of 2.02 (95% CI, 1.15, 3.52, P = 0.014, Tables 1 and 2).
<table>
<thead>
<tr>
<th>Demographic data</th>
<th>Demographic data</th>
<th>Demographic data</th>
<th>Demographic data</th>
<th>Demographic data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>54.0 (48.0, 59.0)</td>
<td>55.0 (48.0, 59.0)</td>
<td>55.0 (48.0, 61.0)</td>
<td>0.28</td>
</tr>
<tr>
<td>Sex (M)</td>
<td>1670 (75.3)</td>
<td>173 (63.4)</td>
<td>171 (62.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>23.8 (21.6, 26.0)</td>
<td>22.8 (20.5, 25.5)</td>
<td>23.5 (21.2, 26.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MELD score</td>
<td>13.0 (9.0, 21.0)</td>
<td>13.0 (9.0, 21.0)</td>
<td>13.0 (9.0, 21.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>505 (22.8)</td>
<td>67 (24.5)</td>
<td>514 (23.2)</td>
<td>0.564</td>
</tr>
<tr>
<td>Hypertension</td>
<td>382 (17.2)</td>
<td>39 (14.3)</td>
<td>373 (16.8)</td>
<td>0.255</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>14 (6.9)</td>
<td>13 (6.9)</td>
<td>13 (6.9)</td>
<td>0.620</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>26 (12.1)</td>
<td>13 (6.9)</td>
<td>13 (6.9)</td>
<td>1.000</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>13 (0.6)</td>
<td>13 (0.6)</td>
<td>13 (0.6)</td>
<td>0.620</td>
</tr>
<tr>
<td>Underlying disease</td>
<td>Others</td>
<td>595 (22.8)</td>
<td>67 (24.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Underlying disease</td>
<td>382 (17.2)</td>
<td>39 (14.3)</td>
<td>373 (16.8)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Underlying disease</td>
<td>14 (6.9)</td>
<td>13 (6.9)</td>
<td>13 (6.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Underlying disease</td>
<td>26 (12.1)</td>
<td>13 (6.9)</td>
<td>13 (6.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Underlying disease</td>
<td>13 (0.6)</td>
<td>13 (0.6)</td>
<td>13 (0.6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Donor and intraoperative variables</td>
<td>Donor and intraoperative variables</td>
<td>Donor and intraoperative variables</td>
<td>Donor and intraoperative variables</td>
<td>Donor and intraoperative variables</td>
</tr>
<tr>
<td>Deceased brain death donor liver transplant</td>
<td>240 (108.8)</td>
<td>280 (120.3, 35.0)</td>
<td>286 (122.3, 37.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Donor age (yr)</td>
<td>505 (22.8)</td>
<td>514 (23.2)</td>
<td>514 (23.2)</td>
<td>0.564</td>
</tr>
<tr>
<td>Donor height (cm)</td>
<td>187.0 (90.1, 117.5)</td>
<td>169.0 (160.0, 175.0)</td>
<td>170.0 (162.0, 175.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Graft-to-recipient weight ratio</td>
<td>11.0 (10.0, 14.0)</td>
<td>8.1 (0.0, 12.2)</td>
<td>8.1 (0.0, 12.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total ischemic time (min)</td>
<td>1259.0 (720.0, 320.0)</td>
<td>1230.0 (1090.0, 320.0)</td>
<td>1270.0 (1090.0, 320.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Massive transfusion</td>
<td>474 (214.4)</td>
<td>474 (214.4)</td>
<td>474 (214.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Laboratory variables</td>
<td>Laboratory variables</td>
<td>Laboratory variables</td>
<td>Laboratory variables</td>
<td>Laboratory variables</td>
</tr>
<tr>
<td>Hemoglobin (g/dL)</td>
<td>6.0 (6.0, 9.4)</td>
<td>8.4 (6.0, 9.4)</td>
<td>8.4 (6.0, 9.4)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>0.8 (0.0, 2.2)</td>
<td>0.8 (0.0, 2.2)</td>
<td>0.8 (0.0, 2.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.0 (0.0, 2.2)</td>
<td>0.0 (0.0, 2.2)</td>
<td>0.0 (0.0, 2.2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Prothrombin time (INR)</td>
<td>0.3 (0.1, 0.9)</td>
<td>0.3 (0.1, 0.9)</td>
<td>0.3 (0.1, 0.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>C-reactive protein (mg/L)</td>
<td>0.3 (0.1, 0.9)</td>
<td>0.3 (0.1, 0.9)</td>
<td>0.3 (0.1, 0.9)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Comorbidities</td>
<td>Comorbidities</td>
<td>Comorbidities</td>
<td>Comorbidities</td>
</tr>
<tr>
<td>Varix bleeding</td>
<td>106 (91.0, 124.0)</td>
<td>106 (91.0, 124.0)</td>
<td>106 (91.0, 124.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Intractable ascites</td>
<td>595 (26.8)</td>
<td>595 (26.8)</td>
<td>595 (26.8)</td>
<td>0.006</td>
</tr>
<tr>
<td>Portal hypertension</td>
<td>325 (14.7)</td>
<td>325 (14.7)</td>
<td>325 (14.7)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>HCV-related</td>
<td>HCV-related</td>
<td>HCV-related</td>
<td>HCV-related</td>
<td>HCV-related</td>
</tr>
<tr>
<td>HBV-related</td>
<td>HBV-related</td>
<td>HBV-related</td>
<td>HBV-related</td>
<td>HBV-related</td>
</tr>
<tr>
<td>Others</td>
<td>Others</td>
<td>Others</td>
<td>Others</td>
<td>Others</td>
</tr>
</tbody>
</table>
| Values are presented as numbers (%), mean ± SD, or median (Q1, Q3). Massive transfusion was defined as ≥ 10 units of red blood cell transfusion. BNP: B-type natriuretic peptide, hsTnI: high-sensitivity troponin I, MELD: model for end-stage liver disease, LC: liver cirrhosis. 

https://doi.org/10.4097/kja.20296
Preoperative hsTnI concentrations

The frequency histogram of the hsTnI of the 2,490 enrolled patients is shown in Fig. 1. The median level of preoperative hsTnI was 6 ng/L (6, 160). A total of 1,463 (58.8%) patients showed normal hsTnI concentration of 6 ng/L, which is the lowest detectable value in the current study; therefore, 1,027 (41.2%) patients’ hsTnI exceeded 6 ng/L. Of 2,490 patients enrolled, 683 patients (27.4%) had levels between 7 ng/L and the 99th percentile URL (≈ 40 ng/L), 344 patients (13.8%) exceeded the 99th percentile URL (> 40 ng/L), and 272 (10.9%) had 1.5 times (> 60 ng/L), 133 (5.3%) had 5 times (> 200 ng/L), 84 (3.4%) had 10 times (> 400 ng/L), and 28 (1.1%) had 30 times the 99th percentile URL (> 1,200 ng/L), respectively.

Non-survivors within 90 days had significantly higher hsTnI values compared with survivors (median, 95 vs. 6 ng/L, P < 0.001). The best cut-off values of hsTnI for patients who died within 90 days and those who died during the entire follow-up period were 65 ng/L and 62 ng/L, respectively. Although the primary end-point of the current study is the 90-day mortality, these two cut-off values are very similar; therefore, we rounded them off to 60 ng/L, which is 1.5 times 99th percentile URL. When dichotomized with these cut-off values, patients with hsTnI ≥ 60 ng/L (n = 272, 10.9%) had higher MELD scores (median, 34 vs. 13, P < 0.001). The 90-day mortality rates according to a cut-off value of hsTnI of 60 ng/L were 1.4% and 15.1% (P < 0.001), with corresponding crude and adjusted HRs of 11.65 (7.31, 18.58; P < 0.001) and 2.65 (1.48, 4.74; P = 0.001), respectively (Tables 1 and 2).

Fig. 1. Histogram and accompanying density plot of baseline BNP and hsTnI. Note the difference in distributions of BNP and hsTnI according to the survival. BNP: B-type natriuretic peptide, hsTnI: high-sensitivity troponin I, POD: postoperative day.
### Table 2. Hazard Ratio for 90-day Mortality according to the Level of Baseline Cardiac Biomarkers Alone and in Combination

<table>
<thead>
<tr>
<th>Baseline BNP</th>
<th>Event (%)</th>
<th>Crude HR (95% CI)</th>
<th>P value</th>
<th>Adjusted HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>As continuous variable (log-transformed)</td>
<td>NA</td>
<td>6.50 (4.55, 9.28)</td>
<td>&lt; 0.001</td>
<td>2.10 (1.32, 3.34)</td>
<td>0.002</td>
</tr>
<tr>
<td>&lt; 400</td>
<td>35/2217 (1.6)</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 400</td>
<td>37/273 (13.6)</td>
<td>9.14 (5.75, 14.50)</td>
<td>&lt; 0.001</td>
<td>2.02 (1.15, 3.52)</td>
<td>0.014</td>
</tr>
<tr>
<td>Baseline hsTnI</td>
<td>NA</td>
<td>3.80 (3.08, 4.69)</td>
<td>&lt; 0.001</td>
<td>2.27 (1.64, 3.13)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>&lt; 60</td>
<td>31/2218 (1.4)</td>
<td>Reference</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 60</td>
<td>41/272 (15.1)</td>
<td>11.65 (7.31, 18.58)</td>
<td>&lt; 0.001</td>
<td>2.65 (1.48, 4.74)</td>
<td>0.001</td>
</tr>
<tr>
<td>Combination of BNP and hsTnI</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>According to the Threshold Analysis of BNP (pg/mL) and hsTnI (ng/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP &lt; 400, hsTnI &lt; 60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BNP ≥ 400, hsTnI &lt; 60</td>
<td>10/134 (7.5)</td>
<td>7.69 (3.62, 16.33)</td>
<td>&lt; 0.001</td>
<td>2.52 (1.07, 5.89)</td>
<td>0.033</td>
</tr>
<tr>
<td>BNP &lt; 400, hsTnI ≥ 60</td>
<td>14/133 (10.5)</td>
<td>11.14 (5.66, 21.90)</td>
<td>&lt; 0.001</td>
<td>3.30 (1.49, 7.31)</td>
<td>0.003</td>
</tr>
<tr>
<td>BNP ≥ 400, hsTnI ≥ 60</td>
<td>27/139 (19.4)</td>
<td>21.19 (11.98, 37.48)</td>
<td>&lt; 0.001</td>
<td>4.23 (1.98, 9.03)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values are presented as numbers (%) or hazard ratio (95% CI). The Cox regression models were adjusted using age, sex, deceased donor liver transplantation, hepatic encephalopathy, pretransplant vasopressor use, massive transfusion (> 10 units of red blood cell transfusion), renal replacement therapy, model for end-stage liver disease score, C-reactive protein, donor age, donor height, total ischemic time, and graft-to-recipient weight ratio. HR: hazard ratio, BNP: B-type natriuretic peptide, hsTnI: high-sensitivity troponin I.

### Relationship between hsTnI and BNP

There was a significant correlation between BNP and hsTnI ($r = 0.567$, $P < 0.001$) in all patients, and non-survivors showed more correlation between BNP and hsTnI compared with survivors ($r = 0.686$ vs. 0.472, interaction $P < 0.001$, Fig. 2). The proportion of patients with hsTnI plasma level ≥ 60 ng/L was 50.9% in the subset of patients with BNP ≥ 400 pg/ml and 6.0% in the subset with a BNP < 400 pg/ml ($P < 0.001$).

### Patients with history of coronary artery disease

Patients with a previous history of CAD (n = 29, 1.2%) had slightly higher baseline hsTnI concentration [15 ng/L (6–47) vs. 6 ng/L (6–16), $P = 0.004$], but the proportion of patients with hsTnI ≥ 40 ng/L (27.6% vs. 13.9%, $P = 0.063$) was not statistically different compared with the patients with no known history of CAD. Additionally, baseline BNP concentration in patients with CAD was not significantly different compared with those without a history of CAD [73 pg/ml (52, 198) vs. 80 pg/ml (39, 178), $P = 0.901$]. Furthermore, 90-day mortality (3.5% vs. 2.9%, $P = 0.999$) and overall mortality during the entire follow-up period (8.9% vs. 6.9%, $P = 0.961$) were similar.

### Mortality according to the BNP and hsTnI cut-off values in combination

Using a combination of two cut-off values: both decreased, either one elevated, or both elevated, three subsets were generated and patients’ characteristics in each of them are described in Supplementary Table 1. One hundred and thirty-nine patients (5.6%) were in the subset with both decreased, 267 (10.7%) were in the subset with either one elevated, and 2,084 (83.7%) were in the subset with both decreased. The subset with both elevated (BNP ≥ 400 pg/ml and hsTnI ≥ 60 ng/L) showed higher MELD scores and suffered more severe hepatic comorbidities compared with the subset with both decreased (Supplementary Table 1). They exhibited higher crude and adjusted HRs of 21.19 (11.98, 37.48; $P < 0.001$) and 4.23 (1.98, 9.03; $P < 0.001$), respectively, compared with that with both decreased (Table 2).

Specifically, when patients are dichotomized by liver disease severity using the MELD score, clear separation of Kaplan-Meier survival curves for mortality depending on the particular combination of BNP and hsTnI values was demonstrated. The number of deaths that occurred in the subset with MELD scores ≥ 15 was greater than the number in the subset with MELD scores < 15 (Fig. 3). Importantly, most of the deaths occurred within 1 year in patients with both biomarkers elevated. Among patients with MELD score ≥ 15, the 90-day mortality rates were 19.9% for pa-

https://doi.org/10.4097/kja.20296
Patients with both cardiac biomarkers elevated and 1.7% for those with both cardiac biomarkers decreased. Both cardiac biomarkers showed significant correlations with MELD scores, with more wide distribution among higher MELD scores (Supplementary Fig. 1). For 1,367 patients with low MELD score (< 15), only 0.2% of the patients showed both BNP and hsTnI elevated, whereas...
survivors (r = 0.472, interaction P < 0.001). (2) The best might be imposed on elevated cardiac strain when compared with stronger correlation, which implies that more myocardial injury scores. The main findings of the present study were: (1) There was mortality rate is clearly stratified into broad levels according to the combinations of preoperative BNP and hsTnI values, particularly among those with advanced liver cirrhosis with high MELD scores. The main findings of the present study were: (1) There was a significant correlation between BNP and hsTnI (r = 0.567, P < 0.001) in LT candidates; non-survivors, in particular, showed a stronger correlation, which implies that more myocardial injury might be imposed on elevated cardiac strain when compared with survivors (r = 0.686 vs. 0.472, interaction P < 0.001). (2) The best cut-off values of BNP and hsTnI for mortality prediction were 400 pg/ml and 60 ng/L (i.e., 1.5 times 99th percentile URL), respectively. (3) A half of those who had BNP ≥ 400 pg/ml are further stratified into having hsTnI ≥ 60 ng/L. (4) Using these cut-off values, patients with elevation of both BNP and hsTnI had a markedly greater risk of early 90-day mortality (19.4%) than those with elevation of either (9.0%) or neither (1.0%) of these 2 biomarkers; this result was profound in patients with MELD score ≥ 15.

In the present study, there was a significant correlation between BNP and hsTnI and this correlation was stronger in non-survivors. Approximately one half of patients (50.9%) with BNP ≥ 400 pg/ml had elevation of hsTnI ≥ 60 ng/L; in contrast, only 6% of patients with BNP < 400 pg/ml had hsTnI ≥ 60 ng/L. These findings suggest that release of hsTnI and BNP might be associated with each other and hsTnI release is activated partly by the increased cardiac strain (reflected by the high BNP) in response to various pathophysiological changes and/or stimuli of advanced liver disease, although the exact mechanism is unclear. It has been known that the physiological stimuli for myocardial production of BNP are an increase in preload and afterload and possibly myocardial ischemia [31,32]; further study will be needed to clarify their role in LT candidates. Indeed, 5.6% patients with both elevated BNP (≥ 400 pg/ml) and hsTnI (≥ 60 ng/L) showed higher MELD scores and suffered more severe comorbidities of advanced liver disease, such as renal replacement therapy, hepatic encephalopathy, and spontaneous bacterial peritonitis, compared with those with both biomarkers decreased (Supplementary Table 1).

We found that the effect of elevation of both cardiac biomarkers was more pronounced among patients with advanced cirrhosis, that is, those with a MELD score ≥ 15. Among patients with a low MELD score, the proportion of elevation of both BNP and hsTnI was small and did not make any difference in mortality rate. When coupled with high MELD score ≥ 15, the 90-day mortality rate of patients with concomitantly elevated cardiac biomarkers was over 10 times higher than that of patients with normal cardiac biomarkers (19.9% vs. 1.7%). This implies that the risk stratification using the combination of those cardiac biomarkers is more effective in more advanced end-stage liver disease patients. It is well known that LT is one of the high-risk non-cardiac surgical procedures, involving massive hemorrhage and inferior vena cava clamping. In addition, dynamic circulation, loss of systemic vascular resistance, need for higher cardiac output, and low hemoglobin, all features of severe end-state liver disease patients, might cause biomarker elevation. And it is often difficult to maintain the vital signs stable without maximized volume resuscitation, which can result in cardiac strain. All those possible causes for pre-LT cardiac biomarker elevation are more pro-

98.2% of them had neither elevated BNP nor elevated hsTnI above the cut-off values.

Restricted cubic spline analysis showing the hazard ratio of 90-day mortality with preoperative BNP on a continuous scale, with BNP 400 pg/ml as the reference value, grouped by a cut-off value for hsTnI of 60 ng/L is shown in Fig. 4.

**Discussion**

In the present study, we provide evidence supporting the feasibility of risk stratification using both cardiac biomarkers (BNP and hsTnI) concomitantly before LT surgery. The early 90-day mortality rate is clearly stratified into broad levels according to the combinations of preoperative BNP and hsTnI values, particularly among those with advanced liver cirrhosis with high MELD scores. The main findings of the present study were: (1) There was a significant correlation between BNP and hsTnI (r = 0.567, P < 0.001) in LT candidates; non-survivors, in particular, showed a stronger correlation, which implies that more myocardial injury might be imposed on elevated cardiac strain when compared with survivors (r = 0.686 vs. 0.472, interaction P < 0.001). (2) The best cut-off values of BNP and hsTnI for mortality prediction were 400 pg/ml and 60 ng/L (i.e., 1.5 times 99th percentile URL), respectively. (3) A half of those who had BNP ≥ 400 pg/ml are further stratified into having hsTnI ≥ 60 ng/L. (4) Using these cut-off values, patients with elevation of both BNP and hsTnI had a markedly greater risk of early 90-day mortality (19.4%) than those with elevation of either (9.0%) or neither (1.0%) of these 2 biomarkers; this result was profound in patients with MELD score ≥ 15.

We found that the effect of elevation of both cardiac biomarkers was more pronounced among patients with advanced cirrhosis, that is, those with a MELD score ≥ 15. Among patients with a low MELD score, the proportion of elevation of both BNP and hsTnI was small and did not make any difference in mortality rate. When coupled with high MELD score ≥ 15, the 90-day mortality rate of patients with concomitantly elevated cardiac biomarkers was over 10 times higher than that of patients with normal cardiac biomarkers (19.9% vs. 1.7%). This implies that the risk stratification using the combination of those cardiac biomarkers is more effective in more advanced end-stage liver disease patients. It is well known that LT is one of the high-risk non-cardiac surgical procedures, involving massive hemorrhage and inferior vena cava clamping. In addition, dynamic circulation, loss of systemic vascular resistance, need for higher cardiac output, and low hemoglobin, all features of severe end-state liver disease patients, might cause biomarker elevation. And it is often difficult to maintain the vital signs stable without maximized volume resuscitation, which can result in cardiac strain. All those possible causes for pre-LT cardiac biomarker elevation are more pro-
nounced in severe end-state liver disease state, which is well reflected by the higher MELD score. For 1,367 patients with low MELD score (< 15), our data showed that only 0.2% of the patients had elevated levels of both BNP and hsTnI, whereas 98.2% of them had neither elevated BNP nor elevated hsTnI above the cut-off values. Therefore, the clinical practice of measuring cardiac biomarkers in those with higher MELD score, which might go unnoticed without monitoring, is clearly recommended based on the current study results.

Circulating BNP, which is secreted into the circulation in response to increased cardiac wall stress, has been widely used in cardiology as a prognostic and diagnostic biomarker. Additionally, multiple studies have demonstrated that elevated preoperative BNP concentrations are independent predictors of perioperative cardiovascular mortality and morbidity [33,34]. Nevertheless, optimal data are still not available for LT surgery and only a few studies with small cohorts attempted to specify the cut-off values. It has been reported that the cut-off value of pre-LT BNP for predicting 180-day mortality was 155 pg/ml (n = 207) [35]. Another study (n = 104) demonstrated a BNP level of 100 pg/ml as a cut-off value for predicting early allograft dysfunction [29]. On the other hand, in the 30,487 patients’ data from the Vanderbilt University Medical Center electronic health record, the risk of death was similar regardless of whether patients had heart failure or not when the BNP level was sufficiently high. Namely, a BNP level of 400 pg/ml was associated with a three-year risk of death of 21% (95% CI, 20%, 23%) in patients with heart failure and 19% (95% CI, 17%, 20%) in those without [30]. In the present study, with a large LT cohort (n = 2,490), the statistically derived optimal cut-off value for the prediction of mortality was also close to 400 pg/ml (325 pg/ml for 90-day mortality and 442 pg/ml for overall mortality during the follow-up period).

Elevated cardiac troponin I levels have been traditionally associated with myocarditis, pericarditis, and myocardial infarction. With the development of high-sensitivity assay, it is now possible to detect myocardial injury at an earlier stage. We found that 344 patients (13.8%) exceeded the 99th percentile URL. However, the reference ranges of 99th percentile URL used for diagnosis of myocardial injury in a healthy population may not have equal predictive value for overall early mortality in LT surgery patients [36]. Hitherto, there are no known reference values for this atypical sub-population. In the current study, we provide the best cut-off value of 60 ng/L in LT candidates, which is 1.5 times the 99th percentile URL, and 10.8% of patients exceeded this cut-off value preoperatively.

With rising prevalence of CAD in LT candidates, patients with a previous history of percutaneous coronary intervention or coronary artery bypass surgery are also increasing. In the current study, such patients showed slightly higher baseline hsTnI concentration, but the proportion of patients exceeding the 99th percentile URL and 90-day mortality was not statistically different from those without a history of treatment of ischemic heart disease. We assume that the elevation of cardiac biomarkers, especially troponin, may be more related to type II myocardial infarction from supply/demand mismatch than type I classical myocardial infarction caused by plaque rupture of coronary arteries. This finding suggests that measurement of hsTnI and BNP before LT might be more important than the history of CAD itself.

Our study has several limitations. First, with its retrospective design, which may have selection bias, this study included a heterogeneous group of patients, which may have affected biomarker results and transplant outcomes. However, our current study cohort was large and included consecutive patients who had hsTnI and BNP measurement during routine preoperative and postoperative workups and we provided multivariable adjusted HR. Nevertheless, prospective randomized control studies are needed to validate our results. Second, we evaluated the cardiac biomarkers only within a week before LT. Considering the frequent incidence of hemodynamic instability in LT candidates, a kinetic analysis of serial cardiac biomarker levels would be more informative. Because of the necessity to exercise caution in drawing conclusions from a single study, future studies on the serial analysis of perioperative cardiac biomarker levels are warranted. Third, our data were based on the characteristics of patients from a single, large-volume center. Studies including multicenter records that include patients of different ethnicities and backgrounds are therefore needed. Fourth, we do not include data on frailty. Because the field of frailty has only recently been highlighted, our data, which include almost 10 years of consecutive LT, could not cover those functional aspects of LT recipients. However, although there is a rapidly growing body of evidence supporting the association between frailty and harmful outcome after LT [37,38], the consensus on its definition, tools for assessment, and implication for transplant seems not to be established yet [39]. Fifth, our study evaluated cardiac biomarkers only measured within a week before transplant. Most of them are measured just a day before transplant. We used very recent cardiac biomarker values to avoid confounding factors between their measurement and surgery as much as possible. Thus, it may not be reasonable to apply our data result directly into the listing system for cadaveric transplant, where the time course takes weeks and months. Although we demonstrated a clear relationship between hsTnI elevation within a week before transplant and poor outcome, we do not know whether the prognosis difference exists between remote and im-
mediate event(s) of preoperative myocardial injury/strain. As reported in a recent study, there is a possibility that longer duration between cardiac biomarker elevation and surgery might reduce the risk of adverse events [40]. Further studies with more frequent measurement of cardiac biomarkers in liver transplantation recipients should be conducted to discuss whether delaying (or even delisting) of those patients is needed. In addition, appropriate management strategies should be sought to minimize the postoperative risk of adverse outcome.

In conclusion, patients with myocardial injury (high hsTnI) in advanced liver disease with elevated cardiac strain (high BNP) had poorer survival after LT. Therefore, the combined use of preoperative BNP and hsTnI would help to recognize high-risk patients for predicting 90-day mortality after LT, especially in those with advanced MELD score. We recommend the routine monitoring of these two biomarkers in at-risk patients to enhance risk stratification of mortality in LT candidates and help administer target therapies that could modify early mortality.

Conflicts of Interest

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

Author Contributions

Young-Jin Moon (Conceptualization; Data curation; Formal analysis; Visualization; Writing – original draft; Writing – review & editing)
Hye-Mee Kwon (Data curation; Formal analysis; Visualization)
Kyeo-Woon Jung (Data curation)
Kyoung-Sun Kim (Data curation)
Won-Jung Shin (Supervision; Writing – review & editing)
In-Gu Jun (Supervision; Writing – review & editing)
Jun-Gol Song (Supervision; Writing – review & editing)
Gyu-Sam Hwang (Conceptualization; Formal analysis; Methodology; Visualization; Writing – original draft; Writing – review & editing)

Supplementary Materials

Supplementary Table 1. Demographics stratified by combinations of cut-off values of baseline BNP and hsTnI
Supplementary Fig. 1. Scatter plot with linear regression lines showing the distribution of baseline cardiac biomarker values (A: BNP, B: hsTnI) according to the MELD score. Both cardiac biomarkers show significant correlation with the MELD score. BNP: B-type natriuretic peptide, hsTnI: high-sensitivity troponin I, MELD: model for end-stage liver disease.

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Gyu-Sam Hwang, https://orcid.org/0000-0002-3627-1107

References

Combined use of BNP and hsTnI in LT

Moon et al. · Combined use of BNP and hsTnI in LT


Introduction

Protecting healthcare providers (HCP) from infection has been a highly prioritized goal during the management of the coronavirus 2019 (COVID-19) pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. While respiratory droplets and contact transmission are recognized as the most important routes of transmission for SARS-CoV-2, airborne dissemination of the virus may occur in settings where aerosol generating procedures (AGPs) are performed [2,3]. It is recommended that HCP use airborne, droplet and contact precautions personal protective equipment (PPE) during AGPs performed on suspected or confirmed COVID-19 patients [4–6].
Inadequate supply of appropriate PPE has been an ongoing worldwide concern, and unacceptably high rates of HCP infection and deaths as a consequence of COVID-19 nosocomial spread have been partially attributed to the shortage of PPE [7–9]. In addition, recent simulation studies looking at the protection of HCP wearing properly donned PPE found droplet markers on exposed neck, ears, hair, and shoes, suggesting that even with available standard recommended PPE there is still a potential risk of safety breaches and contamination [10,11]. A recent comprehensive Cochrane review summarizes the published evidence on PPE preventing infectious disease contamination of HCP, and overall found limited certainty in the evidence due to the limited, low powered studies [12]. This review stated that covering more exposed body surfaces of HCP can lead to better protection but often with more difficulty with donning or doffing, and less user comfort that can both lead to greater HCP contamination [12]. As a response to the inadequate PPE supply and concern for contamination, HCP have considered the use of innovative barrier enclosures during AGPs as supplemental protection against aerosol and droplet exposure [13–18].

There is wide recognition that acceptability should be examined when new interventions in health care are designed and implemented [19]. Both patient and provider acceptance of interventions have been studied, and it has been observed that the degree of acceptability can alter the effectiveness and uptake of the intervention [19–22]. During the COVID-19 pandemic, one of the first protective barriers proposed was an acrylic aerosol box (AB) covering a patient’s head [13]. However, the use of a rigid box has been reported to restrict arm movement [14]. Variations on the original AB design, and other designs that create isolation chambers (ICs) by utilizing a polyvinyl chloride plastic (PVC) rigid frame and a clear plastic bag, have subsequently been described [15–17]. However, no studies comparing acceptability of these devices have been reported.

In this pilot study, we tested two of the novel barrier enclosures, the AB and IC, in a simulated environment. The primary objective was to assess the acceptability of these additional physical barriers during a simulated airway management scenario performed by anesthesia providers. Secondary objectives included comparing the performance of airway management using PPE alone versus PPE plus the additional barrier, comparing the IC to the AB and observing potential limitations of the additional barriers. We hypothesize that the addition of a patient barrier will be acceptable to anesthesia providers without negatively impacting the provider’s ability to perform the simulated airway management procedures.

Materials and Methods

After Research Ethics Board (REB) approval (Human Research Ethics — Western University HSREB 115895, approved May 1, 2020), an open-label, double-armed pilot study was conducted in May 2020 at London Health Sciences Centre (LHSC), a tertiary care center in London, Canada. Study participants were voluntarily recruited from the Department of Anesthesia & Perioperative Medicine at Western University through a department-wide email invitation. Any resident, fellow, or consultant within the Department of Anesthesia & Perioperative Medicine at Western University satisfied the inclusion criteria. Since this was a pilot study, a sample size of 24 — 12 participants in each group was sought [23,24]. The simulation scenario was setup in an operating room at LHSC. Participation occurred during regular clinical shifts at LHSC so neither additional risk of COVID-19 hospital exposure nor any increased use of PPE was incurred by the study. Participants received a letter of information that was reviewed with a study coordinator prior to the simulation, and written informed consent was obtained.

Two physical barriers were assessed — the PVC rigid frame IC covered by a clear plastic bag proposed by Cubillos et al. [17], and a polycarbonate AB (Supplementary Fig. 1). Participants were divided into two groups by alternating assignment on arrival to the simulation. Group 1 was assigned to use the IC and Group 2 was assigned to use the AB. Both barriers were pre-constructed and ready for use by the participant. One of the study coordinators cut vertical armholes in the plastic bag of the IC at approximately mid-abdominal level and shoulder-width apart prior to the simulation session.

A pre-simulation questionnaire was completed by all participants (Table 1). In an effort to preserve supplies of PPE, participants were required to wear limited PPE. As a minimum, limited PPE required a mask (surgical mask or N95 respirator) and eyeshield, as these items were anticipated to most interfere with the use of additional patient barriers in terms of communication and vision, respectively.

During simulation, all participants, wearing limited PPE first performed bag-mask ventilation followed by endotracheal intubation using a GlideScope (Verathon, USA) with a size 3 blade and a 7.5 or 8.0 endotracheal tube with a stylet on a mannequin head (Airsim Advance X by TruCorp., Ireland). Immediately after, all participants wearing the same limited PPE performed the same airway management procedures using their assigned additional patient barrier. During both scenarios, the participant was allowed to make ergonomic and equipment adjustments according to personal preference such as bending of the styleted endotrache-
al tube, positioning of the equipment, and changes in the height of the bed. No verbal cues were given to the participants.

Time to endotracheal intubation was recorded for all simulations. This was standardized to begin when the participant picked up the GlideScope blade and concluded when the endotracheal cuff was inflated. All participants received expert assistance for airway management — either one of the study coordinators or another study participant. Following the simulated activities, the participant completed a post-simulation questionnaire (Table 2).

Both questionnaires consisted of seven five-point Likert-scale questions, in addition to one binomial question (question 1) in the pre-simulation questionnaire, created for this pilot study to address the proposed objectives (Tables 1 and 2) [25]. The primary outcome of acceptability was assessed by evaluating the five-point Likert scale median and interquartile range (Q1, Q3) of the questions assessing acceptability, where a response of 3.5 or greater was considered positive and 2 or less considered negative [26,27]. Intubating times for each group were recorded. Participants identified whether they were assigned to the IC or AB on the post-simulation questionnaire to facilitate comparison of the IC to the AB. Limitations of the additional barriers were assessed through post-simulation questionnaire responses. All questionnaires were completed anonymously.

Statistical analysis comparing intubating times between PPE alone and IC, and PPE alone and AB was completed using a paired t-test. Intubating times and post-simulation questionnaire results between IC and AB were compared using a non-paired t-test. A 95% CI was used, and P value < 0.05 was considered significant.

**Results**

A total of 29 participants from the Department of Anesthesia & Perioperative Medicine were included in the pilot study (Fig. 1). On simulation day 3, the threshold of 24 participants was surpassed and the study ended.

For the questionnaires, responses to the one binomial pre-simulation question (question 1), and to the seven five-point Likert questions in the pre- and post-simulation questionnaire were evaluated and the median (Q1, Q3) values were calculated. A summary of the pre- and post-simulation questionnaire responses can be found in Tables 1 and 2, respectively. Regarding the primary outcome of acceptability, median (Q1, Q3) values for the pre- and post-simulation questions assessing acceptability to anesthesia providers were all positive (> 3.5), indicating acceptability of the additional barriers (Figs. 2 and 3, respectively).

Intubating times were assessed for limited PPE (30.1 ± 11.7 s), Group 1 IC (31.4 ± 20.1 s), and Group 2 AB (31.3 ± 23.3 s). Intu-

### Table 1. Pre-simulation Questionnaires and Median Responses

<table>
<thead>
<tr>
<th>Questions and Likert Scale Response</th>
<th>Median (Q1, Q3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I have used an aerosol tent as an additional patient barrier during AGP</td>
<td>2 (2, 2)</td>
</tr>
<tr>
<td>2. I am familiar with the aerosol tent as a patient barrier</td>
<td>3 (2, 4)</td>
</tr>
<tr>
<td>3. During the COVID-19 pandemic, I worry about exposure to aerosolized viral</td>
<td>5 (4, 5)</td>
</tr>
<tr>
<td>4. Additional patient barriers are appealing during AGP</td>
<td>4 (4, 5)</td>
</tr>
<tr>
<td>5. An aerosol tent will help protect providers during AGP</td>
<td>4 (3, 5)</td>
</tr>
<tr>
<td>6. I worry about the impact of an aerosol tent on my performance during AGP</td>
<td>4 (3, 4)</td>
</tr>
<tr>
<td>7. Enhanced PPE is sufficient protection during AGP</td>
<td>3 (3, 4)</td>
</tr>
<tr>
<td>8. I would like additional patient barrier protection during AGP, in addition to current PPE</td>
<td>3.5 (3, 4)</td>
</tr>
</tbody>
</table>


### Table 2. Post-simulation Questionnaire and Median Responses

<table>
<thead>
<tr>
<th>Questions and Likert Scale Response</th>
<th>Median (Q1, Q3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The aerosol tent/box allowed me to perform all aspects of patient care required (BMV, intubation, etc.).</td>
<td>5 (5, 5)</td>
</tr>
<tr>
<td>2. The aerosol tent/box negatively affected my communication</td>
<td>1 (1, 2)</td>
</tr>
<tr>
<td>3. The aerosol tent/box was difficult to look through to see what was required</td>
<td>1.5 (1, 3)</td>
</tr>
<tr>
<td>4. The aerosol tent/box impeded my movement</td>
<td>2 (1, 4)</td>
</tr>
<tr>
<td>5. The aerosol tent/box worked well overall during AGP</td>
<td>4 (4, 5)</td>
</tr>
<tr>
<td>6. The aerosol tent/box was easy to assemble and use</td>
<td>4.5 (4, 5)</td>
</tr>
<tr>
<td>7. Use of an aerosol tent/box during AGP in addition to my PPE will be safer</td>
<td>4 (4, 5)</td>
</tr>
</tbody>
</table>

1 → 5 = Strongly Disagree → Strongly Agree. BMV: bag-mask ventilation, AGP: aerosol generating procedure, PPE: personal protective equipment.

https://doi.org/10.4097/kja.20464
bating times for PPE to IC and PPE to AB (95% CI, 26.3, 35.1, P = 0.752; 95% CI, 25.9, 35.5, P = 0.824; respectively) and IC to AB (95% CI, 23.6, 39.1, P = 0.995) were compared and there was no statistically significant difference between any of the groups.

Post-simulation IC and AB questionnaire responses to assess the primary outcome demonstrated no significant difference between IC and AB for all questionnaire responses (questions 1–7: P = 0.580, P = 0.899, P = 0.642, P = 0.944, P = 0.613, P = 0.127, P = 0.181, respectively) (Fig. 4).

Post-simulation responses regarding communication, vision, and movement indicated the participants did not find the additional barriers limiting (median [Q1, Q3] responses 1 [1, 2], 1.5 [1, 3] and 2 [1, 4], respectively) (Fig. 5).

**Discussion**

As much is still being learned about COVID-19, several key points suggest the importance of enhanced barrier protection. Viral particles have been found on surfaces and in the air up to 4 m from patients, and viable on surfaces for up to 72 h and as aerosols for at least 3 h [3,28]. Studies investigating respiratory and cough particles have shown contamination of HCP wearing standard PPE, while an AB or plastic drape reduced macroscopic contamination of the HCP and the environment [11,14,18].

Our data suggests additional patient barriers are acceptable to anesthesia providers during simulated bag-mask ventilation and endotracheal intubation using videolaryngoscopy. The majority of participants in this study had not used an additional patient barrier prior to the simulation, but stated they worry about aerosolized viral particles and found additional patient barriers to be appealing. While studies have described limited arm movement with the AB design [14,15], Cubillos et al. [17] did not report restrictions of movement with the IC design. Overall, participant responses indicated that the additional barriers were easy to use, allowed for all simulated airway management maneuvers to be executed, and had the potential to complement the current PPE clinical safety measures.

The results in this study show a high acceptance rate of additional barriers to protect anesthesia providers and indicate that implementation would likely be effective with a high user uptake. This data is translatable to other anesthesia providers, although situational variations encountered in daily practice can limit widespread applicability in all circumstances. The additional patient barriers also have the potential for use in a variety of other clinical settings where risky AGPs are performed. The absence of observed limitations to using a barrier in this study may not be applicable to all other scenarios.

Limitations of this study include the physical, psychological, and semantic realism of the simulation environment that differ significantly from the real clinical environment where challenging circumstances such as a potentially difficult airway can significantly affect airway management outcomes and overall acceptability of the barriers [29]. Additionally, the results cannot be extrapolated to conclude that similar results would be obtained during airway management using different equipment, such as direct laryngoscopy or a supraglottic device. There was no randomization in this study, as participants were alternately allocated upon arrival to the simulation, although their arrival was not

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**Fig. 1.** CONSORT flowchart of participants enrolled in the pilot study, including allocation, follow-up, and analysis.
planned or pre-arranged. A selection bias might result from having volunteers. Finally, all participants performed the AGPs with PPE alone prior to the additional barrier and may have become more familiar with the mannequin airway.

Further research into the additional patient barriers is warranted before they can be safely recommended for clinical use. Barriers may inadvertently create a false sense of security causing more harm than benefit. Additionally, prior to the use of any additional patient barrier, HCP should receive proper orientation and simulation-based training in order to optimally benefit from the device. However, there is no evidence that novel barrier devices are associated with less viral transmission. Each barrier, although intuitively appealing, could have unintended consequences such as infection transmission caused by PPE breaches or inadequate donning and cleaning between uses. Quantitative studies comparing barriers, and examining their enhanced level of protection are pertinent and needed. Moreover, investigating other barrier modifications, such as the application of continuous suction to create a negative pressure environment and flow to further enhance the safety of the environment, is essential. In the long-term, it will also be crucial to monitor any meaningful and significant difference in the rate of nosocomial spread with the addition of patient barriers.

Overall, with the worldwide crisis generated by this pandemic that significantly impacts HCP safety and health care system stability, we have learned that further study is warranted when new tools are introduced as potential devices that might impact critical outcomes. This novel study is the first to assess the acceptability of additional patient barriers, and to further compare two differently designed devices. Our pilot data suggests that anesthesia providers positively accept the use of additional patient barriers during AGP and there would be support to have these barriers as an option to complement the standard PPE recommendations.

Fig. 2. Pre-simulation questions assessing the acceptability of additional barriers to anesthesia providers. PPE: personal protective equipment, HCP: healthcare providers, AGP: aerosol generating procedures.

Fig. 3. Post-simulation questions assessing the acceptability of additional barriers to anesthesia providers. BMV: bag-mask ventilation, AGP: aerosol generating procedures.
Fig. 4. Post-simulation questionnaire average responses for five-point Likert scale questions. Comparison between Group 1 IC and Group 2 AB for questions 1–7. IC: isolation chamber, AB: aerosol box.

Fig. 5. Post-simulation questionnaire responses to barrier limitations.

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Conflicts of Interest

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

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Supplementary Materials

Supplementary Fig. 1. Images of the additional barriers used in the simulation. (A) Picture of the IC, (B) Picture of the AB. IC: isolation chamber, AB: aerosol box.

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References

Endotracheal intubation using a three-dimensional printed airway model in a patient with Pierre Robin sequence and a history of tracheostomy - a case report -

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Background: Pierre Robin sequence (PRS) patients have an increased risk of difficult intubation due to anatomical airway abnormalities, and intubation simulation with a three-dimensional (3D) printed airway model before anesthesia may facilitate safe airway management.

Case: We describe the case of a 6.5-year-old boy with a history of PRS (a triad of micrognathia, glossoptosis, and airway obstruction), tracheostomy, and subglottic fibrosis who required general anesthesia. Preparation for this potentially difficult intubation included estimation of endotracheal tube size using a 3D printed airway model derived from 3D computed tomography of the airway, which enabled successful endotracheal intubation via video laryngoscopy.

Conclusions: If general anesthesia is necessary in patients with dysmorphic features such as PRS and there is a history of tracheal pathology, the possibility of difficult intubation should always be considered and simulation of endotracheal intubation using a 3D printed model of the airway can be helpful clinically in such situations.

Keywords: Airway management; Computer simulation; Endotracheal intubation; Pierre Robin sequence; Pierre-Robin syndrome; 3D printing.
old boy with PRS (height 110 cm, weight 15.46 kg) who was admitted due to persistent leakage at the closure site after percutaneous endoscopic gastrostomy removal. He had a history of failed intubation and emergent tracheostomy at birth due to severe micrognathia and glossoptosis. Granular tissue removal at the tracheostomy site was performed due to subglottic fibrosis four months after tracheostomy. Micrognathia and repaired cleft palate were identified by physical examination.

We decided to use 3D printed airway modeling, because there was a possibility of difficult intubation and it was difficult to predict the appropriate endotracheal tube size. The open-source program InVersalius (InVersalius 3.0, Renato Archer Information Technology Center, Brazil) was used for 3D printed airway modeling and for the generation of .stl files, and the 3D airway model was printed using CreatBot (CreatBot F430, Henan Suwei Electronic Technology Co., Ltd., China). The 3D printed airway model did not reveal airway narrowing (Fig. 1A), and simulation of endotracheal intubation was successful with an internal diameter (ID) 5.5 sized cuffed endotracheal tube (Hi-contour oral cuffed tracheal tube, Covidien, USA) (Fig. 1B).

The patient had a small chin and his range of movement from ear to orbit was estimated to be over 120 degrees (Fig. 1C). General anesthesia induction and intubation were planned with reference to the difficult airway algorithm described in the 2013 American Society of Anesthesiologists guidelines [3]. Before the induction of anesthesia, ID 4.5, 5.0, 5.5, and 6.0 cuffed and uncuffed endotracheal tubes were secured, and pre-emptive preparations were made for laryngeal mask airway, video laryngoscope (KoMAC video laryngoscope, KoMAC Co., Ltd., Korea), stylet, nasopharyngeal airway, oropharyngeal airway, and fiberoptic bronchoscope. Mask ventilation was possible after the administration of intravenous thiopental 75 mg, followed by rocuronium 10 mg. Successful endotracheal intubation was performed via video laryngoscopy with a #2 blade, a stylet, and an ID 5.5 cuffed endotracheal tube. Ventilation was performed after confirming the suitability of the endotracheal tube using a leakage test. There were no subsequent complications, and he was discharged on postoperative day 6.

**Discussion**

Two aspects of the current patient’s pre-anesthesia plan were focused on: the potential for difficult airway intubation and the difficulty of determining the appropriate endotracheal tube size due to his history of tracheostomy and subglottic fibrosis. Predictors of difficult intubation in congenital syndromes include the presence of dysmorphic features, limited neck, limited mouth opening, restricted mobility of temporo-mandibular joints, a large tongue, limited submandibular space, and the presence of structural abnormalities in the laryngo-tracheal passage [4]. All patients with PRS have airway obstruction, as it is a requirement for the clinical diagnosis [1]. Although airway obstruction tends to improve with age, the very difficult intubation with direct laryngoscopy should be always considered in the pre-anesthesia plan [5]. In the patients with PRS, fiberoptic intubation is the gold standard, but numerous other approaches have been used successfully including direct video laryngoscopy and fiberoptic intubation via laryngeal mask airway [4]. Successful intubation was

![Fig. 1.](https://doi.org/10.4097/kja.20430)

Printed three-dimensional (3D) airway model and patient’s dysmorphic face. (A) Printed 3D airway model derived from 3D chest airway computed tomography. (B) Simulation of intubation with a 3D printed airway model. Simulated endotracheal intubation was successful with an internal diameter 5.5 sized cuffed endotracheal tube. (C) The patient’s dysmorphic facial features. He had a small chin, mild retrognathia, and a short thyromental distance.
performed on the first attempt using video laryngoscopy in the present case.

An important consideration during the pre-anesthesia planning in the present case was the undesirability of using the age-dependent formula to determine endotracheal tube size because the patient had a history of tracheostomy. Many reports have described methods for measuring airway size via imaging modalities such as X-ray, CT, and ultrasonography, but two-dimensional imaging methods have inherent limitations [6–8]. X-ray tends to overestimates of tracheal diameter [9], and high-quality laryngeal images by CT are not routinely warranted because images by CT can be affected by airway size, reconstruction algorithm, composition of the airway phantom, and CT scanner types [10]. The quality of ultrasonography also depends on the experience of the operator [11].

Following advances in medical technology, many studies that have successfully implemented two-dimensional radiographic images in three dimensions have been reported in the surgical field [12,13]. Various attempts to use 3D models have been made in the field of anesthesia, but there have been only a few resulting reports and the reality is that those attempts were focused on education rather than actual clinical application [14].

In the current case, a 3D printed airway model was successfully used to confirm that there were no anatomical abnormalities of the airway. It was also possible to predict the appropriate endotracheal tube size. This indicates that simulation of intubation via 3D printed airway modeling before anesthesia can be helpful with regard to safe airway management, and reducing the risks of airway irritation, injury, and edema by reducing the number of endotracheal intubation attempts in cases where difficult intubation is expected due to anatomical abnormalities of the face and airway. Accurate airway evaluation using 3D printing may help anesthesiologists to understand the anatomy of the airways and is useful for developing a better pre-anesthesia plan via simulation of intubation.

However, there are several limitations to the approach. Three-dimensional implementation of medical imaging data requires high-quality imaging, and it is more difficult to apply 3D conversion software programs to airway images than to images of solid organs because of the air layer. In addition, 3D printed airway models may differ from the actual airway because of flexibility.

In conclusion, if general anesthesia including endotracheal intubation is necessary in patients with dysmorphic features such as PRS and there is a history of tracheal pathology, the possibility of difficult intubation should always be considered, and the difficult airway algorithm should be followed. Simulation of endotracheal intubation using a 3D printed model of the airway can be helpful clinically in such situations.

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

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Pregnancy-related infection is the third most common cause of maternal death worldwide [1]. Sepsis represents one of the common causes of pregnancy-related mortality, the most frequent being hypertension, abortion, and hemorrhagic complications [2]. The most common conditions and procedures leading to severe infection and sepsis in obstetrics include chorioamnionitis, septic thrombophlebitis, septic abortion, postpartum endometritis, puerperal sepsis, infection after cesarean section, episiotomy, wound infection, necrotizing fasciitis, pelvic abscess as well as hospital acquired infections such as ventilator-associated pneumonia, urinary tract infection, and central line-associated infection [3]. Refractory septic shock is defined as “the presence of hypotension with end-organ failure, requiring high-dose vasopressor support, often greater than 0.5 μg/kg/min of norepinephrine or equivalent” [4]. Despite recent advances, it is associated with a mortality rate of 15–50%; furthermore, if the required dose of norepinephrine exceeds 1.0

**Case Report**

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**Refactory gram-negative septic shock complicated by extended purpura fulminans and multiple organ failure in a 23-year-old puerpera -a case report-**

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**Background:** Pregnancy-related infections are the third most common cause of maternal death worldwide. The aim of this report is to present a case of pregnancy-related infection, which progressed into refractory septic shock accompanied by purpura fulminans and multiple organ failure.

**Case:** A 23-year-old woman in the postpartum period developed fulminant, refractory septic shock complicated by purpura fulminans and multiple organ failure syndrome (acute respiratory distress syndrome, acute kidney injury, and encephalopathy). Management included antibacterial therapy, fluid and transfusion therapy, nutritional support, protective mechanical ventilation, hydrocortisone, a large dose of ascorbic acid, and thiamine. There were no neurological consequences and all organ functions returned to normal, although the predicted hospital mortality based on the Sequential Organ Failure Assessment (SOFA) score was more than 90%.

**Conclusions:** Septic shock is a significant, yet not completely understood life-threatening condition, which can be associated with purpura fulminans, multiple organ dysfunction, disseminated intravascular coagulation, and massive tissue necrosis.

**Keywords:** Disseminated intravascular coagulation; Hypercoagulability; Purpura fulminans; Sepsis; Septic shock; Therapeutic use; Vasoconstrictor agents.
μg/kg/min, the mortality can be as high as 80–90% [5]. The key component of refractory shock is severe tissue hypoperfusion, and critical cellular and metabolic failure.

Lipopolysaccharide is a component of the outer membrane of gram-negative bacteria and is one of the key causative factors of septic shock in ICU patients [6]. The intravasation of gram-negative bacteria can trigger a cascade of systemic inflammatory reactions that frequently result in lethal outcomes [7]. *Purpura fulminans* is a serious condition, which usually occurs secondary to sepsis; it can be associated with disseminated intravascular coagulation (DIC) and is characterized by dermal vascular thrombosis and hemorrhagic infarction of the skin [8]. Sepsis-induced *purpura fulminans* involves an imbalance of anticoagulant and procoagulant activities of the endothelial cells [9]. This imbalance is induced by the endotoxins or exotoxins in gram-negative or gram-positive sepsis respectively, mediated by cytokines, resulting in the consumption of proteins C and S, and antithrombin III [9]. There are three main etiologic subtypes of *purpura fulminans*:

1. idiopathic *purpura fulminans*—occurs in patients without known or acute infections or abnormalities of the protein C pathway,
2. acute infectious *purpura fulminans*—occurs mainly in patients with acute severe gram-negative bacterial infections,
3. occurs in patients with preexistent inherited or acquired abnormality of protein C or S anticoagulant pathway [9]. In this case report, we present a case of pregnancy-related infection, which progressed into refractory septic shock accompanied by *purpura fulminans* and multiple organ failure.

**Case Report**

A 23-year-old postpartum woman with septic shock was transferred to the intensive care unit of the University Medical Center, from a regional rural hospital. During pregnancy, she was diagnosed with severe iron deficiency anemia (hemoglobin concentration 8.6 g/dl), gestational hypertension, meconium-stained amniotic fluid, and prolonged rupture of the membranes. There was no evidence of infection during the period of pregnancy and no *Streptococcus spp.* was detected in the vaginal smear. The course of pregnancy was complicated by chorioamnionitis, and urgent cesarean section was performed several days before transfer to our department. There was no evidence of shock/end-organ dysfunction during labor. About 24 hours following cesarean section, the patient developed clinical manifestations of purulent postpartum endometritis with fever of 39°C, chills, purulent uterine discharge, and fundal tenderness. An arterial line was placed following the diagnosis of endometritis. The sample for blood culture was obtained before initiation of empiric antibacterial therapy (vancomycin and gentamicin). Several hours later, she developed sepsis that abruptly progressed to septic shock (arterial pressure decreased to 60/40 mmHg) and organ failure with a sequential organ failure assessment (SOFA) score of 16–20 (10–12 points on the Glasgow Coma Scale, acute respiratory distress syndrome [ARDS] with PaO₂/FiO₂ 180 mmHg, norepinephrine > 0.3 μg/kg/min [weight 60 kg], bilirubin 23 mmol/L, platelets 35 × 10⁹/μL, and urine output 300 ml/day). Laboratory tests showed multiple abnormalities including hemoglobin concentration of 7.7 g/dl, white blood cells 25 × 10⁹/L, prothrombin time 21 s, fibrinogen concentration 89 mg/dl, antithrombin III 53%, D-Dimer 2.4 μg/ml (normal range < 0.5), C-reactive protein 309.5 mg/L, procalcitonin 45 ng/ml, lactate 7.5 mmol/L, and brain natriuretic peptide (BNP) 4,000 ng/ml (Table 1). Protein C and protein S tests were not available due to technical limitations. A bolus of normal saline (30 ml/kg) was administered and immediate norepinephrine infusion (0.3 μg/kg/min) was initiated. Due to the patient’s unstable condition, she was intubated and respiratory support in assist-control mode was initiated. Within a short span of time, the dose of norepinephrine was increased to 3.0 μg/kg/min to maintain the mean arterial pressure in the range of 60–65 mmHg. Two hours after the onset of shock, the color of her fingers and toes as well as abdominal wall appeared mottled. Several hours later, the echocardiogram demonstrated left ventricular systolic dysfunction with an ejection fraction of 32%, and dobutamine infusion (20 μg/kg/min) was initiated to improve cardiac contractility. Attempts to reduce the doses of catecholamines were unsuccessful due to inadequate hemodynamic response to fluid therapy. After initial stabilization of the puerperal condition, hysterectomy was performed. Two days later, the patient was transferred to our hospital by sanitary aviation.

Physical examination on admission to our department revealed massive aseptic necrosis of all fingers (I–V), toes (I–V), metatarsal region, and anterior abdominal wall (Figs. 1 and 2). The patient also had had sepsis/septic shock-induced multiple system failure including ARDS, encephalopathy,ystolic heart failure, and acute kidney injury. Invasive blood pressure was 100/70 mmHg, heart rate was 150/min, arterial oxygen saturation was 85–92%, and body temperature was 38.4°C. The patient was sedated with dexmedetomidine (0.4 μg/kg/h) and mechanically ventilated (assist/control ventilation with positive end expiratory pressure of 14 cmH₂O and FiO₂ 0.7). Auscultation revealed crackles over the right middle and lower zones of the lungs. Hemodynamic support required intravenous norepinephrine 2 μg/kg/min and dobutamine 20 μg/kg/min.

Investigations revealed the following abnormalities: Hb 9 g/dl, WBC 22 × 10⁹/L, C-reactive protein 200.5 mg/L, lactate 4 mmol/L.
bial pathogens were identified in the necrotic tissues. Patient management plan included antibacterial therapy, goal-directed fluid therapy, nutritional support, protective mechanical ventilation, hydrocortisone, fresh frozen plasma, and high dose of ascorbic acid and thiamine. The skin wounds were managed with dressing and moist healing products. Three weeks after admission to our intensive care unit the patient was weaned off mechanical ventilation as well as from vasopressor therapy. There were no neurological consequences and all end-organ functions returned.

<table>
<thead>
<tr>
<th>Organ dysfunction</th>
<th>Patient's parameters at the time of onset of septic shock</th>
<th>Patient's parameters two days later</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulatory failure (reduced tissue perfusion); disorder of coagulation</td>
<td>Blood pressure 60/40 mmHg, Pulse rate 120 beats/min, Hyperlactatemia 7.5 mmol/L, Decreased capillary refill (Ischemia and necrosis of fingers, toes, skin of the abdominal wall), D-Dimer 2.4 µg/ml</td>
<td>Lactate 4 mmol/L, Creatine kinase-MB 15.1 IU/L, BNP 5000 ng/ml, Massive aseptic necrosis of the fingers (I–V); toes (I–V), metatarsal region, and anterior abdominal wall, D-Dimer 1.5 µg/ml</td>
</tr>
<tr>
<td>Myocardial dysfunction</td>
<td>Myocardial hypokinesis of the anterior wall of left ventricle, Reduced left ventricular contractility, Ejection fraction 32%</td>
<td>Myocardial hypokinesis of the anterior wall of left ventricle, Ejection fraction 38%</td>
</tr>
<tr>
<td>Acute respiratory distress syndrome</td>
<td>PaO$_2$/FiO$_2$ 180 mmHg</td>
<td>PaO$_2$/FiO$_2$ 250 mmHg</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Paralytic ileus</td>
<td>Paralytic ileus</td>
</tr>
<tr>
<td>Systemic inflammatory response and infection</td>
<td>Procalcitonin 45 ng/ml, CRP 175.8 mg/L</td>
<td>Procalcitonin 32 ng/ml, CRP 200.5 mg/L, <em>Escherichia coli</em>, <em>Pseudomonas aeruginosa</em>, and <em>Acinetobacter baumannii</em> were positive on blood culture</td>
</tr>
<tr>
<td>Cerebral dysfunction</td>
<td>Delirium, 12 points on the Glasgow Coma Scale</td>
<td>Delirium, 13 points on the Glasgow Coma Scale</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>Urine output 300 ml/day</td>
<td>Urine output 320 ml/day</td>
</tr>
</tbody>
</table>

CRP: C-reactive protein, PaO$_2$: partial pressure of oxygen, FiO$_2$: fraction of inspired oxygen, BNP: brain natriuretic peptide.

Fig. 1. Massive necrosis of the anterior abdominal wall.

Fig. 2. Necrosis of toes of the right foot.
to normal (although the SOFA score-predicted hospital mortality was more than 90%); however, the necrotic area was quite large. The duration of vasopressor support totaled 8 days. After stabilization of the general condition, the necrotic masses were debrided and autodermoplasty was performed signed informed consent for publication was obtained.

**Discussion**

In our patient, refractory septic shock was complicated by *purpura fulminans*—a relatively infrequent symptom of DIC [10], which resulted in progressive tissue necrosis.

The presentation of such a massive lesion can be explained by the critical reduction of tissue perfusion due to *purpura fulminans*, probable heterogeneity in the distribution of blood flow, endothelial injury, and impaired oxygen utilization. Success in septic shock management depends on early recognition and resuscitation. The outcomes of treatment can be improved and complications can be minimized by a balanced combination of fluid and vasopressor/inotropic therapy; both should be initiated as soon as possible to improve microcirculation, blood viscosity, and to normalize coagulation to prevent severe ischemia-hypoxic tissue injury. Vasopressor therapy is one of the key components of septic shock management, especially if early fluid therapy cannot achieve hemodynamic stabilization. However, high-dose vasoconstrictor therapy in a hypovolemic patient might result in exacerbation of tissue ischemia and development of irreversible ischemic injuries such as digital necrosis as well as necrosis of the internal organs. Advanced hemodynamic monitoring might be useful for the customization of fluid and vasopressor/inotropic therapy.

This condition was complicated by the failure of cardiovascular, pulmonary, cerebral, renal, and intestinal systems, and massive necrosis of the skin and subcutaneous tissue. Another interesting finding in our patient was that she developed sepsis-induced cardiac dysfunction several hours after the onset of sepsis. BNP was significantly elevated to 5,000 ng/ml and the ejection fraction was severely reduced to 32%, although the patient had no history of cardiac problems. It has been reported that cardiac dysfunction in patients with septic shock was associated with a significant increase in the rate of mortality up to 70–90%, compared to 20% in those without cardiac dysfunction [11].

The clinical manifestations of sepsis-induced *purpura fulminans* commonly include purpuric rash as well as symptoms and signs of sepsis, which is usually preceded by fever or chills, sore throat, and malaise. It has been reported that *purpura fulminans* was associated in about 67% of patients with septic shock and in 78% of patients with DIC [12]. The differential diagnoses include thrombotic thrombocytopenic purpura, postinfectious thrombocytopenic purpura, and Henoch-Schönlein purpura [12]. *Purpura fulminans* can be associated with a mortality of up to 50%. The standard management of *purpura fulminans* includes aggressive fluid resuscitation, inotropic therapy, respiratory support, coagulation control and management (fresh frozen plasma, anticoagulants), treatment of underlying infection, renal replacement therapy, and management of complications [13]. In addition, we believe that our patient might have benefited by early initiation of blood purification therapy with cytosorbent or its analogues. However, it is uncertain whether this would have prevented the development of *purpura fulminans* and massive necrosis, since the onset of septic shock was abrupt and blood purification therapy would require time before visible effect. In our opinion, early removal of the endotoxins and inflammatory cytokines could probably attenuate multiple organ dysfunction and reduce the extent of organ failure.

In conclusion, septic shock is a significant, yet not completely understood life-threatening condition, which can be associated with *purpura fulminans*, multiple organ dysfunction, disseminated intravascular coagulation, and massive tissue necrosis.

**Conflict of Interest**

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

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The erector spinae plane block (ESPB) has been reported to have several complications. However, there has been no report of local anesthetic systemic toxicity (LAST). Here, we describe a case of LAST in a patient receiving levobupivacaine for ESPB.

Informed consent for publication was obtained from the patient, and this report was approved by Shimane University Hospital Institutional Review Board (approval no. 4685). We performed ultrasound-guided bilateral ESPB in a 50-year-old male (weight 58 kg, height 163 cm) who underwent endoscopic laminectomy for lumbar spinal canal stenosis. The patient had no medical history other than lumbar spinal canal stenosis.

Before the block, we administered 1 mg of midazolam intravenously (IV) and 1 μg/kg (lean body mass) fentanyl IV. The patient was placed in a prone position. First, we identified the right L4 transverse process on ultrasound after placing a transducer (15-6 Hz, FUJIFILM SonoSite, Japan) in the longitudinal plane. The needle was inserted in-plane, and 15 ml of 0.5% levobupivacaine was injected. We observed linear fluid spreading deep to the erector spinae muscle between the L1 and sacral levels. Next, we performed left-side ESPB as well as right-side ESPB and observed linear fluid spreading between the L2 and sacral levels. Thus, we used a total of 30 ml of 0.5% levobupivacaine. No blood aspiration was observed before or during the local anesthetic injection on either side. However, immediately after the block, the patient engaged in verbal communication with the medical staff. While turning him to the supine position, he suddenly stopped responding to our questions, and when he became supine, he convulsed. At the time of the event, vital signs were as follows; blood pressure: 119/91 mmHg, Heart rate: 61/min, respiratory rate: 12/min; saturation of percutaneous oxygen: 97%.

We did not find arrhythmia on the electrocardiogram monitor. By that time, 15 min had elapsed after the right-side ESPB, and it had been 7 min since the left-side ESPB. We administered 5 mg of midazolam intravenously and 1 μg/kg fentanyl IV. The patient was placed in a prone position. First, we identified the right L4 transverse process on ultrasound after placing a transducer (15-6 Hz, FUJIFILM SonoSite, Japan) in the longitudinal plane. The needle was inserted in-plane, and 15 ml of 0.5% levobupivacaine was injected. We observed linear fluid spreading deep to the erector spinae muscle between the L1 and sacral levels. Next, we performed left-side ESPB as well as right-side ESPB and observed linear fluid spreading between the L2 and sacral levels. Thus, we used a total of 30 ml of 0.5% levobupivacaine. No blood aspiration was observed before or during the local anesthetic injection on either side. However, immediately after the block, the patient engaged in verbal communication with the medical staff. While turning him to the supine position, he suddenly stopped responding to our questions, and when he became supine, he convulsed. At the time of the event, vital signs were as follows; blood pressure: 119/91 mmHg, Heart rate: 61/min, respiratory rate: 12/min; saturation of percutaneous oxygen: 97%.

We did not find arrhythmia on the electrocardiogram monitor. By that time, 15 min had elapsed after the right-side ESPB, and it had been 7 min since the left-side ESPB. We administered 5 mg of midazolam IV, and the patient’s convulsions subsided. We additionally administered a lipid emulsion (20% soybean oil 250 ml). No circulatory symptoms, respiratory arrest, or organ damage were detected on blood testing. The patient regained consciousness 30 min after the convulsions. We were unable to check the plasma concentration of levobupivacaine in this case, but the patient had no medical history of epilepsy, and there was no bleeding observed on computed tomography imaging. The operation was performed as planned, and the patient had no sequelae.

Interfascial plane blocks have recently been developed and have attracted attention in large part because they are less technically demanding and safer (i.e., the target is not the nerves, which may be damaged, but rather the space between muscle planes). In particular, ESPB is known to be a simple and safe technique because sonoanatomy is easily recognizable, and there are no structures at risk of needle injury in the immediate vicinity [1]. However, there is a relatively brief history of ESPB in clinical practice; the technique...
was first reported in 2016 by Forero et al. [1]. LAST is a rare event and is a potentially fatal complication of local anesthetic use. This is the first case report to demonstrate LAST after ultrasound-guided bilateral ESPB.

No information is available on how local anesthetic absorption occurs after ESPB. The differences in the time course of plasma concentrations are caused by the number of blood vessels around the space where the local anesthetic was injected [2].

Levobupivacaine is commonly used as the local anesthetic of choice in peripheral nerve blocks because its long-acting duration is useful for postoperative analgesia. Thus, we used levobupivacaine in this case because we expected it to have a longer effect than other local anesthetics.

Some reviews of ESPB have been published in the literature [3,4]. These studies reported the use of lidocaine, bupivacaine, ropivacaine, and levobupivacaine as local anesthetics in ESPB. When ESPB was performed bilaterally, the maximum volume of local anesthetics was 60 ml (in one case, 60 ml 0.5% ropivacaine = 300 mg ropivacaine was used, and in the other case, 20 ml 0.5% bupivacaine + 20 ml 2% lidocaine + 20 ml saline mixture = 100 mg bupivacaine and 400 mg lidocaine was used). When ESPB was performed, the maximum concentration of local anesthetics was 0.75% (20 ml 0.75% ropivacaine = 150 mg ropivacaine). We used 30 ml 0.5% levobupivacaine = 150 mg levobupivacaine. This dose was not greater than that in previous reports. One study reported plasma concentrations of local anesthetics after IV injection in rats [5]. The plasma concentrations at the onset of seizure did not differ significantly between levobupivacaine and ropivacaine. However, the plasma concentration of local anesthetic at the onset of dysrhythmia and asystole was higher with the administration of ropivacaine than with levobupivacaine. Therefore, it is possible that levobupivacaine is associated with a higher risk of LAST than ropivacaine.

This case report underscores the importance of awareness of possible LAST after ESPB, even though it is considered a simple and safe technique. Care must be taken when performing bilateral ESPB because large volumes of local anesthetics are used. Best practice might include using ropivacaine rather than levobupivacaine and reducing the dose of local anesthetics as much as possible. Further studies to evaluate the changes in plasma concentrations of local anesthetics after ESPB are needed to increase the safety of ESPB.

Conflicts of Interest

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

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Pediatric difficult airway is defined as a situation wherein the operator (anesthesiologist or intensivist) experiences difficulty with mask ventilation, direct or assisted laryngoscopy, tracheal intubation, supraglottic airway device use, or surgical airway. It is a clinical scenario that can quickly escalate into an emergency, and it is a risk factor for morbidity and mortality. The incidence of difficult tracheal intubation is up to 3%, and 1 of 5 cases are unanticipated (mostly related to unidentified facial dysmorphic features). Complications occur in ≥ 20% of children (mainly hypoxemia), and they are frequently associated with repeated attempts at laryngoscopy (≥ 3 attempts) and intubation (≥ 2 attempts) [1].

Written informed consent for the publication of this article was obtained from the parents of the patients.

We present the case of 2 toddlers with Pierre Robin sequence and difficult airway, who underwent rescue intubation with an i-gel® (Intersurgical Ltd, Wokingham, Berkshire, UK) supraglottic airway device during the perioperative care of cleft palate surgery. Both were 20-month-old children who were classified as American Society of Anesthesiologists physical status II and weighed 9–10 kg. Multiple attempts at laryngoscopy (Cormack-Lehane ≥ 3b) and videolaryngoscopy were performed by experienced pediatric operators, and episodes of desaturation (with abundant secretions and some blood) occurred in both cases [2]. Considering the difficult airway, repeated attempts at laryngoscopy, and hypoxemia episodes, we decided to perform intubation using a supraglottic airway device. We inserted an i-gel® airway device (nº 2) for mechanical ventilation and performed a fibroscopy (2.8 mm) through a double-swivel elbow (with seal-opening), while visualizing the following structures: epiglottis partially covering the larynx (classification of fiber optic vision through supraglottic device grade 3–4), larynx with supraglottic edema and secretions, trachea, and carina [3]. We passed an uncuffed tracheal tube (nº 4) through the elbow (maintaining mechanical ventilation), removed the supraglottic device using another tracheal tube as a stabilizer, and connected it again to the ventilator. Finally, we checked the waveform capnography and the correct placement of the tube proximal to the carina by performing a new fibroscopy again.

We present the case of 2 toddlers with Pierre Robin sequence and difficult airway, who underwent rescue intubation with an i-gel® (Intersurgical Ltd, Wokingham, Berkshire, UK) supraglottic airway device during the perioperative care of cleft palate surgery. Both were 20-month-old children who were classified as American Society of Anesthesiologists physical status II and weighed 9–10 kg. Multiple attempts at laryngoscopy (Cormack-Lehane ≥ 3b) and videolaryngoscopy were performed by experienced pediatric operators, and episodes of desaturation (with abundant secretions and some blood) occurred in both cases [2]. Considering the difficult airway, repeated attempts at laryngoscopy, and hypoxemia episodes, we decided to perform intubation using a supraglottic airway device. We inserted an i-gel® airway device (nº 2) for mechanical ventilation and performed a fibroscopy (2.8 mm) through a double-swivel elbow (with seal-opening), while visualizing the following structures: epiglottis partially covering the larynx (classification of fiber optic vision through supraglottic device grade 3–4), larynx with supraglottic edema and secretions, trachea, and carina [3]. We passed an uncuffed tracheal tube (nº 4) through the elbow (maintaining mechanical ventilation), removed the supraglottic device using another tracheal tube as a stabilizer, and connected it again to the ventilator. Finally, we checked the waveform capnography and the correct placement of the tube proximal to the carina by performing a new fibroscopy again.

Pierre Robin sequence is defined as the presence of micrognathia, glossoptosis, and airway obstruction (as well as cleft palate in 50% of patients); it is associated with respiratory and feeding difficulties to varying degrees. The incidence varies from 1 : 5,000 to 1 : 85,000, owing to variable clinical presentations, which may lead to underdiagnosis of patients with mild symptoms who may present with unanticipated difficult airways [4]. The latter occurred in 1 patient who had not been diagnosed with the Pierre Robin sequence when scheduled for surgery. The second child had a history of the Pierre Robin sequence. However, as his anatomical conditions seemed favorable, the anesthesiologist decided to perform a direct laryngoscopy under sedation as a first approach to case management.
The management of unanticipated difficult tracheal intubation in pediatric patients should be based on early identification and the use of evidence-based algorithms. Such algorithms should be adapted to the available resources and clinical experience and simplified to the minimum necessary information to ensure the adherence of professionals and ease of use. Moreover, intubation attempts should be limited, techniques and/or operators should be changed at every attempt, and intubation assistance devices should be used promptly. The damage produced by repeated attempts at intubation (secretions, bleeding, and supraglottic edema) may compromise ventilation and oxygenation. Supraglottic airway devices are the best choice for rescue ventilation, and they can be used as conduits for intubation (Video 1). Fibroscopy-guided intubation through a supraglottic device is well described in the literature, but however, guidelines for the difficult airway management indicate to perform this technique in the late stages of the process [5].

*i-gel®* supraglottic airway devices have an optimal profile for the management of difficult airways in children, given the ease of insertion (non-inflatable cuff), high leak pressures (>$25 \text{ cmH}_2\text{O}$) that permits more demanding positive pressure ventilation, a gastric channel for decompression of the stomach, and a wide airway diameter that allows the introduction of endotracheal tubes and fiberscopes with different diameters [6].

Fibroscopy-guided intubation through a supraglottic airway device has higher rates of global success, higher rates of first-attempt success in children younger than 1 year, and lower rates of hypoxemia than videolaryngoscopy (permits mechanical ventilation during the procedure). Since laryngoscopy and videolaryngoscopy are performed in apnea cases, they may be associated with hypoxemia, a higher number of intubation attempts (given the need to interrupt the technique for patient ventilation), and more airway damage. It is also important to check the compatibility of the diameters of the fiberscope, tracheal tube, and supraglottic airway device and examine the passage of the tracheal tube through the elbow with seal-opening to complete the intubation procedure without disconnecting from mechanical ventilation [6,7].

Therefore, based on our experience, we strongly recommend the early use of fibroscopy-guided intubation using the *i-gel®* supraglottic device for unanticipated tracheal intubation with a Cormack-Lehane ≥ 3 (Fig. 1) or secretions, bleeding, or hypoxemia to achieve a high success rate. Although the first-line supraglottic devices for this technique are Air-Q® and Aura-i® (having more studies published), *i-gel®* has the following advantages over them: (1) provides a wider airway channel that provides better visual field and permits the passage of tracheal tubes and fiberscopes with larger diameters; (2) obviates the need to disconnect mechanical ventilation for the passage of tracheal tubes, unlike with the use of Air-Q®.

In conclusion, we consider fibroscopy-guided intubation through a supraglottic device as a safe and effective procedure,

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**Fig. 1.** Algorithm for the management of unanticipated difficult intubation in our pediatric anesthesia program. BURP: backward upward rightward pressure.
which should be performed promptly as an intubation rescue technique in pediatric patients, since it reduces the number of attempts at laryngoscopy and intubation. Moreover, we consider i-gel® as an excellent supraglottic device for performing this procedure, although further studies providing new evidence on its application are needed.

Conflicts of Interest

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

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Supplementary Material

Video 1. Fibroscopy-guided intubation via i-gel® supraglottic device.

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The prone position is among the many positions used during various neurosurgical and orthopedic surgeries (posterior fossa tumors and spine). Complications associated with prone positioning include stroke, upper airway obstruction, endotracheal tube dislodgement and brachial plexus injury, among others. Arterial cannula displacement during positioning or in the middle of an ongoing major surgery is a nightmare to anesthesiologists, due to difficulties of accessing commonly used arteries for arterial cannulation. It becomes even more challenging when the extremities are not available for cannulation in patients with polytrauma. The popliteal artery can be a very useful option in this situation.

Point-of-care ultrasonography (POCUS) has made vascular structures easily accessible for diagnostic and therapeutic purposes, which were previously impossible with blind techniques [1,2]. POCUS can be an invaluable tool for popliteal artery cannulation due to its deeper location and presence of the popliteal vein above it [3].

Written informed consent obtained from the patient. A 60-year-old woman with history of fall from a 6-m height was scheduled for pedicle screw fixation of L1 vertebral fracture. She also had bilateral upper limb fractures along with right metatarsal fracture. She was known to be diabetic and hypertensive with irregular medications. Due to intraoperative hemodynamic instability and difficulty of measuring noninvasive blood pressure, arterial cannulation (over the needle technique) was performed in the left dorsalis pedis artery. During the intraoperative period, the arterial cannula was displaced, as indicated by damping in the arterial wave tracing. After repeated failed attempts to cannulate the left posterior tibial artery, we decided to cannulate the left popliteal artery. The left popliteal fossa was cleaned and draped. An ultrasound image of the popliteal artery with the vein lying above and the nerve bundle below was obtained (Fig. 1A). Colored Doppler was used to improve identification of the artery. The artery was found just below the vein from the roof of the popliteal fossa. Hence, it could not be punctured perpendicularly. The vein was to be bypassed by puncturing the artery from the medial or lateral side using the Seldinger technique (Fig. 1B).

The popliteal artery is accessed in the popliteal fossa, which is bound by the biceps femoris, plantaris, and lateral head of the gastrocnemius laterally and by the semitendinosus, semimembranosus, and medial head of the gastrocnemius medially. The floor is formed by the knee joint, and the roof is formed by the skin, subcutaneous, and fascia lata [2]. The popliteal artery has an average diameter of 7.4–9.5 mm [3]. The popliteal artery and vein are present in the common sheath, and the vein crosses the artery from the lateral to medial as we move from above to below. Easy accessibility in the prone position, reliable anatomy, and large diameter were advantages of popliteal artery cannulation. However, because of its deep location and adjacent placement to the popliteal vein, only...
ultrasound-guided placement is feasible, and the Seldinger technique is a better option than the over-the-needle technique.

A paucity of published literature regarding the popliteal artery cannulation has been observed. Villelli et al. [4] reported the popliteal artery cannulation for digital subtraction angiography in the prone position in three patients without any complications. Bala et al. [5] performed popliteal artery cannulation in a patient with severe ARDS in the intensive care unit. Our patient was followed up in the postoperative period after the arterial cannula removal with ultrasonography for the popliteal artery patency. No thrombus or hematoma was detected around the popliteal artery. We suggest further studies on cannulation of popliteal artery required to establish the safety and feasibility for invasive blood pressure monitoring.

Conflicts of Interest

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

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The case reported by Singh et al. [1] describing a rare case of Wilson’s disease with intracranial hemorrhage (ICH), which concluded that penicillamine administration in this particular patient may have caused bone marrow suppression and low platelet count was very interesting. Bone marrow suppression and thrombocytopenia are known complications of penicillamine use reported in up to 10% of cases [2] that can cause bleeding, including ICH. However, the level of coagulopathy based on laboratory parameters (platelet count: $43 \times 10^9$/L, international normalized ratio [INR]: 1.65) was not severe enough to have caused massive bleeding leading to intraventricular extension in a patient with cirrhosis [3].

The authors have also commented that marijuana users are more likely to have ICH. The patient being an alcohol user as well could have had inadvertent head injuries [4]. Although not independent predictors of ICH, marijuana and alcohol use are more likely to cause ICH.

Additionally, we would like to point out that in a young patient presenting with ICH, a search for an intracranial aneurysm should have been considered and cerebral angiography could have been performed.

It is also our observation that the trigger for transfusion was the absolute levels of platelets and INR in the presence of an intracranial bleed in a patient with cirrhosis. However, the current practice is to transfuse products based on viscoelastic hemostatic assays such as TEG or ROTEM, as such patients could be in a procoagulant state despite the deranged coagulation parameters [5].

Conflicts of Interest

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

References

We would like to convey our gratitude to the readers for showing interest in our article [1]. In the InCiTe study on intracranial hemorrhage (ICH) in patients with thrombocytopenic hematology, a platelet count < 50 × 10^9/L is considered low enough to cause ICH [2]. We agree that the functional activity of platelets is a better marker for bleeding risk than the platelet count. However, a patient with ICH and confirmed uncal herniation on non-contrast computed tomography (NCCT) with pancytopenia, including thrombocytopenia, is an ideal candidate for platelet transfusion. The current practice of transfusing blood products based on viscoelastic hemostatic assays such as thromboelastography or rotational thromboelastometry is predominantly used in non-cardiac surgery with ongoing bleeding, usually intraoperatively, where there is an acute need for multiple blood transfusions [3].

In the recent literature, few case reports have reported the correlation of active cannabis smoking with ischemic and hemorrhagic cerebral stroke. Of the 107 neurovascular cases reported on active cannabis smokers, almost 84% were related to ischemic stroke [4]. Our patient was a reformed, not an active, cannabis smoker. Furthermore, hemorrhagic stroke in our patient, in contrast to ischemic stroke caused by cannabis, makes cannabis use a less likely cause of ICH in this case.

The most common location of aneurysm rupture is the anterior communicating artery, and 90% of all ruptures present with subarachnoid hemorrhage. Basal ganglia hematomas resulting from the rupture of aneurysms of the distal middle cerebral artery are extremely rare [5]. Most aneurysms develop after the age of 40 years, and the occurrence of basal ganglia bleeding caused by an aneurysmal rupture in a 35-year-old man is highly unlikely. As our patient was diagnosed with uncal herniation in an urgent NCCT of the head, we immediately intubated him and transferred him to the operating theater rather than performing a cerebral angiography to rule out an aneurysm, which was a very unlikely possibility.

**Conflicts of Interest**

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

**Author Contributions**

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Priya Taank (Writing – original draft; Writing – review & editing)
References


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1. Conflict-of-interest statement

Conflict of interest exists when an author or the author’s institution, reviewer, or editor has financial or personal relationships that inappropriately influence or bias his or her actions. Such relationships are also known as dual commitments, competing interests, or competing loyalties. These relationships vary from being negligible to having a great potential for influencing judgment. Not all relationships represent true conflict of interest. On the other hand, the potential for conflict of interest can exist regardless of whether an individual believes that the relationship affects his or her scientific judgment. Financial relationships such as employment, consultancies, stock ownership, honoraria, and paid expert testimony are the most easily identifiable conflicts of interest and the most likely to undermine the credibility of the journal, the authors, or of the science itself. Conflicts can occur for other reasons as well, such as personal relationships, academic competition, and intellectual passion (http://www.icmje.org/conflicts-of-interest/). If there are any conflicts of interest, authors should disclose them in the manuscript. The conflicts of interest may occur during the research process as well; however, it is important to provide disclosure. If there is a disclosure, editors, reviewers, and reader can approach the manuscript after understanding the situation and the background of the completed research.

2. Statement of informed consent and Institutional Review Board approval

If the study in the article is on human subjects or human-originated material, informed consent for the study and the Institutional Review Board (IRB) approval number needs to be provided. Copies of written informed consents and IRB approval for clinical research should be kept. If necessary, the editor or reviewers may request copies of these documents to make potential ethical issues clear.

3. Statement of human and animal right

Clinical research should be done in accordance of the Ethical Principles for Medical Research Involving Human Subjects, outlined in the Helsinki Declaration of 1975 (revised 2013) (available from: https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/). Authors should indicate whether the procedures were conducted in accordance with the Helsinki Declaration-2013 in the Text. Clinical studies that do not meet
the Helsinki Declaration will not be considered for publication. Human subjects should not be identifiable, such that patients' names, initials, hospital numbers, dates of birth, or other protected healthcare information should not be disclosed. For animal subjects, research should be performed based on the National or Institutional Guide for the Care and Use of Laboratory Animals, and the ethical treatment of all experimental animals should be maintained.

4. Registration of the clinical trial research
Any researches that deals with clinical trial should be registered with the primary national clinical trial registration site such as Korea Clinical Research Information Service (cris.nih.go.kr/) or other sites accredited by WHO or International Committee of Medical Journal Editor such as ClinicalTrials.gov (clinicaltrials.gov/).

5. Reporting guidelines
The KJA recommends a submitted manuscript to follow reporting guidelines appropriate for various study types. Good sources for reporting guidelines are the Enhancing the QUAlity and Transparency Of health Research (EQUATOR) Network (www.equator-network.org/) and the U.S. National Library of Medicine's (NLM's) Research Reporting Guidelines and Initiatives (www.nlm.nih.gov/services/research_report_guide.html). The appropriate checklist (and flow diagram, if applicable) must be included with each submission.

6. Authorship
Authorship credit should be based on: 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; AND 2) drafting the article or revising it critically for important intellectual content; AND 3) final approval of the version to be published; AND 4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet these 4 conditions. If the number of authors is equal to or greater than 2, there should be a list of each author's role in the submitted paper. Authors are obliged to participate in peer review process. All others who contributed to the work who are not authors should be named in the Acknowledgements section. KJA has a strict policy on changes to authorship after acceptance of the article and will only consider changes in the most extraordinary situations once the article is accepted.

7. Plagiarism and duplicate publication
Plagiarism is the use of previously published material without attribution. The KJA editorial office screens all submitted manuscripts for plagiarism, using a sophisticated software program, prior to peer review. When plagiarism is detected at any time before publication, the KJA editorial office will take appropriate action as directed by the standards set forth by the Committee on Publication Ethics (COPE). For additional information, please visit http://www.publicationethics.org. It is mandatory for all authors to resolve any copyright issues when citing a figure or table from a different journal that is not open access.

8. Secondary publication
It is possible to republish manuscripts if the manuscripts satisfy the condition of secondary publication of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, available at: www.icmje.org/.

9. Feedback after publication
If the authors or readers find any errors, or contents that should be revised, it can be requested from the Editorial Board. The Editorial Board may consider erratum, corrigendum or a retraction. If there are any revisions to the article, there will be a CrossMark description to announce the final draft. If there is a reader's opinion on the published article with the form of Letter to the editor, it will be forwarded to the authors. The authors can reply to the reader's letter. Letter to the editor and the author's reply may be also published.

9-1. Process to manage the research and publication misconduct
When the Journal faces suspected cases of research and publication misconduct such as a redundant (duplicate) publication, plagiarism, fabricated data, changes in authorship, undisclosed conflicts of interest, an ethical problem discovered with the submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and other issues, the resolving process will follow the flowchart provided by the Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts). The Editorial Board of KJA will discuss the suspected cases and reach a decision. KJA will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

9-2. Policy of Article withdrawal, retraction, and replacement
1) Article withdrawal
Articles in Press (articles that have been accepted for publication but which have not been formally published and will not yet have the complete volume/issue/page information) that include errors, or are discovered to be accidental duplicates of
other published article(s), or are determined to violate our jour-
nal publishing ethics guidelines in the view of the editors (such
as multiple submission, bogus claims of authorship, plagiarism,
fraudulent use of data or the like), may be “Withdrawn”.

2) Article retraction
Errors serious enough to invalidate a paper’s results and conclu-
sions (Infringements of professional ethical codes, such as mul-
tiple submission, bogus claims of authorship, plagiarism, fraud-
ulent use of data or the like) may require retraction.

3) Article replacement
Replacement (retraction with republication) can be considered
in cases where honest error (e.g., a misclassification or miscal-
culation) leads to a major change in the direction or signifi-
cance of the results, interpretations, and conclusions. If the er-
or is judged to be unintentional, the underlying science ap-
pears valid, and the changed version of the paper survives fur-
ther review and editorial scrutiny, then replacement of the
changed paper, with an explanation, allows full correction of
the scientific literature.

See also the National Library of Medicine’s policy on retractions
and the recommendations of the International Committee of
Medical Journal Editors (ICMJE) concerning corrections and re-
tractions, or https://publicationethics.org/resources/guidelines.

9-3. Appeals and complaints
KJA adheres to COPE guidelines regarding appeals to editorial
decisions and complaints. For additional information, please
visit https://publicationethics.org/core-practices.

Data sharing statement
KJA accepts the ICMJE Recommendations for data sharing state-
ment policy (http://icmje.org/icmje-recommendations.pdf). All
manuscripts reporting clinical trial results should submit a data
sharing statement following the ICMJE guidelines from 1 July
2018. Authors may refer to the editorial, “Data Sharing statements
for Clinical Trials: A Requirement of the International Committee
of Medical Journal Editors,” in Annals on 6 June 2017 (http://www.

Manuscript preparation

1. Word processors and format of manuscript
A manuscript must be written in proper and clear English. The
manuscript, including tables and their footnotes, and figure leg-
ends, must be typed in one double space. Materials should be
prepared with a standard 12-point typeface or greater (Times
New Roman typeface is preferred). The manuscript should be in
the following sequence: cover letter (optional), title page file,
manuscript (title and running title, abstract and keywords, in-
roduction, materials and methods, results, discussion, referenc-
es, tables, and figure legends), figures, other submission ele-
ments. All pages should be numbered consecutively starting
from the title page. All numbers should be written in Arabic nu-
merals throughout the manuscripts. Our preferred file format is
DOCX or DOC. A single PDF file containing all materials in a
file including figures and figure legends. In that case, authors
should add line numbers throughout the document. Manuscript
containing anything in headers and footers, except of page num-
bers, will be returned to authors. If your PDF submission is ac-
cepted, you will be asked to upload your final document file in
DOCX or DOC format as well. Make sure to update your PDF
file with the most recent version of your manuscript.

2. Abbreviation of terminology
Abbreviations should be avoided as much as possible. When
they are used, full expression of the abbreviations following the
abbreviated word in parentheses should be given at the first use.
Common abbreviations, however, may be used, such as DNA.
Abbreviation can be used if it is listed as a MeSH subject head-

3. Word-spacing
1) Leave 1 space for each side, using arithmetic marks as +, −,
×, etc.
Leave no space for hyphen between words.
2) Leave 1 space after “,” “;” and “;” Leave 2 spaces after “.” “;” “;”
3) Using parentheses, leave 1 space each side.
4) Brackets in parentheses, apply square brackets.

4. Citations
1) If a citation has 2 authors, write as “Hirota and Lambert.” If
there are more than 3 authors, apply ‘et al.’ at the end of the
first author’s surname. Ex) Kim et al. [1].
2) Citation should be applied after the last word or author’s sur-
name.
3) Apply citation before a comma or period.
4) Identify reference by several or coupled Arabic numbers, en-
closed in square brackets on the line as [1,3,5].

5. Arrangement of manuscript
ALL articles should be arranged in the following order.
Cover letter (optional)
6. Statistical Analysis

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

2) Authors should describe the objective of the study and hypothesis appropriately. The primary/secondary endpoints are predetermined sensibly according to the objective of the study.¹

3) The characteristics of measured variables should determine the use of a parametric or nonparametric statistical method. When a parametric method is used, the authors should describe whether the basic statistical assumptions are met.²,³

4) For an analysis of a continuous variable, the normality of data should be examined. Describe the name and result of the particular method to test normality.

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

6) The Korean Journal of Anesthesiology (KJA) strongly encourages authors to show confidence intervals. It is not recommended to present the P value without showing the confidence interval. In addition, the uncertainty of estimated values, such as the confidence interval, should be described consistently in figures and tables.⁴

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

8) A priori sample size calculation should be described in detail. Sample size calculation must aim at preventing false negative results pertaining to the primary, instead of secondary, endpoint. Usually, the mean difference and standard deviation (SD) are typical parameters in estimating the effect size. The power must be equal to or greater than 80 percent. In the case of multiple comparisons, an adjusted level of significance is acceptable.⁵

9) It is recommended using mean ± SD or median (Q1, Q3) format to present representative values of continuous variables. Results must be written in significant figures. The measured and derived numbers should be rounded off to reflect the original degree of precision. Calculated or estimated numbers (such as mean and SD) should be expressed in no more than one significant digit beyond the measured accuracy. Therefore, the mean ± SD of body weight in patients measured on a scale that is accurate to 0.1 kg should be expressed as 65.45 ± 2.52 kg.

10) Except when otherwise stated herein, authors should conform to the most recent edition of the American Medical Association Manual of Style.⁷

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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.
⁷http://www.amamanualofstyle.com/
7. Organization of manuscript

1) Clinical or Experimental research

(1) Title page
   ① Title
   Title should be concise and precise.
   For the title, only the first letter of the first word should be capitalized.
   ② Author information
   First name, middle initial, and last name of each author, with their highest academic degree(s) (M.D., Ph.D., etc.), and institutional affiliations; make sure the names of and the order of authors as they appear on the Title Page and entered in the system match exactly.
   ③ Running title
   A running title of no more than 40 characters, including letters and spaces, should be described. If inappropriate, the editorial board may revise it.
   ④ Corresponding Author
   Name, mailing address, phone number, and e-mail address of the corresponding author
   ⑤ Previous presentation in conferences
   Title of the conference, date of presentation, and the location of the conference may be described.
   ⑥ Conflict of interest
   It should be disclosed here according to the statement in the Research and publication ethics regardless of existence of conflict of interest. If the authors have nothing to disclose, please state: “No potential conflict of interest relevant to this article was reported.”
   ⑦ Funding
   Funding to the research should be provided here. Providing a FundRef ID is recommended including the name of the funding agency, country and if available, the number of the grant provided by the funding agency. If the funding agency does not have a FundRef ID, please ask that agency to contact the FundRef registry (e-mail: fundref.registry@crossref.org). Additional detailed policy of FundRef description is available from http://www.crossref.org/fundref/.
   ⑧ Acknowledgments
   Any persons that contributed to the study or the manuscript, but not meeting the requirements of an authorship could be placed here. For mentioning any persons or any organizations in this section, there should be a written permission from them.
   ⑨ IRB number
   ⑩ Clinical trial registration number

If any of these elements are not applicable to your submission, write “not applicable” after the number and topic; for example, “Prior Presentations: Not applicable.”

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

- Reports of randomized trials must conform to the revised CONSORT guidelines and should be submitted with the CONSORT flow diagram. The CONSORT checklist should be submitted as a separate file along with the manuscript. The CONSORT statement, checklist, and flow diagram can be found at http://www.consort-statement.org or EQUATOR Network (https://www.equator-network.org/home/)

- Units

Laboratory information should be reported in International System of Units [SI]. Please refer to A Guide for Biological and Medical Editors and Authors, 6th Edn. Baron DN and Clarke HM, ed. (2008), CRC Press. or visit http://www.icmje.org/about-icmje/faqs/icmje-recommendations/

- Exceptions
  A. The unit for volume is "L", others in "dl, ml, μl".
  B. The units for pressure are mmHg or cmH₂O.
  C. Use Celsius for temperature
  D. Units for concentration are M, mM, μM.
  E. When more than 2 items are presented, diagonal slashes are acceptable for simple units. Negative exponents should not be used.
  F. Leave 1 space between number and units.
  Exception) 5%, 36°C

- Drug Names and Equipment

Use generic names. If a brand name must be used, insert it in parentheses after the generic name. Provide ® or ™ as a superscript and manufacturer's name, and country.

- Ions

Ex) Na⁺ [O], Mg²⁺ [O], Mg²⁺ [X], Mg²⁺ [X]

- Statistics

Statistical methods must be described with enough detail so that readers can reproduce the same results if the original data available. The KJA strongly encourages authors to show confidence intervals. It is not recommended to present the P value without showing the confidence interval. A sample size calculation should be described in detail. Sample size calculation must aim at preventing false negative results pertaining to the primary, instead of secondary, endpoint.

© Results

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

© Discussion

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

© References


- References should be obviously related to documents and should not 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


Ex) '2006; 7(Suppl 1): 64-96 '2007; 76: H232-8'

B. Monographs


· If reference page is only 1 page, mark 'p'.

· Mark if it is beyond the 2nd edition.


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.


Table

- Type or print each table on a separate sheet of paper.
- Number tables consecutively in the order of their first citation in the text.
- Supply a brief title

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 *, †, ‡, §, ††, ‡‡... 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.

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

- 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.

- 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.

- 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).
⑤ 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.
⑥ In horizontal and vertical legends, the letter of the first English word should be capitalized.
⑦ Connections between numbers should be denoted by “-”, not “~”. Do not space the numbers (ex. 2–4).
⑧ Figures (line drawings) should be clearly printed in black and white.
⑨ Figures should be explained briefly in the footnotes. The format is the same as the table format.
⑩ An individual should not be recognizable in the photographs or X-ray films unless written consent of the subject has been obtained and is provided at the time of submission.
⑪ Pathological samples should be pictured with a measuring stick.

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

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

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

Video clips are uploaded as the last file(s) at the time of manuscript submission and should be marked as supplementary video files.
① The video clip(s) should have simple file names (e.g., Video 1***, Video 2****) and include the appropriate extension (e.g., .mov, .mpg).
② The maximum number of video clips is 20.
③ The video clip(s) should be playable on both Windows and MAC computers. The video clip(s) should be tested for playback before submission, preferably on computers not used for their creation, to check for any compatibility issues.
④ Individual video files should be a minimum of 480 x 320 pixels (smaller clips will not be accepted) and a maximum of 2 GB. Files of < 15 MB will be rejected outright unless special arrangements have been made with the editorial board prior to submission. Approval of files of > 2 GB will be made at the end of the review process.
⑤ Supplemental still images that correspond to the respective video clip(s) should be, but are not always required to be, accompanied by legends. The video clip file name(s) should refer to the corresponding figure number(s).

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

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

- All systematic reviews and meta-analyses should be registered at an appropriate online public registry (eg, PROSPERO; http://www.crd.york.ac.uk/PROSPERO/), and registration information should be included with the submission.
- Authors of reports of meta-analyses of clinical trials should submit the PRISMA flow diagram. The PRISMA checklist should be submitted as a separate file along with the manuscript. For information regarding PRISMA guidelines, please visit http://www.prisma-statement.org or EQUATOR Network (https://www.equator-network.org/home/). Systematic reviews and meta-analyses of observational studies in epidemiology should be reported according to MOOSE guidelines. For more information regarding MOOSE guidelines, please visit http://www.equator-network.org/reporting-guidelines/meta-analysis-of-observational-studies-in-epidemiology-a-proposal-for-reporting-meta-analysis-of-observational-studies-in-epidemiology-moose-group/.
- No limitation the number of the references.

3) Case Reports
A case report is almost never a suitable means to describe the efficacy of a treatment or a drug; instead, an adequately powered and well-controlled clinical trial should be performed to demonstrate such efficacy. The only context in which a case report can be used to describe efficacy is in a clinical scenario, or
population, that is so unusual that a clinical trial is not feasible.

Case reports of humans must state in the text that informed consent to publication was obtained from the patient or guardian. Authors should submit copies of written informed consents by using the online manuscript submission system. If it is unavailable, the IRB approval should be needed. Copy of IRB approval should be kept. If necessary, the editor or reviewers may request copies of these documents. Rarity of a disease condition is itself not an acceptable justification for a case report.

1) Title page: Same as clinical and experimental studies.
2) Manuscript
   a) Title and Running title.
   b) Abstract: All case reports should contain a structured abstract that is written only in English. Provide an abstract of no more than 150 words. It should contain 3 subsections: Background, Case, and Conclusions. A list of keywords, with a minimum of 6 and maximum of 10 items, should be included at the end of the abstract. The selection of keywords should be from MeSH (http://www.ncbi.nlm.nih.gov/mesh) and should be written in small alphabetic letters with the first letter in capital letter. Separate each word by a semicolon (;), and mark a period (.) at the end of the last word.
   c) Introduction: Should not be separately divided. Briefly describe the case and background without a title.
   d) Case report: Describe only the clinical statement that is directly related to diagnosis and anesthetic management.
   e) Discussion: Briefly discuss the case, and state conclusions at the end of the case. Do not structure the conclusion section separately.
   f) References: Do not exceed 15 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.
3) Letters to the Editor
   a) Title and Running title.
   b) Abstract: Letters to the Editor also should include brief constructive comments on the articles published in KJA and interesting cases. Book reviews as well as news of scientific societies and scientific meeting dates in Korea or abroad can be included. Letters to the editor of humans must state in the text that informed consent to publication was obtained from the patient or guardian. Authors should submit copies of written informed consents by using the online manuscript submission system. If it is unavailable, the IRB approval should be needed. Copy of IRB approval should be kept. If necessary, the editor or reviewers may request copies of these documents. Letters to the Editor cover individual articles not described by any of the above categories. The short manuscripts with a constructive note on the Journal or the anesthesiology at large are welcome.
   c) 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.

4) Reviews
   a) Title and Running title.
   b) Abstract: Review articles synthesize previously published material into an integrated presentation of our current understanding of a topic. Review articles should describe aspects of a topic in which scientific consensus exists, as well as aspects that remain controversial and are the subject of ongoing scientific disagreement and research. Review articles should include unstructured abstracts equal to or less than 250 words in English. Figures and tables should be provided in English. References should be obviously related to documents and should not be exceed 100. For exceeding the number of references, it should be negotiated with the Editorial Board. Body text should not exceed 30 A4 pages, and the number of figures and tables should be equal to or less than 6.
5) Letters to the Editor
   a) Title and Running title.
   b) Abstract: Letters to the Editor also should include brief constructive comments on the articles published in KJA and interesting cases. Book reviews as well as news of scientific societies and scientific meeting dates in Korea or abroad can be included. Letters to the editor of humans must state in the text that informed consent to publication was obtained from the patient or guardian. Authors should submit copies of written informed consents by using the online manuscript submission system. If it is unavailable, the IRB approval should be needed. Copy of IRB approval should be kept. If necessary, the editor or reviewers may request copies of these documents. Letters to the Editor cover individual articles not described by any of the above categories. The short manuscripts with a constructive note on the Journal or the anesthesiology at large are welcome.
   c) Cover pages should be formatted as those of clinical research papers. The body text should not exceed 1,000 words and should have no more than 5 references. For exceeding the number of references, it should be negotiated with the Editorial Board. A figure or a table may be used. A maximum of five authors is allowable. Letter may be edited by the Editorial Board and if necessary, responses of the author of the subject paper may be provided.

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

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