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

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Artificial intelligence in perioperative medicine: a narrative review

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Recent artificial intelligence (AI) technology development has enabled precise outcome prediction using clinical big data. In the field of perioperative medicine, AI models have been developed to predict preoperative risk stratification, intraoperative events, and postoperative outcome assessment. Some of these models have been validated using external data sets and randomized control trials. If these models are implemented in electronic medical records or medical software, anesthesiologists can accurately predict complications and develop optimal treatment plans to improve clinical outcomes. This review provides an overview of AI technology used in perioperative medicine and a summary of the research published in this area. Understanding these techniques can help in appropriately applying them in clinical practice.

Keywords: Artificial intelligence; Deep learning; Machine learning; Outcome assessment; Perioperative care; Risk assessment.

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Therapeutic hypothermia for acute myocardial infarction: a narrative review of evidence from animal and clinical studies

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Keywords: Anesthesia; Animals; Hypothermia; Humans; Myocardial infarction; Myocardial ischemia; Myocardial reperfusion injury; Rewarming; Shivering.
Regional analgesia techniques for video-assisted thoracic surgery: a frequentist network meta-analysis

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Keywords: Nerve block; Network meta-analysis; Opioid analgesics; Postoperative pain; Review; Video-assisted thoracic surgery.
Preoperative dexmedetomidine and intraoperative bradycardia in laparoscopic cholecystectomy: a meta-analysis with trial sequential analysis

Alessandro De Cassai, Nicolò Sella, Federico Geraldini, Francesco Zaratonello, Tommaso Pettenuzzo, Laura Pasin, Margherita Iuzzolino, Nicolò Rossini, Elisa Pesenti, Giovanni Zecchino, Marina Munari, Paolo Navalesi, Annalisa Boscolo

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Keywords: Bradycardia; Cholecystectomy; Dexmedetomidine; Laparoscopy; Meta-analysis; Review.
Efficacy of perineural versus intravenous dexamethasone in prolonging the duration of analgesia when administered with peripheral nerve blocks: a systematic review and meta-analysis

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배경: 신경주위 텍사메타손은 신경 차단의 지속 시간을 연장하는 전도유망한 보조제로 여겨져 왔다. 그러나 그것의 효과가 신경에 대한 국소적인 영향 때문인지 아니면 전체적인 흡수 때문인지는 불확실하다. 이 체계적 문헌 검토는 말초신경 차단의 보조제로 신경주위와 정맥 내 텍사메타손과 관련된 수술 후 통증 기간을 비교하는 것을 목표로 하였다.


결과: 15건의 무작위 대조군 시험(1,467건, 경막 외 텍사메타손 738건, 정맥 내 텍사메타손 729건)이 적절하였다. 1차 결과(진통 지속 시간)는 정맥 내 (평균 차이 [MD]: 2.72 h, 95% CI [1.42, 4.01], P < 0.001)보다 경막에서 상당히 길었다. 또한, 신경주위의 텍사메타손은 감각 차단을 연장하는 것으로 나타났고 (MD: 3.45 h, 95% CI [1.36, 5.54], P = 0.001) 수술 후 24시간 통증 점수 (MD: -0.74 h, 95% CI [-1.40, -0.07], P = 0.03)는 낮혔다.

결론: 이 검토는 정맥 내 텍사메타손과 비교해 말초신경 차단의 진통 지속 시간 연장에 있어 신경 주위 텍사메타손의 효과: 체계적 문헌검토 및 메타분석

Keywords: Acute pain; Conduction anesthesia; Enhanced recovery after surgery; Nerve block; Pharmaceutic adjuvants; Postoperative pain.
Standard digit-based versus 90° rotation technique for supraglottic airway device insertion: a meta-analysis of randomized controlled trials

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배경: 기도를 적절히 유지하기 위해서는 성문위 기도유지 기구(supraglottic airway device, SGA)를 올바른 위치에 적절히 삽입을 해야한다. 본 메타분석은 마취된 환자에게 성문위 기도유지 기구를 삽입하기 위한 표준 방법과 비교하여 90° 회전방법의 유용성을 삽입 성공률, 삽입 시간 및 수술 후 합병증 측면에서 검증하기 위해 수행되었다.

방법: PubMed, EMBASE, Central, CINAHL, Scopus, Web of Science에 대한 문헌 검색이 수행되었다. 2021년 7월까지 출판 기간, 언어, 저널 또는 지역에 제한 없이 검색된 무작위 대조군 시험(RCTs)의 결과들을 메타분석하여 마취된 환자의 SGA 장치 삽입을 위한 표준 방법과 90° 회전방법을 비교하였다.

결과: 첫 번째 시도(위험비[RR]: 1.16, 95% CI [1.09, 1.25], P < 0.001) 및 전체 성공률(RR: 1.06, 95% CI [1.03, 1.09], P < 0.001)은 90° 회전군에서 유의하게 더 높았다. 반면 삽입 시간은 90°회전군(평균 차이 −4.42초, 95% CI [−6.70, −2.15], P < 0.001)에서 더 짧았다. 수술 후 인후통증(RR: 0.63, 95% CI [0.49, 0.83], P < 0.001) 및 혈흔(RR: 0.28, 95% CI [0.20, 0.39], P < 0.001) 발생률은 90°회전군에서 더 낮았다.

결론: 전신마취 환자에게 성문위 기도유지기구 삽입시 90° 회전방법이 표준방법에 비해 삽입 성공률이 높고 인후통증 등의 수술 후 합병증이 감소하였다.

Keywords: Airway management; General anesthesia; Laryngeal masks; Meta-analysis; Postoperative complications; Rotation.
The effect of ultrasound-guided bilateral thoracic retrolaminar block on analgesia after pediatric open cardiac surgery: a randomized controlled double-blind study

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Keywords: Analgesia; Cardiac surgical procedures; Child; Fentanyl; Nerve block; Sternotomy; Ultrasonography.
On the road to make KJA’s review process robust, transparent, and credible: retracted study in systematic review

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While a systematic review is meant to provide a high-quality appraisal of the evidence regarding a healthcare intervention, the conclusions are predicated on the reliability of the included studies [1]. The existence of unreliable or problematic studies in the literature presents difficulties for researchers performing systematic reviews and jeopardizes the credibility of their results. Retracted studies have the most obvious flaws. Retraction is defined as the removal of a published paper from a journal to warn readers of the significant problems identified in the article as a means of maintaining the integrity of scientific literature [2]. Including retracted studies in a systematic review may impact the outcomes and level of evidence, and ultimately provide inaccurate medical guidelines [3,4]. Thus, handling retracted studies in systematic reviews is a critical issue.

Recently, we discovered that one of the studies cited in a systematic review and meta-analysis (SRMA) [5], which was accepted through the peer review process in the Korean Journal of Anesthesiology (KJA), was confirmed to have been retracted during the proofreading stage. Given the ambiguous timing, several rounds of editorial discussions were necessary to thoroughly consider the options regarding how to proceed. The KJA editorial board made a concerted effort to perform peer review and editorial assessment in a robust, transparent, and credible manner regarding this disputed SRMA [6].

What happened during the review process?

Following acceptance of the SRMA [6], a manuscript editor evaluating the proof found that one [5] of the included studies had been retracted for containing too many flaws to be corrected on September 9, 2021. The SRMA protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on April 29, 2021 (registration number: CRD42021252062), and a literature search was conducted in May 2021 on papers published between January 2000 and January 2021. The authors first submitted their original SRMA to the KJA on July 26, 2021. The revised paper was submitted on September 28, 2021, and the final acceptance date after the revision was reviewed was October 12, 2021. During the KJA editorial board review process for the revision of the original SRMA, neither the reviewers nor the editors requested that the related studies be searched again, and the authors did not perform a second search.

A systematic review focuses on selecting and analyzing the findings of previously published papers; thus, each included study per se can be considered important material of the systematic review. The inclusion of a retracted study in the analysis could have significantly impacted the overall content and findings of the systematic review. Consequently, determining how to deal with this SRMA under these circumstances became a
top priority. To resolve this issue, the following concerns had to be addressed through multiple rounds of discussion by the KJA editorial board.

**How should a retracted study be dealt with at this point?**

Our editorial board had two conflicting points of view. One view was to publish the SRMA with the retracted study included. The retraction date was September 9, 2021, and the first submission date of the original SRMA was July 26, 2021. Therefore, the SRMA had already been completed at the time of retraction and the SRMA was not in progress at that time. Given that requesting the authors to conduct further research after the study had been completed could be interpreted as not following protocol, it would be acceptable to publish the SRMA with the retracted study included, according to this viewpoint. In PROSPERO, the literature search was planned to begin in May 2021, and study searches in systematic reviews should be conducted systematically, transparently, and reproducibly, according to a pre-defined process. The retraction had not yet occurred at this stage. Proofreading is the last step in the process to ensure that the text is accurate and ready for publication. Thus, according to this viewpoint, altering the contents of an SRMA should not occur at this stage.

The other viewpoint of the editorial board was to publish the SRMA following additional revisions in light of the recent retraction. Because a study is not completed until it is published, and this SRMA was still in the proofreading stage, it was argued that revisions at this stage are feasible when necessary. Readers have the right to see the most accurate and up-to-date research; therefore, it is appropriate to revise the content if it can be amended, even if it goes against the concept of the purpose of the proofreading stage. Readers also have the right to know whether a study has been retracted, as well as the reasons of its retraction. If the reason for retraction is that a published paper has too many flaws to be corrected, as in this case, the results of the SRMA may contain significant bias. Publishing the results of an SRMA that may contain errors could be regarded as unethical as it would infringe on the readers’ right to know the truth. Because the SRMA had not yet been published, according to this viewpoint, it was reasonable to consider the proofreading process as a stage where alterations could occur and to conduct a systematic review again, if necessary.

**What should be considered in the review process if a retracted study is to be excluded?**

In this case, the decision was made regarding the two previous viewpoints and the SRMA was to be re-submitted following a new analysis that excluded the retracted study [5]. The review process for the re-submitted SRMA could be seen from three perspectives: 1) treat the re-submitted SRMA as a completely new submission, for which a new peer review process for acceptance, revision, or rejection would be required, 2) treat the re-submitted SRMA as an extension of the previously submitted SRMA, and add an extension to the review process, and 3) only review the new additions with the retracted study excluded and uphold the editorial decision of the previously submitted SRMA.

Once a retracted study is excluded, the results of the analyses may change, affecting the effect size and statistical significance. Additionally, the main flow of the SRMA may be altered if the outcomes change as a result of excluding the retracted study.

In this case, the SRMA was eventually accepted following a defined peer review process and proofreading conducted by the KJA editorial board. The research protocol of the SRMA was registered with PROSPERO and the SRMA was performed according to the registered protocol. Importantly, the process of omitting the retracted paper did not result in a deviation from the registered protocol. At least at the time of the original SRMA submission, all the processes appear to have been completed appropriately. Therefore, including a retracted study should have had no influence on the acceptance or rejection of an SRMA, as this could be to the cause of another publication bias.

**How did the KJA reach a consensus?**

The editorial decision made regarding the previously submitted SRMA was upheld after the retracted paper was discovered. However, we had to account for the fact that excluding the retracted study could have altered the results of the SRMA. From a broad perspective, proofreading is deemed to be a part of the review process, which includes everything from submitting to evaluating papers. In this case, we requested that the authors add a new section to the latest version of their manuscript by performing a systematic review without the retracted paper. The authors were also asked to declare that a retracted study was included in their previous SRMA to provide the reason for the retraction. A second literature search, data extraction process, and analysis were conducted and the results were included as supplemental files at the time of retraction.

This topic may be relevant to readers in terms of the decision to include or exclude retracted studies in systematic reviews, and it may also be intriguing on its own given the various potential viewpoints on the issue. The following message was conveyed to all the study participants: systematic reviews may involve retract-
ed citations, which journal editors, reviewers, and researchers should be aware of [4]. Ensuring that the included references have not been retracted should be part of the peer-review process. The authors must regularly check the status of the included studies and ensure that they do not cite retracted papers [7]. In this case, it was impossible to avoid including a retracted study when submitting the original version, whereas it was possible to exclude a retracted study before publication because the retraction occurred during the proofreading stage. Given this ambiguous timing, establishing an appropriate review process was our primary challenge. Because no similar cases have been reported to date, clearly disclosing our process here allows for this to be used as a reference when a similar scenario arises in the future. It can also be used to demonstrate how the editorial board at the KJA strives to make the review process robust, transparent, and credible, as well as how it handles problems that occur during the review process using a rigorous and reasonable approach.

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**Conflicts of Interest**

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

**Author Contributions**

Geun Joo Choi (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing – original draft; Writing – review & editing)

Hyun Kang (Conceptualization; Data curation; Formal analysis; Funding acquisition; Validation; Writing – original draft; Writing – review & editing)

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Another new kid on the BLOCK for pain control in pediatric cardiac surgery

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Cardiac surgery under median sternotomy remains one of the most painful procedures in pediatrics. Adequate pain control is vital for fast tracking in this vulnerable patient group and has been shown to be associated with decreased morbidity and a shorter hospital stay. In recognition of the importance of adequate pain control, early studies evaluated the long-term effects of caudal or epidural analgesia. Unfortunately, studies have reported inconsistent results with caudal analgesia, and many have been reluctant to perform higher-level epidural analgesia due to the risk of hypotension or hematoma formation. Thus, recent studies have focused on evaluating the efficacy and safety of more superficial non-neuraxial regional fascial plane blocks [1,2]. Although these studies have reported favorable results regarding pain scores and opioid consumption, whether these favorable effects lead to positive long-term outcomes remains unknown.

In this issue of the Korean Journal of Anesthesiology, to further address the positive role of regional blocks in pediatric patients undergoing cardiac surgery, Abdelbaser et al. [3] reported their experience using the ultrasound-guided bilateral thoracic retrolaminar block (TRLB). The TRLB is a relatively novel plane block proposed as an alternative to the classic paravertebral block, with a lower risk of pleural injury. The authors prospectively evaluated 66 patients aged 2–8 years who underwent cardiac surgery via midline sternotomy for repair of simple congenital heart diseases. By comparing patients who received either normal saline (control group) or bupivacaine (study group) during the TRLB, they reported the following significant findings: a reduction in perioperative fentanyl consumption, faster extubation, and a shorter ICU stay. The results are consistent with those of previous studies using alternative regional blocks [1,2], and most valuably, they report the first collection of prospective data regarding the use of the TRLB in this specific patient group.

The results are significant in that they agree with the recent trend of perioperative opioid sparing [4]. In the pediatric population, the potential reduction in the total amount of anesthetics administered with TRLBs may also be particularly beneficial. Although the risk of anesthesia-induced neurotoxicity in young brains remains unknown and has not been well studied in pediatric patients undergoing cardiac surgery, studies have reported the possibility of neurotoxicity with the use of anesthetics during neurodevelopment [5]. Thus, by providing effective analgesia, the bilateral TRLB may reduce the neurotoxic properties of anesthetics by reducing the required dose. However, while most studies have measured changes in opioid consumption, the effects of regional blocks on the total anesthetic dose have not been studied. Abdelbaser et al. [3] stated that sevoflurane was controlled at 1–2% regardless of the use of the bilateral TRLB. The lack of studies addressing the dose of anesthetics may be due to difficulties in measuring the depth of anesthesia, as the use of processed EEG monitoring remains less reliable in pediatric pa-
tients. Future studies should address the need for anesthesia dose adjustment, as this would also affect the use of opioids.

While this prospective study conducted by Abdelbaser et al. [3] strongly supports the bilateral TRLB as an effective regional block for pediatric cardiac surgery, additional studies are needed to acquire in-depth knowledge regarding long-term benefits and potential risks (including the systemic toxicity of local anesthetics). Future studies comparing safety and efficacy among various regional blocks, such as the erector spinae plane block and transversus thoracis muscle plane block, are also necessary to identify the most appropriate treatment method.

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**Conflicts of Interest**

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**References**

Recent advancements in computing power, data storage, and the accumulation of clinical data in electronic health records (EHRs), as well as picture archiving and communication systems, have played a major role in introducing artificial intelligence (AI) into various fields of medicine \[1\]. Numerous studies have been published that use AI techniques in radiology \[2\], pathology \[3\], cardiology \[4\], and surgery \[5\]. For perioperative medicine, AI models for perioperative risk stratification, intraoperative event prediction, biosignal analyses, and intensive care medicine have been developed in the field of perioperative medicine. Some of these models have been validated using external datasets and randomized controlled trials. Once these models are implemented in electronic health record systems or software medical devices, they could help anesthesiologists improve clinical outcomes by accurately predicting complications and suggesting optimal treatment strategies in real-time. This review provides an overview of the AI techniques used in perioperative medicine and a summary of the studies that have been published using these techniques. Understanding these techniques will aid in their appropriate application in clinical practice.

**Keywords:** Artificial intelligence; Deep learning; Machine learning; Outcome assessment; Perioperative care; Risk assessment.

### Introduction

Recent advancements in computing power, data storage, and the accumulation of clinical data in electronic health records (EHRs), as well as picture archiving and communication systems, have played a major role in introducing artificial intelligence (AI) into various fields of medicine \[1\]. Numerous studies have been published that use AI techniques in radiology \[2\], pathology \[3\], cardiology \[4\], and surgery \[5\]. For perioperative medicine, AI models for perioperative risk stratification, intraoperative monitoring, and intensive care management have been studied \[6,7\]. In some cases, these models outperform conventional statistical models and even human experts \[8–10\]. Many of these models can be used in clinical practice if their performance is maintained in future prospective validation studies and their clinical utility is confirmed by randomized controlled trials.

This narrative review addresses the various AI techniques used in clinical studies. Additionally, existing evidence from clinical studies that have used AI for important perioperative outcomes is summarized.

### Overview of AI techniques

**Modeling algorithms**

Machine learning, which can learn patterns from data, is the most widely used AI algo-
algorithm in perioperative medicine [11]. Machine learning algorithms are typically classified into three categories: supervised, unsupervised, and reinforcement learning (Fig. 1).

Supervised learning algorithms learn patterns from pairs of input and output variables. Supervised learning algorithms are typically divided into classification and regression algorithms. Gradient boosting machine (GBM) and random forest (RF) are widely used supervised learning-based classification algorithms with excellent performance. GBM and RF use collections of decision trees whose results are summed and averaged to produce a single result. Gradient-boosted regression trees and RF regressors are regression variants of GBM and RF. For survival analyses, they are called gradient-boosting survival trees and random survival forests. Deep learning (DL) is another technique widely used in supervised learning-based classification and regression algorithms that uses a network of mathematical models of a neuron (perceptron). A multilayer perceptron (MLP) is the most basic DL model and consists of multiple fully connected layers of perceptrons. A convolutional neural network (CNN), which is frequently used in image analyses and biosignal processing, uses perceptrons that are

![Diagram of Machine Learning Algorithms](https://doi.org/10.4097/kja.22157)
activated only by specific patterns of geographically adjacent neurons in the previous layer. A recurrent neural network (RNN), which is frequently used in natural language processing and time-series data analyses, includes long short-term memory (LSTM) or gated recurrent units. RNNs include a recurrent loop for analyzing time-dependent sequences in a network. Recently, new structures of the DL model, including a self-attention layer, have emerged and have shown better performance than canonical RNN or CNN models [12–15].

Unsupervised learning algorithms can learn patterns from unlabelled data. Because there are no labels to learn, unsupervised learning algorithms use the distributions or patterns of the samples in the training dataset. For example, the k-means clustering algorithm uses sample distributions to classify the data into a specific number of groups. An autoencoder is a DL model that uses the input data as the labels. However, as the autoencoder has a structural bottleneck, it can reduce the dimensions of the dataset. Autoencoders can be used to detect abnormalities in a sample and remove noise from the biosignal [16].

Reinforcement learning algorithms can learn the optimal policy from data. Because it is impossible to build a model to simulate the strategy, a model-free offline reinforcement learning algorithm is used for most medical problems. Value-based algorithms, such as Q-learning, learn the value of each action in each status [17]. Conversely, policy-based algorithms, such as proximal policy optimization (PPO) and the advantage actor-critic (A2C), learn the optimal action in each status [18].

Hyperparameters

The number of neurons in each layer of the MLP and the number of decision trees in the GBM are examples of hyperparameters, whose values are used to control or tune the learning process of AI algorithms. Although AI models can automatically learn patterns from the input data, the range of these hyperparameters should be specified by humans. A grid search, which simply searches through grids in the search space, is the traditional method for determining the best hyperparameter. Random search [19] and Bayesian optimization [20] can be used to achieve better results in a limited number of searches.

Outcome variables

Clinical outcomes are the most common output variables of AI models in the medical field. They are selected based on clinical requirements. The label should be determined by expert consensus, because the performance of the supervised learning model depends on the quality of the labeling, and several decisions must be made even for studies with simple outcomes. For example, for a study of in-hospital mortality within 30 postoperative days, researchers must decide whether the date is based on the beginning or end of the surgery and whether the time of death is defined as the time of the declaration or certificate. Additionally, researchers must decide whether mortality should be treated as a binary or survival outcome, which includes the censoring time.

Input variables

All variables that can affect the outcome should be considered as input variables to improve the model performance. However, any variable that is affected by the outcome variable itself should be removed as an input variable since this could result in a causality problem, which decreases the external validity [21]. Examples include using the fraction of inspired oxygen to predict intraoperative hypoxia or using postoperative pain to predict postoperative nausea and vomiting.

Reducing the number of input variables by removing irrelevant variables can improve the performance, robustness, and interpretability of the model while reducing the learning time [22]. Several techniques have been suggested for optimal feature selection, such as recursive feature estimation or the Boruta algorithm [23].

In linear regression, multicollinearity between the input variables can cause algorithm instability and distortion of parameter estimates. However, most AI algorithms can converge even with correlated input variables. Nevertheless, removing collinear variables can help improve performance by reducing the number of input variables. Additionally, the multicollinearity of the input variables can have a significant impact on feature importance in explainable AI algorithms [24]. Therefore, if the effect of a specific input variable on the outcome is the opposite of what is expected, it may be the result of multicollinearity.

Study population

As with the outcome variable, the study population selected has a significant influence on the performance of the AI model. Having clear and appropriate inclusion and exclusion criteria is essential to determine the scope of the model. Because the AI model learns the pattern of the training dataset, it is critical to create a training set with as many clinical scenarios as possible. Therefore, multicenter and multinational data are preferable, particularly for AI studies.

The test dataset should be used only to evaluate the performance of the final model. It is imperative to confirm that patients
in the training dataset are excluded from the test dataset. For example, if a patient undergoes surgery twice, the test dataset randomized to surgery may contain the same patient’s data in the training dataset.

**Performance metrics**

Accuracy is an inappropriate metric to use when evaluating the performance of a model on an imbalanced dataset, where the frequency of events is significantly lower than that of nonevents. For example, if the event frequency of the test dataset is 1%, even the all-negative predictor has an accuracy of 99%. This problem is important when dealing with rare complications, such as postoperative mortality or organ failure. The F1-score, which is the harmonic average of the precision and recall, or the balanced accuracy, which is the arithmetic mean of the recall for each class, might be better indicators in this case.

If the label is a binary variable and the output of the model is the risk of an event expressed as a continuous variable, the area under the receiver operating characteristic (AUROC) curve can be used as a performance metric. However, in severely imbalanced data, the AUROC easily becomes a high value; therefore, the area under the precision-recall curve (AUPRC) may be a better choice. Survival analysis performance is usually evaluated using the Harrell’s concordance index (C-index).

In the reinforcement learning model, performance is evaluated by comparing the expected reward between the AI-suggested policy and the clinician’s policy by replaying the clinically-defined trajectory.

**AI models for perioperative risk stratification**

Accurate perioperative risk stratification is important for facilitating shared decision-making and the allocation of medical resources. Several preoperative risk scores have been developed and used in clinical practice, including the American Society of Anesthesiologists Physical Status (ASA-PS) classification [11], American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) surgical risk calculator [25], surgical Apgar score [26], and Risk Stratification Index [27].

However, recent studies have shown that AI models for perioperative risk stratification have excellent performance (Table 1) in evaluating the risk of postoperative complications.

**Prediction of mortality risk**

Since its proposal in 1963, the ASA-PS classification for preoperative risk assessment has been used for most surgical patients. However, the limitations of the ASA-PS classification include the subjective nature of the clinicians’ evaluations and high inter-rater variability [28].

Lee et al. [29] developed a DL model to predict postoperative in-hospital mortality using features extracted at the end of surgery from the data of 59,985 patients. This model used 45 intraoperative features and the ASA-PS classification to achieve an AUROC of 0.91, which is comparable to that with existing methods, such as logistic regression (LR).

Hill et al. [30] developed a fully automated score to predict postoperative in-hospital mortality using RF from the EHRs of 53,097 surgical patients. This model consisted of 58 preoperative variables that were automatically obtained from the EHR. The AUROC of the model (0.93) was larger than that of the existing risk scores (the ASA-PS, PreOperative Score to predict PostOperative Mortality [POSPOM], and Charlson Comorbidity Index scores).

Fritz et al. [31] constructed a CNN model to predict postoperative 30-day mortality from the data of 95,907 patients who underwent surgery under general anesthesia with tracheal intubation. The model consisted of 54 preoperative parameters, including patient characteristics, comorbidities, laboratory values, and 28 intraoperative variables. Its performance was compared with that of other algorithms, such as DL, RF, support vector machine (SVM), and LR. According to the results of the study, the CNN model had the best performance when using time-series data.

Chiew et al. [32] tested various machine learning algorithms to predict postoperative 30-day mortality and intensive care unit (ICU) stay > 24 h using data from 90,785 patients who underwent non-cardiac and non-neurological surgeries. GBM outperformed all other machine learning algorithms, with an AUPRC of 0.23.

Bertsimas et al. [33] developed a surgical risk calculator to predict postoperative 30-day mortality and 18 postoperative complications using optical classification trees from the data of 382,960 emergency surgery patients in the ACS-NSQIP database. The AUROC of the model for mortality was 0.92. The predictive performance of this calculator was tested in other populations, such as patients aged > 65 years [34] and patients undergoing emergency general surgery and laparotomy [35], and its performance in predicting mortality remained stable.

Lee et al. [36] developed an interpretable neural network to predict postoperative in-hospital mortality from the data of 59,985 surgical patients using generalized additive models (GAMs) with neural networks. The model had an AUROC of 0.92. To improve the interpretability and transparency of the pre-
diction model, feature contributions were visualized, enabling clinicians to better understand the model's prediction process.

**Prediction of cardiac risk**

The most widely used classical model in this field is the Revised Cardiac Risk Index (RCRI), which has been incorporated into the guidelines of the American College of Cardiology/American Heart Association and European Society of Cardiology/European Society of Anesthesiology [37–39]. The RCRI, which was reported in 1999 by Lee et al. [37], consists of six variables: high-risk surgery, history of congestive heart failure, history of ischemic heart disease, history of cerebrovascular disease, preoperative serum creatinine > 2.0 mg/dl, and preoperative insulin treatment. However, a recent large-scale retrospective validation study using the Danish National Patient Registry revealed that the estimated odds ratio for each variable in the RCRI varies between 1.45 for serum creatinine and 10.02 for a history of cerebrovascular disease [40]. Additionally, in a systematic review of 24 studies (792,740 patients), the RCRI showed only modest performance (AUROC = 0.75) [41].

Bihorac et al. [42] developed a machine learning model called MySurgeryRisk for predicting eight major postoperative complications: mortality; acute kidney injury (AKI); sepsis; venous thromboembolism; ICU stay > 48 h; mechanical ventilation > 48 h; and wound, neurologic, and cardiovascular complications using the GAM. The model had an AUROC of 0.85 for predicting cardiovascular complications.

Mathis et al. [43] developed a GBM model to predict heart failure after non-cardiac surgery. Using 499 preoperative and 263 intraoperative data points from 67,697 patients, the AUROC of the model was 0.87.

**Prediction of pulmonary risk**

Postoperative pulmonary complications frequently develop after major surgery, and even a mild form of these complications is associated with a prolonged hospital stay and an increased mortality rate [44,45]. The most commonly used classical model in this field is the Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score. Canet et al. [46] developed the ARISCAT score to predict postoperative pulmonary complications in surgical patients using LR, which is the only risk score that maintains discriminatory power for external validation [47]. In a pro-

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**Table 1. AI-based Perioperative Risk Stratification Models**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Outcome variable</th>
<th>AUC</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu [60]</td>
<td>2016</td>
<td>Postoperative nausea and vomiting</td>
<td>0.93</td>
<td>Single center</td>
</tr>
<tr>
<td>Lee [29]</td>
<td>2018</td>
<td>Postoperative in-hospital mortality</td>
<td>0.91</td>
<td>Single center</td>
</tr>
<tr>
<td>Lee [52]</td>
<td>2018</td>
<td>AKI after cardiac surgery</td>
<td>0.78</td>
<td>Single center</td>
</tr>
<tr>
<td>Lee [53]</td>
<td>2018</td>
<td>AKI after liver transplantation</td>
<td>0.86</td>
<td>Single center</td>
</tr>
<tr>
<td>Bertsimas [33]</td>
<td>2018</td>
<td>Postoperative 30-day mortality &amp; morbidity (POTTER)</td>
<td>0.84–0.92</td>
<td>Multi-center</td>
</tr>
<tr>
<td>Chen [59]</td>
<td>2018</td>
<td>Postoperative bleeding</td>
<td>0.82</td>
<td>Single center</td>
</tr>
<tr>
<td>Fritz [31]</td>
<td>2019</td>
<td>Postoperative 30-day mortality</td>
<td>0.87</td>
<td>Single center</td>
</tr>
<tr>
<td>Bihorac [42]</td>
<td>2019</td>
<td>Mortality; AKI; sepsis; VTE; ICU &gt; 48 h; MV &gt; 48 h; &amp; wound, neurologic, cardiovascular complication (MySurgeryRisk)</td>
<td>0.77–0.94</td>
<td>Single center</td>
</tr>
<tr>
<td>Lei [55]</td>
<td>2019</td>
<td>AKI after major non-cardiac surgery</td>
<td>0.82</td>
<td>Single center</td>
</tr>
<tr>
<td>Hill [30]</td>
<td>2019</td>
<td>Postoperative in-hospital mortality</td>
<td>0.93</td>
<td>Single center</td>
</tr>
<tr>
<td>Adhikari [54]</td>
<td>2019</td>
<td>Postoperative AKI</td>
<td>0.86</td>
<td>Single center</td>
</tr>
<tr>
<td>Bolourani [48]</td>
<td>2020</td>
<td>Postoperative respiratory failure</td>
<td>NA</td>
<td>Multi-center</td>
</tr>
<tr>
<td>Tseng [36]</td>
<td>2020</td>
<td>AKI after cardiac surgery</td>
<td>0.78–0.84</td>
<td>Single center</td>
</tr>
<tr>
<td>Rank [10]</td>
<td>2020</td>
<td>AKI after cardiothoracic surgery</td>
<td>0.89</td>
<td>Single center</td>
</tr>
<tr>
<td>Hofer [57]</td>
<td>2020</td>
<td>Postoperative mortality, AKI, and reintubation</td>
<td>0.79–0.91</td>
<td>Single center</td>
</tr>
<tr>
<td>Mathis [43]</td>
<td>2020</td>
<td>Postoperative heart failure</td>
<td>0.87</td>
<td>Single center</td>
</tr>
<tr>
<td>Chiew [32]</td>
<td>2020</td>
<td>Postoperative 30-day mortality &amp; ICU admission</td>
<td>0.96</td>
<td>Single center</td>
</tr>
<tr>
<td>Chen [49]</td>
<td>2021</td>
<td>Pneumonia after liver transplantation</td>
<td>0.73</td>
<td>Single center</td>
</tr>
<tr>
<td>Xue [58]</td>
<td>2021</td>
<td>Postoperative pneumonia, AKI, DVT, PE, delirium</td>
<td>0.76–0.91</td>
<td>Single center</td>
</tr>
<tr>
<td>Lee [36]</td>
<td>2021</td>
<td>Postoperative in-hospital mortality</td>
<td>0.92</td>
<td>Single center</td>
</tr>
</tbody>
</table>

All of these studies are retrospective. AUC: area under curve, AKI: acute kidney injury, POTTER: machine-learning-based Predictive Optimal Trees in Emergency Surgery Risk, VTE: venous thromboembolism, ICU: intensive care unit, MV: mechanical ventilation, DVT: deep vein thrombosis, PE: pulmonary embolism, NA: not applicable.
spective validation study involving 5,859 patients, the ARISCAT score achieved an AUROC of 0.80 [47].

Additionally, Bolourani et al. [48] developed a machine learning model to predict postoperative respiratory failure in 4,062 patients who underwent pulmonary lobectomy. Although the sensitivity and specificity were 83.3% and 94.5%, respectively, the AUROC was not provided.

Chen et al. [49] investigated various machine-learning algorithms, including LR, SVM, RF, adaptive boosting, and GBM, to predict pneumonia after orthotopic liver transplantation in 786 patients. Fourteen features, which included laboratory and clinical variables, were associated with postoperative pneumonia in this study.

Prediction of AKI

AKI is associated with increased morbidity, length of hospital stay, and mortality [50]. Although there are various criteria and time frames for diagnosing AKI, a recent consensus statement recommended that postoperative AKI be defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria, which defines it as an AKI that occurs within the first seven days after surgery [51].

Lee et al. [52] compared the performance of various machine-learning algorithms (e.g., decision tree, RF, GBM, SVM, and DL) for predicting postoperative AKI using LR in 2,010 patients undergoing cardiac surgery. GBM showed the highest AUROC of 0.78 and the lowest error rate of 26%. This group also conducted another study using preoperative, intraoperative, and surgery-related variables to test the performance of various algorithms on AKI prediction using data from 2,911 patients undergoing liver transplantation. GBM also showed the best performance, with an AUROC of 0.90 [53].

Adhikari et al. [54] developed a machine learning model containing intraoperative time-series variables to predict postoperative AKI in 2,911 surgical patients. Compared to the model using only preoperative variables, the model that included both preoperative variables and intraoperative time-series data showed better predictive performance, with an AUROC of 0.86.

Lei et al. [55] investigated whether combining preoperative and intraoperative data could improve the prediction of postoperative AKI in 42,915 patients undergoing major noncardiac surgery. The GBM algorithm outperformed LR with elastic net selection and RF. The authors found that adding intraoperative data slightly improved the predictive performance.

Tseng et al. [56] used a machine learning model to predict postoperative AKI in cardiac surgical patients using preoperative and intraoperative time-series hemodynamic variables. The combination of RF and GBM showed the highest AUROC (0.84). They used the SHapley Additive exPlanation method to explain how the model’s predictions were made, thus improving the interpretability of the model.

Rank et al. [10] used an RNN and 96 routinely collected variables to develop a DL model for the real-time prediction of postoperative AKI (stage 2 or 3 based on the KDIGO criteria) in patients undergoing cardiothoracic surgery until discharge from the ICU or post-anesthesia care unit. They compared the predictive performance of the DL model with that of experienced clinicians and found that the DL model outperformed experienced clinicians.

Prediction of other complications

Hofer et al. [57] developed a DL model to predict multiple postoperative complications, including AKI, reintubation, and mortality, using a single-input feature set available at the end of surgery. Its performance was compared with that of the ASA-PS classification. The AUROCs of the models were 0.79, 0.88, 0.91, and 0.87 for AKI, reintubation, mortality, and the composite outcome, respectively.

Xue et al. [58] tested five machine learning algorithms (LR, SVM, RF, GBM, and DL) to predict five postoperative complications (pneumonia, AKI, deep vein thrombosis, pulmonary embolism, and delirium) using preoperative and intraoperative data. The best-performing model for each complication showed the following AUROCs: pneumonia (GBM), 0.91; AKI (GBM), 0.85; deep vein thrombosis (GBM), 0.88; pulmonary embolism (MLP), 0.83; and delirium (GBM), 0.76. A model for predicting other postoperative complications was also developed. Chen et al. [59] developed an AI model using 299 perioperative variables to predict bleeding after colorectal surgery. The GBM model had an AUROC of 0.82, which was higher than that of the LR model (AUROC = 0.74).

Wu et al. [60] developed an SVM model to predict postoperative nausea in orthopedic surgery patients receiving patient-controlled epidural analgesia. Their model showed an AUROC of 0.93, which was higher than that of the LR model (AUROC = 0.73).

AI models for intraoperative event prediction and biosignal analysis

Anesthesiologists play a pivotal role in monitoring and maintaining hemodynamic stability during surgery, which can affect

https://doi.org/10.4097/kja.22157
postoperative clinical outcomes [61]. Several AI algorithms that can assist anesthesiologists in intraoperative management by calculating secondary indices using real-time data have been published (Table 2). These algorithms can help anesthesiologists improve intraoperative management by predicting future events, such as intraoperative hypotension [62–65] or desaturation [8], and by processing biosignals [10,66].

**Prediction of intraoperative hypotension**

Kendale et al. [63] developed a machine learning model to predict post-induction hypotension, which was defined as a mean arterial pressure (MAP) < 55 mmHg within 10 min of anesthesia induction, in 13,323 surgical patients. GBM outperformed the other algorithms (e.g., LR, SVM, naïve Bayes, k-nearest neighbor, linear discriminant analysis, RF, neural nets, and GBM).

Kang et al. [62] investigated four machine learning techniques (LR, naïve Bayes, RF, and artificial neural network) to predict post-induction hypotension, which was defined as a systolic blood pressure < 90 mmHg or MAP < 65 mmHg occurring between tracheal intubation and surgical incision. RF showed the highest AUROC. The patients' lowest systolic blood pressure, lowest MAP, and mean SBP before tracheal intubation were the most important features in terms of prediction accuracy.

Hatib et al. [67] developed a machine learning model to predict upcoming hypotensive events (MAP < 65 mmHg) using features from arterial pulse waveforms in 1,334 patients, and the Hypotension Prediction Index (HPI) was externally validated in 204 patients from a prospectively collected cohort. The AUROC of the prediction 5–15 min before a hypotensive event was 0.95–0.97. The HPI was tested in 255 patients undergoing major surgery, and it predicted hypotension 5–15 min before a hypotensive event with an AUROC of 0.879–0.926 [68].

Wijnberge et al. [69] conducted a single-center randomized controlled study of 68 patients undergoing elective non-cardiac surgery under general anesthesia to evaluate the effect of early prediction of hypotension using the HPI on the number of hypotensive events. The primary outcome of the study was time-weighted average hypotension (MAP < 65 mmHg). Patients were randomly assigned to two groups: those who received standard care and those who received an early warning when their HPI value exceeded 85. In this study, the HPI-guided early warning system significantly reduced intraoperative hypotension. However, Maheshwari et al. [70] failed to report the benefits of HPI-guided management during moderate- to high-risk non-cardiac surgery.

In this study, the patients were randomly assigned to either the HPI-guided or HPI-unguided group. In the HPI-guided group, if the HPI exceeded 85, clinicians received electronic alerts and treatment algorithms, such as fluid administration, inotrope or vasopressor administration, or observation, which they could choose to follow or not. However, approximately half of the clinicians who received electronic alerts did not follow the recommended treatment algorithm, indicating the need for a simpler treatment algorithm and lower alert threshold.

Lee et al. [65] developed DL algorithms for real-time predictions 5–15 min before the occurrence of a hypotensive event based on biosignals collected using routine invasive and noninvasive intraoperative monitoring of 3,301 patients from the VitalDB database [71]. Using an arterial pressure waveform, electrocardiography, photoplethysmography, and capnography, the multichannel DL model predicted hypotensive events 15 min before the occurrence of an actual hypotensive event, with an AUROC of 0.90.

**Prediction of intraoperative hypoxemia**

Lundberg et al. [8] developed an AI model to predict intraoperative hypoxemia, which is defined as an oxygen saturation ≤ 92% within 5 min. They extracted more than 20 preoperative and 45 intraoperative features at 1-min intervals from the data of 53,126 patients from a prospective database [8]. Using an arterial oxygen saturation waveform, an electrocardiogram, arterial pressure, and an arterial blood gas waveform, the machine learning model predicted hypoxic events 5–15 min before the occurrence of a hypoxic event. The primary outcome of the study was the number of hypoxic events. The model predicted hypoxemia with an AUROC of 0.83–0.95, and the HPI exceeded 85. In this study, the HPI-guided early warning system significantly reduced intraoperative hypoxemia. However, Maheshwari et al. [70] failed to report the benefits of HPI-guided management during moderate- to high-risk non-cardiac surgery.

Yoon et al. [6] conducted a single-center randomized controlled study of 68 patients undergoing elective non-cardiac surgery under general anesthesia to evaluate the effect of early prediction of hypoxemia using the HPI on the number of hypoxic events. The primary outcome of the study was time-weighted average hypoxemia (MAP < 92% of arterial oxygen saturation). Patients were randomly assigned to two groups: those who received standard care and those who received an early warning when their HPI value exceeded 85. In this study, the HPI-guided early warning system significantly reduced intraoperative hypoxemia. However, Maheshwari et al. [70] failed to report the benefits of HPI-guided management during moderate- to high-risk non-cardiac surgery.

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Outcome variable</th>
<th>AUC</th>
<th>Population</th>
<th>Design</th>
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<tr>
<td>Landberg [8]</td>
<td>2018</td>
<td>Intraoperative hypoxemia (Prescience)</td>
<td>0.83</td>
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<td>Retrospective</td>
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<td>Kendale [63]</td>
<td>2018</td>
<td>Postinduction hypotension</td>
<td>0.74</td>
<td>Single center</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Hatib [67]</td>
<td>2018</td>
<td>Intraoperative hypotension (HPI)</td>
<td>0.95–0.97</td>
<td>Multi-center</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Solomon [64]</td>
<td>2020</td>
<td>Intraoperative bradycardia associated with hypotension</td>
<td>0.89</td>
<td>Single center</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Kang [62]</td>
<td>2020</td>
<td>Postinduction hypotension</td>
<td>0.84</td>
<td>Single center</td>
<td>Retrospective</td>
</tr>
<tr>
<td>Wijnberge [69]</td>
<td>2020</td>
<td>HPI vs. conventional</td>
<td>NA</td>
<td>Single center</td>
<td>RCT</td>
</tr>
<tr>
<td>Maheshwari [70]</td>
<td>2020</td>
<td>HPI vs. conventional</td>
<td>NA</td>
<td>Single center</td>
<td>RCT</td>
</tr>
<tr>
<td>Lee [65]</td>
<td>2021</td>
<td>Intraoperative hypoxemia</td>
<td>0.90</td>
<td>Single center</td>
<td>Retrospective</td>
</tr>
</tbody>
</table>

AUC: area under curve, HPI: hypotension prediction index, N/A: not applicable, RCT: randomized controlled trial.
surgical patients on EHRs and trained the GBM model. The AI model had a significantly higher AUROC than the anesthesiologists (0.81 vs. 0.66).

**Model for the electroencephalography analysis**

Saadeh et al. [66] developed a machine learning model based on several features from electroencephalography (EEG) signals to estimate the depth of anesthesia, irrespective of age and type of anesthetic drugs. Their model showed an average accuracy of 92% for all stages of anesthesia.

Park et al. [10] developed a DL model to perform real-time estimation of the depth of anesthesia. This model, which combined an EEG-based depth of anesthesia monitoring system with DL, had a stronger correlation with the minimum alveolar concentration than the bispectral index.

**Model for anesthetic titration**

Underdosing anesthetic agents can cause intraoperative awareness during general anesthesia, whereas overdosing can cause complications, such as hypotension, delayed recovery, and delirium after surgery. The target-controlled infusion (TCI) algorithm, developed by Shafer and Greg [72] in 1992, has been used to titrate fast-acting anesthetics and opioids. However, because the TCI algorithm relies on population pharmacokinetic and pharmacodynamic models that can have high inter-individual variability, control methods using EEG-based anesthesia depth monitors, such as the bispectral index have been proposed [73].

However, AI models for achieving and maintaining an appropriate depth of anesthesia without complications can be developed. Reinforcement learning algorithms for propofol titration based on Q-learning and PPO-based algorithms have been reported [74,75]. In a recent study, a deep reinforcement learning model using the A2C algorithm outperformed a proportional integral derivative controller [76].

**AI models for patients in the ICU**

Several studies using AI techniques for ICU patient management have been published (Table 3). These algorithms are aimed at predicting ward or ICU complications and helping clinicians respond early. The Medical Information Mart for Intensive Care (MIMIC) database, a single-center open dataset from the Beth Israel Deaconess Medical Center (Boston, MA, USA) [77], and the eICU, a multicenter open dataset in the USA [78], are frequently used in studies in the field for model development and validation.

**Prediction of mortality in the ICU**

To stratify acutely ill patients and evaluate the effects of therapy, the Acute Physiology, Age, Chronic Health Evaluation (APACHE) II was developed in 1985, using 12 variables [79]. The APACHE III, a revised version of the APACHE II system using different variables, was developed from 17,440 patients in the ICU of 40 US hospitals [80]. The authors of the original study reported that the APACHE III predicted in-hospital mortality with an AUROC of 0.90. However, in a multicenter prospective study involving 1,144 patients, the AUROCs of the APACHE II and APACHE III were 0.806 and 0.847, respectively [81].

Delahanty et al. [82] developed a risk-adjustment algorithm for in-hospital mortality in 237,173 patients in 131 ICUs across 53 hospitals. This study was not designed to evaluate the predictive performance of the APACHE III. However, the authors reported that the APACHE III predicted in-hospital mortality with an AUROC of 0.90. However, in a multicenter prospective study involving 1,144 patients, the AUROCs of the APACHE II and APACHE III were 0.806 and 0.847, respectively [81].

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Table 3. AI-based Prediction Models for Intensive Care Unit Patients

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Outcome variable</th>
<th>AUC</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delahanty [82]</td>
<td>2018</td>
<td>ICU mortality (RIPD)</td>
<td>0.94</td>
<td>Multi-center</td>
</tr>
<tr>
<td>Rojas [84]</td>
<td>2018</td>
<td>ICU readmission</td>
<td>0.73</td>
<td>Multi-center</td>
</tr>
<tr>
<td>Mao [88]</td>
<td>2018</td>
<td>Sepsis in ICU (Insight)</td>
<td>0.92</td>
<td>Multi-center</td>
</tr>
<tr>
<td>Nemati [87]</td>
<td>2018</td>
<td>Sepsis in ICU (AISE)</td>
<td>0.83–0.85</td>
<td>Multi-center</td>
</tr>
<tr>
<td>Giannini [89]</td>
<td>2019</td>
<td>Sepsis in ICU</td>
<td>0.88</td>
<td>Multi-center</td>
</tr>
<tr>
<td>Scherp [90]</td>
<td>2019</td>
<td>Sepsis in ICU</td>
<td>0.81</td>
<td>Single center</td>
</tr>
<tr>
<td>Kong [93]</td>
<td>2020</td>
<td>Mortality in patient with sepsis</td>
<td>0.83–0.85</td>
<td>Single center</td>
</tr>
<tr>
<td>Burdick [94]</td>
<td>2020</td>
<td>Severe sepsis and septic shock</td>
<td>0.83–0.93</td>
<td>Multi-center</td>
</tr>
<tr>
<td>He [91]</td>
<td>2020</td>
<td>Sepsis in ICU</td>
<td>NA</td>
<td>Multi-center</td>
</tr>
<tr>
<td>Hur [85]</td>
<td>2021</td>
<td>Delirium in ICU (PRIDE)</td>
<td>0.92</td>
<td>Multi-center</td>
</tr>
<tr>
<td>Goh [92]</td>
<td>2021</td>
<td>Sepsis in ICU (SERA)</td>
<td>0.94</td>
<td>Single center</td>
</tr>
</tbody>
</table>

All of these studies are retrospective. AUC: area under curve, ICU: intensive care unit, RIPD: risk of inpatient death, AISE: Artificial Intelligence Sepsis Expert, NA: not applicable, PRIDE: Prediction of Intensive Care Unit Delirium, SERA: sepsis early risk assessment.
hospitals. This model, which used the GBM algorithm and had 17 features, including clinical and administrative data, showed excellent discrimination, with an AUROC of 0.94.

Baker et al. [83] developed a continuous mortality risk prediction model for ICU mortality using a hybrid neural network approach that combined a CNN and bidirectional LSTM. Using the MIMIC III database, the authors predicted in-hospital mortality within 3, 7, and 14 days using vital signs over a 24 h period. This model achieved the highest AUROC of 0.88.

**Prediction of ICU readmission**

Rojas et al. [84] developed a prediction model for ICU readmission using data from 24,885 patients, and validated the model’s performance using MIMIC data. Their GBM model showed an AUROC of 0.71, which was significantly better than the Stability and Workload Index for Transfer score (SWIFT; AUROC = 0.58) and the Modified Early Warning Score (MEWS; AUROC = 0.57).

**Prediction of delirium in the ICU**

Hur et al. [85] developed a model called the Prediction of Intensive Care Unit Delirium to predict the risk of delirium in patients in the ICU. This RF model used 59 variables extracted from 37,543 patients and had an AUROC of 0.72. Jauk et al. [86] prospectively verified the performance of an RF-based delirium prediction model over seven months in internal medicine patients. The retrospective performance of this model had an AUROC of 0.91, whereas the prospective validation performance had an AUROC of 0.86.

**Prediction and management of sepsis in the ICU**

Several GBM-, SVN-, and DL-based prediction models for sepsis in ICU patients have been developed [87–92]. These models have been found to predict sepsis 3–12 h before onset, with an AUROC of 0.81–0.92. They showed better performance than conventional scoring systems, such as the systemic inflammatory response syndrome (SIRS), Sequential Organ Failure Assessment (SOFA), quick SOFA, and MEWS. Implementing these algorithms into EHR systems could help clinicians respond to high-risk patients early.

Kong et al. [93] evaluated various machine-learning algorithms for predicting in-hospital mortality in 16,688 ICU patients with sepsis from the MIMIC III database. Among the tested algorithms (least absolute shrinkage and selection operator, RF, GBM, and traditional LR), GBM showed the highest AUROC of 0.845.

Burdick et al. [94] created a machine learning prediction model using GBM for severe sepsis and septic shock 48 h before the onset of events from the data of 270,438 patients. The predictive performances had AUROCs of 0.83 and 0.75 for the internal test and external validation datasets, respectively. The model showed superior performance to previous prediction models, such as the SIRS, SOFA, and MEWS.

Raghu et al. [95] developed a reinforcement learning model that suggests a policy for sepsis treatment using a Q-learning algorithm. The model proposes the optimal volume of intravenous fluids and dosage of vasopressors that should be administered to improve the SOFA score and lactate concentrations. A retrospective validation of the model showed that their algorithm was expected to reduce mortality by up to 3.6%.

**Models for ventilator control**

Mechanical ventilation is one of the most common treatments in the ICU [96]. Although there is evidence that a lung-protective ventilatory strategy improves survival in patients with acute respiratory distress syndrome (ARDS), the optimal ventilatory strategy for patients without ARDS remains unknown [97,98]. In a recent study of AI-based ventilator control algorithms, the Q-learning-based reinforcement learning model outperformed the clinician’s policy in terms of rewards defined as in-hospital or 90-day mortality [9].

**Conclusion**

Although the above-described AI-based predictive models showed high predictive performance in various perioperative settings, most of the results were obtained from single-center retrospective studies. Before applying AI models in clinical practice, additional external and prospective validation and randomized clinical trials are required. Reinforcement learning models may suggest optimal strategies to overcome inter-individual variability; however, their clinical utility must be verified. If the high performance of AI algorithms is well maintained in future studies, they can be widely used in clinical practice as a powerful tool to help clinicians improve patient safety and outcomes.

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

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91. He Z, Du L, Zhang P, Zhao R, Chen X, Fang Z. Early sepsis prediction using ensemble learning with deep features and artificial features extracted from clinical electronic health records. Crit
Introduction

Coronary heart disease (CHD) is the leading cause of death worldwide. CHD mortality in the United States in 2017 was over 360,000 [1] and worldwide, 3.8 million men and 3.4 million women die of the disease each year [2,3]. Myocardial infarction (MI), also known as a heart attack, is the major cause of death in CHD and over 100,000 Americans died of MI in 2017 [1].

The myocardium performs structural and biomechanical functions that are essential for health and survival. Myocardial loss caused by injury, disease, or aging accounts for a
significant number of clinical disorders and substantial human suffering at an enormous social and economic cost [4]. Infarctions usually result in the formation of fibrotic scars that permanently impair the biomechanical function of the heart because the heart exhibits a minimal capacity for self-repair [5].

MI occurs when the blood supply to the heart is severely reduced or completely blocked. As a result, cardiac muscle cells do not receive sufficient oxygen and may die through forms of necrosis and apoptosis that contribute to the death of cardiomyocytes [6]. This most commonly occurs when a coronary artery becomes occluded and blood clot forms acutely following the rupture of an atherosclerotic plaque. Major surgery and anesthesia may also induce cardiovascular risk, particularly in patients with cardiovascular disease [7]. For example, cardiac ischemia/reperfusion (I/R) injury is frequently induced or may occur during coronary angioplasty, cardiac valve replacement, coronary artery bypass grafting, and cardiac transplantation [7,8,9].

Early myocardial reperfusion with the use of thrombolytic therapy or primary percutaneous coronary intervention (PCI) is the most effective strategy to reduce infarct size and improve clinical outcomes [3,8]. However, the process of restoring blood flow to the ischemic myocardium can cause injury, and this phenomenon, termed ‘myocardial reperfusion injury’, can diminish the beneficial effects of myocardial reperfusion [2,3,8]. The mechanism of I/R injury is unclear, but several hypotheses have been proposed: formation of free radical or reactive oxygen species (ROS), calcium overload, hyperglycemia, mitochondrial dysfunction, inflammation, neutrophil-mediated vascular damage, microvascular hypoperfusion, and depletion of high energy phosphates [3,6]. Reperfusion has deleterious effects and reperfusion injury can contribute to up to half of the final myocardial infarct size (MIS) [2,3,8].

The development of effective adjunct therapy is necessary to improve clinical outcomes in acute MI (AMI) and to reduce the risk of heart failure (HF) and sudden death after MI. For these reasons, various approaches and therapies have been tested to reduce the detrimental effects of I/R. However, these have not shown any beneficial cardioprotective effects in the clinical setting [8,10–12].

Mild hypothermia has been introduced as a potential inhibitor of myocardial I/R injury. Although animal studies have demonstrated that mild hypothermia significantly reduces or delays I/R myocardial damage [13–18], human trials have not replicated clinical benefits in AMI [10–12,19,20]. In this article, we review the evidence and issues from animal and clinical studies regarding the effects of hypothermia therapy on AMI.

Pathophysiology of MI and I/R injury

Ischemia

MI results from an imbalance in the myocardial oxygen supply/demand, typically due to insufficient coronary blood flow. Various causes of coronary stenoses, such as atherosclerosis, vasoconstriction, or mechanical pressure can cause coronary ischemia. Usually, coronary blood flow is maintained through autoregulation, which controls the tone and coronary artery luminal size through mediators of the myocardium or endothelium [21]. However, when the coronary endothelial function is abnormal due to coronary artery disease, coronary blood flow cannot be sufficiently maintained through this mechanism.

Factors influencing the size of subsequent infarcts include the duration of ischemia, the size of the ischemic territory (area at risk [AAR]), collateral blood flow, myocardial metabolic rate, and temperature during ischemia [22,23]. Ischemia duration longer than 40 min results in irreversible myocardial damage and loss of cardiac function, and I/R injury may occur after 50 min [2,24]. In the absence of collateral circulation, necrosis occurs in most of the AARs if reperfusion is not performed in a timely manner. Long-term consequences of MI include ventricular remodeling of the remaining myocardium, ventricular failure, arrhythmia, and sudden death [25,26].

Reperfusion & reperfusion injury

Reperfusion therapy, such as PCI or thrombolysis, is essential for the survival of damaged myocardial tissue by ischemia, especially in the setting of acute ST-segment elevation myocardial infarction (STEMI) [3,22]. Clinically, reperfusion significantly reduces mortality after MI by approximately 75% [23]. However, reperfusion can be a ‘double-edged sword’ due to I/R injury [27–29].

The pathological mechanisms of I/R injury are multifactorial [2,8,23,24]. Infarcted myocardium undergoes necrosis characterized by calcium overload with contracted myofibrils, sarcomenal rupture with edema, mitochondrial collapse, microvascular obstruction, capillary rupture, hemorrhage, and leukocyte infiltration [2,8]. Necrotic changes during reperfusion are accelerated by multiple pathways, such as calcium overload, oxidative stress by ROS, inflammatory response, and activation of the calpain system [2,8,23]. In addition to necrotic cell death, the regulated process of cell death via apoptosis, autophagy, and necroptosis also occurs through the regulation of the calpain system [24]. Myocardial reperfusion results in four types of cardiac dysfunc-
tion: 1) myocardial stunning, 2) no-reflow phenomenon, 3) reperfusion arrhythmias, and 4) irreversible fatal reperfusion injury, which involves severe myocardial damage including increased infarct size and impairment of myocardial contractility [3].

**Inflammation & remodeling**

After MI, macrophages, monocytes, and neutrophils migrate and trigger intracellular signaling processes, resulting in inflammatory responses [25,30,31]. The degradation of collagen struts by matrix metalloproteinases activation and serine proteases results in infarct expansion. Infarct expansion leads to wall thinning and ventricular dilatation, increasing myocardial wall stress. This early remodeling occurs within 72 h, and the expansion of the infarct zone leads to changes in loading conditions.

When ventricular load increases and cardiac output decreases, there is a release of norepinephrine, and activation of the renin-angiotensin-aldosterone system, resulting in myocardial hypertrophy. During late remodeling (more than 72 h), reparative changes occur in the global ventricle including both infarcted and non-infarcted myocardium. The release of transforming growth factor-β (TGF-β) facilitates fibroblast proliferation and angiotensin II production. Macrophage activation stimulates nitric oxide stimulation that increases vascular permeability.

Oxidative stress facilitates post-MI inflammatory responses in both infarcted and non-infarcted myocardium through enhanced ROS production and impaired antioxidant capacity. These changes induce an inflammatory response in the infarct zone and stimulate fibrosis by collagen synthesis. Ventricular dilatation, myocyte hypertrophy, and the formation of collagen scar result in distortion of the shape of the ventricle until the ventricular wall stress is balanced with the tensile strength of fibrous tissue [25,26].

Survival after MI is determined by the effect of ventricular remodeling on contractile function and end-systolic volume, which is based on the infarct size, location, and shape of the left ventricle [30,32]. Adverse ventricular remodeling, which does not normalize the intracavitary stress of the ventricular wall, results in excessive dilatation of the ventricles and fibrosis and decreased contractile function [8,25,31]. Patients with preserved left ventricular systolic function have a higher survival rate, while adverse ventricular remodeling is associated with significantly higher mortality [30]. Therefore, left ventricular remodeling is considered a surrogate for HF, and maintaining a normal end-systolic volume and ejection fraction during remodeling is an important goal for survival [30,32].

**MI size measurement**

The size of MI in the clinical trials can be measured by the techniques as below:

**Single-photon emission computed tomography (SPECT)**

SPECT imaging with Technetium-99m 2-methoxy isobutylisonitrile (99mTc-sestamibi, also termed as 99mTc MIBI) is the most practical and widely used tool for the clinical evaluation of MI [33]. SPECT imaging is used to visualize areas of reduced blood flow due to physiologic/pharmacologic stress or pathological conditions and to determine the viability of cardiac tissue. There is a close association between SPECT MI size and other parameters including left ventricular function, end-systolic volume, creatine kinase release, and magnetic resonance imaging (MRI) infarct size, as well as patient mortality [33]. There is also a good correlation between the SPECT MI size and the actual amount of pathological fibrosis in the human heart [33]. The major limitation is that radioisotopes are required as contrast agents. In addition, due to the spatial resolution (10 mm) of SPECT images, SPECT misses small infarcts, particularly subendocardial infarcts that do not involve the entire heart wall, and their sizes exceed the spatial resolution of SPECT.

**MRI**

Although SPECT is an established method for infarct quantification, cardiovascular MR techniques play an important role in the assessment of myocardium viability and infarct detection because of their advantages of superior spatial resolution (60-fold greater than SPECT) and tissue characterization performed under resting condition, and without exposure of radiation [34]. Contrast-enhanced MRI allows real-time visualization of cardiac motion with superior anatomical and functional definition, and is useful and accurate for the noninvasive determination of infarct size. In addition, contrast-enhanced MRI enables accurate delineation between infarct and viable myocardium, while cardiac MR can visualize both reversible and irreversible injury and determine the presence of residual MI [34]. This allows a comprehensive assessment of the sequel of AMI that can help guide patient management [34].

Since the contrast agent (gadolinium) is extracellular and interstitial, the volume of distribution of the contrast increases within the infarcted imaging voxel. Since the increased gadolinium concentration in the infarcted tissue shortens the relaxation time, the infarct appears to be hyper-enhanced [34]. MRI shows excellent
accuracy in the delineation of scars when compared to scintigraphic techniques (e.g., SPECT) \cite{35}. The hyper-enhanced area of the MR images shows a near-perfect correlation with the irreversibly injured regions defined by triphenyl tetrazolium chloride staining \cite{35}.

Recently, MRI techniques have demonstrated high accuracy in measuring microvascular obstruction, necrotic core, total infarct size, and the AAR in reperfused infarcts, which allows direct quantification of myocardial salvage \cite{36,37}. In addition, infarct size by MRI has higher reproducibility than SPECT \cite{38}. In humans, MRI accurately predicts the reversibility of associated myocardial dysfunction \cite{39,40}.

**Animal models for AMI**

The normal core temperature of animals is higher (i.e., pig: 38.5–39°C) than that of humans (36.5–37.5°C). However, experimental animal models can help to evaluate the effect of hypothermia on I/R injuries before conducting clinical trials, and it would be recommended to focus on the degree of changes in infarct size with changes in core temperature rather than the absolute temperature of hypothermia.

**Techniques**

There are several animal models of MI that include small animals such as rodents, or large animals such as swine and sheep. The pig model is an attractive choice given its similarity to humans in terms of cardiac circulatory anatomy and cardiac contraction relaxation kinetics, and cardiac output \cite{41}. In pigs, the left coronary artery is larger and longer than the right coronary artery, as in humans. There is little collateral blood flow with scant collateral arteries that localize to the mid myocardium and sub-endocardium. These properties of the coronary system allow for predictable infarct size. Pigs have a heart rate of about 105 ± 10.6 beats/min and a mean arterial blood pressure of 102 ± 9.3 mmHg \cite{42,43}. After the occlusion of a coronary artery, the ischemic myocardium ceases aerobic metabolism within a few seconds, resulting in severe systolic dysfunction \cite{44}. An occlusion period of less than 15 min in pigs causes reversible myocardial ischemia, and ischemic myocardial tissues may survive after the restoration of coronary blood flow \cite{44}. A duration of occlusion between 15 and 30 min causes irreversible myocardial damage with histological changes as mentioned above in the infarction area \cite{44}.

**Effect of the duration of occlusion on the infarct size** \cite{13,18,45–65}

In pigs, the percentage of infarct size in the risk area after reperfusion increases with the duration of coronary artery occlusion: percentage of infarct size was 30 ± 15% AAR after 30 min occlusion, 66 ± 12% AAR after 60 min occlusion, and 68% AAR after 90 min occlusion. A duration of occlusion of about 180 min results in a complete infarct with an AAR size greater than 80% \cite{23}.

**Hypothermia therapy**

**Effects of hypothermia on infarct reduction**

During mild hypothermia, the heart rate decreases while cardiac contractility is preserved, thus reducing myocardial work and oxygen consumption \cite{66,67}. In addition, as the metabolism of the whole body, as well as the heart, is suppressed, the oxygen demand decreases. Reduction of cellular metabolism, preservation of adenosine triphosphate (ATP) concentration, reduction of ROS production, and regulation of apoptosis is associated with energy preservation and reduction in infarct size. The prophylactic effect of hypothermia on I/R injury is also associated with modulation of the mitochondrial permeability transition pore, reduction of calcium overload during hypothermia, and regulation of cellular signaling (Akt pathways, heat-shock proteins, extracellular-regulated kinase, etc.), reducing the inflammatory response \cite{67}.

**Animal studies**

Table 1 summarizes the effect of mild hypothermia therapy on infarct size in animal models. Therapeutic mild hypothermia in the setting of AMI, usually left anterior descending (LAD) occlusion, in animal models has effectively reduced MIS and microvascular dysfunction, particularly when initiated before reperfusion, but not after reperfusion \cite{13–15,17,18}. Duncker et al. \cite{49} found a positive correlation between infarct size and temperature. Other studies have demonstrated a beneficial temperature-related effect of hypothermia on infarct size. However, Maeng et al. \cite{61} found no benefit of hypothermia induced in conjunction during or after reperfusion. In addition, studies that reached the target temperature after perfusion in which cooling was initiated concurrently with rapid reperfusion failed to show the same level of protection \cite{61}. These previous studies have suggested that the timing of cooling relative to end-ischemia and early reperfusion is critical for optimizing its benefit.
Table 1. Summary of Previous Hypothermia Research

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Subject</th>
<th>Period of ischemia</th>
<th>Objectives</th>
<th>Details of study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duncker, 1996 [49]</td>
<td>Pig</td>
<td>45 min of left coronary occlusion</td>
<td>1) The effect of body core temperature in the normothermic range on myocardial infarct size (MIS); 2) The effect of blockade of endogenous adenosine on MIS in relation to body core temperature</td>
<td>8-phenyltheophylline (5 mg/kg iv), adenosine deaminase (25 U/kg) into the coronary artery</td>
<td>1) Profound effect of core body temperature on the MIS; 2) No protective effect of endogenous adenosine against irreversible damage</td>
</tr>
<tr>
<td>Hale, 1997 [15]</td>
<td>Rabbit</td>
<td>30 min of circumflex occlusion</td>
<td>To test the hypothesis that regional myocardial hypothermia reduces infarct size</td>
<td>Bag with ice and water on the surface of the heart; 20 min before occlusion</td>
<td>Profound reduction in MIS with hypothermia</td>
</tr>
<tr>
<td>Hale, 1997 [16]</td>
<td>Rabbit</td>
<td>30 min of circumflex occlusion</td>
<td>To test the hypothesis that regional myocardial hypothermia after coronary occlusion reduces size</td>
<td>Bag with ice and water on the surface of the heart; 10 min and 25 min after occlusion</td>
<td>Reduction in MIS with hypothermia during coronary occlusion in early stage but not late-stage</td>
</tr>
<tr>
<td>Miki, 1998 [17]</td>
<td>Rabbit</td>
<td>30, 45, or 60 min of left coronary artery occlusion</td>
<td>To test the effect of hypothermia on infarct size with various onset times</td>
<td>Extracorporeal heat exchanger (32°C or 35°C); 5 min before and 10 and 20 min after occlusion</td>
<td>Significant reduction in MIS with hypothermia; reduction effect even during occlusion in early stage</td>
</tr>
<tr>
<td>Dave, 1998 [7]</td>
<td>Rabbit</td>
<td>30 min of circumflex occlusion</td>
<td>To investigate the effect of pericardial space cooling on MIS</td>
<td>Pericardial fluid exchange with continuous cold Ringer's lactate; 30 min before occlusion</td>
<td>Significant reduction in myocardial temperature and MIS</td>
</tr>
<tr>
<td>Schwartz, 2001 [18]</td>
<td>Swine</td>
<td>40 min of coronary occlusion</td>
<td>To test the effect of regional topical hypothermia on MIS</td>
<td>Bag with iced saline slush on the epicardial surface; 20 min before and 15 min after occlusion</td>
<td>Significant reduction in myocardial necrosis with regional hypothermia</td>
</tr>
<tr>
<td>Dae, 2002 [13]</td>
<td>Swine</td>
<td>60 min of left coronary occlusion</td>
<td>To test the hypothesis that endovascular cooling would reduce the temperature in a large heart rapidly and decrease infarct size</td>
<td>Cooling (target temperature = 34°C) started 20 min after occlusion and continued for 15 min after reperfusion</td>
<td>Significant reduction in MIS with hypothermia</td>
</tr>
<tr>
<td>Hale, 2003 [14]</td>
<td>Rabbit</td>
<td>30 min of circumflex occlusion</td>
<td>To test the effects of myocardial hypothermia, instituted late in the ischemic period</td>
<td>Cooling (target temperature = 32°C) started 20 min after occlusion and continued for 120 min after reperfusion</td>
<td>Hypothermia protected against impaired reflow and reduced infarct size</td>
</tr>
<tr>
<td>Maeng, 2006 [61]</td>
<td>Swine</td>
<td>45 min of left coronary occlusion</td>
<td>To evaluate a method for regional myocardial cooling (RMC) during reperfusion that reduces the myocardial size</td>
<td>RMC (target temperature = 33°C). Started 2 min before reperfusion and sustained 2 h and then re-warming (2°C every 5 min)</td>
<td>RMC did not reduce MIS</td>
</tr>
<tr>
<td>Tissier, 2007 [108]</td>
<td>Rabbit</td>
<td>30 min of left coronary occlusion</td>
<td>To evaluate whether total liquid ventilation (TLV) can rapidly cool and protect the infarcting heart</td>
<td>Five different groups: 1) 100% oxygen (38°C); 2) liquid warm (38°C); 3) liquid cool (32°C); 4) liquid cool (32°C) with 2 cmH2O positive end expiratory pressure; 5) liquid cool (32°C) 5 min before reperfusion</td>
<td>Hypothermia protected against impaired reflow and reduced infarct size</td>
</tr>
<tr>
<td>Olivecrona, 2007 [68]</td>
<td>Swine</td>
<td>10 min of left coronary occlusion</td>
<td>To test whether hypothermia can attenuate the post-ischemic reactive hyperemia</td>
<td>Intravenous cooling, hypothermia (34°C) vs. control (37°C)</td>
<td>Mild hypothermia significantly reduces (by 43%) post-ischemic hyperemia</td>
</tr>
<tr>
<td>Goberg, 2008 [51]</td>
<td>Swine</td>
<td>40 min of coronary occlusion</td>
<td>To test the hypothesis that hypothermia had to be induced before reperfusion to reduce myocardial injury</td>
<td>Cold saline (4°C) infusion and endovascular cooling, three groups: hypothermia 15 min before and immediately after reperfusion and no hypothermia, hypothermia target temperature = 33°C</td>
<td>Rapid hypothermia before reperfusion reduces MIS and microvascular obstruction</td>
</tr>
<tr>
<td>Kanemoto, 2009 [109]</td>
<td>Rabbit</td>
<td>30 min of circumflex occlusion</td>
<td>To understand the temporal effect of mild hypothermia to achieve a salutary effect on myocardial salvage</td>
<td>Surface cooling (target temperature = 2 to 2.5°C below initial body temp). Normothermia and five different cooling start times before reperfusion</td>
<td>1) Mild hypothermia significantly reduced MIS; 2) The temperature at reperfusion correlated strongly with infarct size</td>
</tr>
<tr>
<td>Hamamoto, 2009 [110]</td>
<td>Sheep</td>
<td>60 min of left coronary occlusion</td>
<td>To determine the effect of mild hypothermia on the regional distribution of myocardial reperfusion injury</td>
<td>Cooling pad and ice bags. Five different temperature groups (39.5 to 35.5°C)</td>
<td>Temperature reduction improved myocardial salvage and microvascular integrity</td>
</tr>
</tbody>
</table>
Dae et al. [13] studied the cooling effect on MI in a human-sized pig model. Systemic cooling with an endovascular temperature catheter was started 20 min into a total 60 min coronary occlusion followed by gradual rewarming during reperfusion for about 3 h. The size of the AAR was comparable in the hypothermic (19 ± 3%) and normothermic (20 ± 7%) animals. However, infarct size significantly decreased in hypothermic animals (9 ± 6% vs. 45 ± 8%).

The mechanism by which mild hypothermia exerts its effect is not fully elucidated yet. The protective effect of hypothermia is mediated in part through reduced reperfusion injury [68]. Cardiac hypothermia is known to decrease myocardial oxygen consumption and slow the rate of ATP depletion during ischemia [69]. This may be mediated by decreased release of vasodilatory mediators but may also reflect decreased responsiveness of endothelial and vascular smooth muscle cells. Shao et al. [70] suggested that significant acceleration of myocardial death occurs within the first hour of reperfusion, preceded by a burst of oxidants, and cytochrome c release that occurs within minutes of reperfusion.

It has been difficult to translate this finding into a clinical setting because the methods used to induce hypothermia (e.g., cardiac surface cooling, arteriovenous extracorporeal heat exchangers, and peritoneal cooling) and the cooling rate are different and rapid intervention times are impractical for implementation. In addition, porcine myocardium, the most popular animal model for MI studies, has little collateral blood flow, unlike human myocardium; this may lead to a slower onset of infarction in humans.

**Human clinical trials**

**Effect of target temperature**

Several human clinical trials were conducted to evaluate the effect of hypothermia on the reduction of infarct size and HF in patients with AMI (Table 2). Most human clinical trials have used mild hypothermia of 32–34°C as a target hypothermia temperature for adjuvant PCI therapy [11].

The COOL-MI InCor Trial (cooling as an adjunctive therapy to percutaneous intervention in AMI), in which hypothermia was maintained using the endovascular cooling method with a target temperature of 32 ± 1°C showed no difference in AAR (14.1% vs. control 13.8%) and ventricular function (43.3 ± 11.2% vs. control 48.3 ± 10.9%) [71]. However, hypothermia less than 35°C applied to anterior MI patients resulted in a significant decrease in infarct size (9.3% vs. control 18.2%). A small pilot study, Rapid MI-ICE (the rapid cooling by cold saline and endovascular cooling before reperfusion in patients with ST-elevation MI), in which hypother-
Hypothermia was maintained with a target temperature of 33°C by forced infusion of 4°C cold saline for 3 h [72], showed a 38% reduction in infarct size/AAR and no HF development.

A multicenter randomized clinical trial, CHILL-MI Trial (a randomized controlled study of the use of central venous catheter core cooling combined with cold saline as an adjunct for the treatment of AMI) aimed at rapid induction of hypothermia (33°C for 1 h) but did not achieve an overall reduction in infarct size/AAR [73]. Relatively longer door to balloon time in the study group (about 9 min longer) and failure to achieve goal temperature in some patients may be responsible for the failure to reduce infarct size. However, the trial showed a 33% reduction in infarct size/AAR on the anterior wall and a lower incidence of HF at 45-day follow-up (3% vs. 14% of control).

Interestingly, the VELOCITY trial (the evaluation of ultrafast hypothermia before reperfusion in STEMI patients) that used an automated peritoneal lavage device for mild hypothermia targeting a temperature below 35°C did not yield meaningful results [74]. The VELOCITY trial showed no change in infarct size or microvascular obstruction and an increase in major cardiac adverse events in 30 days. In addition, the door to balloon time was increased by about 15 min, and stent thrombosis occurred only in the hypothermia group. These results indicate that the potential risk of peritoneal cooling methods for therapeutic hypothermia and duration of ischemia may be more important factors for infarct size than prevention of I/R injury by hypothermia.

The COOL AMI EU pilot trial (a multicenter, prospective, randomized controlled trial to assess cooling as adjunctive therapy to percutaneous intervention in patients with AMI) showed a successful reduction in infarct size/left ventricular mass up to 30% in anterior STEMI patients (16.7% vs. 23.8% of control) [75]. This trial used a rapid cooling protocol that achieved 33.6°C during reperfusion and lowered the temperature by more than 1.1°C compared to the previous clinical trials with 17 min cooling-related delay to reperfusion.

Most randomized clinical trials have not shown positive results with hypothermia as an adjunct therapy to primary coronary intervention in patients with AMI [19,71,73,74]. However, clinical trials have demonstrated the safety and feasibility of adjuvant hypothermia induced by cold saline and endovascular cooling during coronary intervention in patients with AMI; mild hypothermia at the time of reperfusion is effective in reducing infarct size and the incidence of HF [11]. In particular, in the subgroup analysis, patients with body temperature reaching < 35°C before reperfusion and significant anterior wall MI showed a decrease in infarct size, suggesting a benefit of inducing hypothermia before reperfusion. Moreover, a pooled analysis of clinical trials showed a reduction in ischemia size and HF incidence in patients with large AARs, at least 30%, when the core temperature reached ≤ 35°C at the time of reperfusion [76,77]. These results suggest that it is essential to reach a core body temperature of < 35°C before reperfusion to reduce the size of MI and that a lower temperature close to 32°C, the lower limit of mild hypothermia, may be more effective.

**Consideration for hypothermia in clinical practice**

Although animal studies have demonstrated the cardioprotective effects of hypothermia during reperfusion procedures, clinical trials have shown poor clinical relevance. A systematic review and meta-analysis of hypothermia trials after AMI confirmed that hypothermia is a safe and feasible intervention. However, there are controversies about the reduction of infarct size and major adverse cardiovascular events (MACE). Mottillo et al. [78] suggested that more evidence is needed although mean infarct size decreased according to the subgroup analysis of anterior wall infarction and there was no significant difference in the cardiac outcome. Villablanca et al. [79] reported that hypothermia had limited benefits in reducing infarct size only in anterior wall MI and no significant benefit in reducing MACE and mortality. These results suggest that further studies are needed for different indications and protocols in humans by comparing the methods and results of animal studies.

In animal studies showing the benefits of hypothermia, hypothermia and MI were typically undertaken simultaneously, and hypothermia was maintained throughout the ischemic period. However, it is almost impossible to apply hypothermia in humans from the onset of MI in clinical situations. It is also difficult to apply rapid hypothermia to humans, and a sufficiently low temperature may not be achieved before reperfusion. Moreover, the benefits of hypothermia may be lost in some patients with spontaneous reperfusion of an occluded coronary artery prior to the reperfusion procedure [67]. Also, the actual temperature of myocardial tissues may differ from the core temperature or blood temperature measured by a cooling device [80].

As the ischemic myocardium is a part of the loss of blood circulation, the measured temperature does not reflect the tissue of interest and may be insufficient to protect against I/R injury. Salvage of reperfused myocardial tissue is correlated with tissue temperature at the border of the ischemic region, not with core temperature. Therefore, hypothermia precisely confined to the infarct region may be effective to prevent I/R injury in humans.

Consequently, adequate hypothermia with practically optimal temperature and time duration is considered to be limited in some areas of emergency care, cardiac surgery, or post-conditioning.
ing strategies, and further research and technology development are required.

The temporal window for efficacy

According to the results from the studies on small animals, a pooled analysis showed that the reduction in infarct size decreased exponentially with increasing hypothermia induction time [66]. In addition, delayed hypothermia, initiated just prior to reperfusion, may have little effect on reducing ischemic size after reperfusion. The protective effect of hypothermia was completely lost when cooling was delayed 15 min post-reperfusion [70]. Interestingly, hypothermia induced after reperfusion reduced the no-reflow phenomenon without the benefit of reduced infarct size [61,81]. Therefore, it is clear that hypothermia should be applied prior to reperfusion and initiated as soon as possible for the reduction of infarct size, no-reflow phenomenon, and remodeling [14,51,81,82].

Optimal target temperature

Therapeutic hypothermia is classified as mild (32–35°C), moderate (28–32°C), severe (20–28°C), and profound (< 20°C) depending on the target body temperature [83]. There is still no optimal target temperature in clinical practice. Experimental results show that the reduction in infarct size is closely related to the target temperature, which decreases by 10–20% for every 1°C decrease in temperature [11]. Therefore, a lower temperature is associated with a reduction in infarct size. However, in clinical practice, only mild hypothermia is acceptable except under special circumstances such as surgery or cardiac arrest because the life-threatening risks associated with hypothermia are less with mild grade. Mild hypothermia reduces heart rate and cardiac output while maintaining stroke volume and mean arterial pressure. In general, a target temperature of 32–34°C is recommended [11,84].

Safety during hypothermia

Deep hypothermia may be associated with various complications such as hemodynamic deterioration, ventricular arrhythmia, or coagulopathy. However, mild to moderate hypothermia does not appear to cause these complications [19]. The feasibility and safety were successfully confirmed in clinical trials using endovascular cooling to lower core body temperature to below 34–35°C [19,72,85,86]. There was no hemodynamic instability or bleeding complications during mild to moderate hypothermia with endovascular cooling. Although some patients with anterior MI may develop ventricular arrhythmias during hypothermia with endo-

vascular cooling [19] or intracoronary cooling [87], these arrhythmias can be easily controlled by DC cardioversion, so mild hypothermia seems to be safe in patients with AMI. However, peritoneal cooling appears to be associated with some safety concerns. Peritoneal cooling increases stent thrombosis due to increased platelet activation and respiratory suppression due to effects on diaphragmatic excursion [74]. Yet, the application of mild to moderate hypothermia is well tolerated in patients with MI and does not cause serious complications when it is controlled by adequate treatment and sedation.

Future studies

Optimal cooling & rewarming pattern

Although the potential of mild hypothermia for myocardial recovery strategies after MI has been introduced by animal and human studies, there are few studies on optimal rewarming patterns. Unfortunately, while most studies on rewarming after hypothermia have focused on neurological outcomes after cardiac arrest, few studies have focused on the cardiac outcomes after MI, such as infarct size or cardiac function. Rewarming may induce adverse effects, such as ‘rewarming shock,’ characterized by hypotension, tachycardia, and acidosis due to the return of altered cardiovascular functions during hypothermia [88]. For example, increased metabolic rate and cardiac output can cause a mismatch between oxygen demand and supply.

Changes in oxygen delivery can occur due to changes in body temperature associated with changes in oxygen extraction rates, hemoglobin dissociation curve, and blood viscosity. In addition, increased oxygen consumption may occur due to the resumption of the inflammatory process and free radical oxidation. Shivering during rewarming may also contribute to the mismatch. Ventricular dysfunction associated with decreased sensitivity of myofibrils to calcium due to increased troponin C phosphorylation may also occur after rewarming [89].

Animal studies have shown worse results at faster rewarming rates [88]. Therefore, a slow and targeted rewarming protocol is necessary after applying hypothermia. In the case of mild hypothermia after cardiac arrest, a slow rewarming of 0.25°C/h to normothermia (37°C) is suggested because of the long duration of hypothermia application (12 to 24 h) with a cooler temperature than coronary reperfusion (32–33°C) [84]. This slow rewarming takes almost 12 h or more. However, previous clinical trials of AMIs using both active and passive rewarming protocols showed somewhat rapid rewarming time [71–75,90].

The duration of rewarming took 3–4 h for the active rewarming
protocols and 3–6 h for the passive or spontaneous rewarming protocol. It seems the shorter duration of hypothermia (1–3 h), the higher temperature at reperfusion period (33–35°C), and the absence of risks of neurological damage unlike cardiac arrest or cerebral ischemia make the immediate rewarming with a shorter duration possible in hypothermic therapy during reperfusion procedure in patients with AMI. However, further controlled studies using longer rewarming duration or programmed rewarming protocol with shivering prophylaxis using sedatives or analgesics, oxygen balance optimization, and goal-directed hemodynamic optimization are needed to identify the optimal rewarming protocol.

**Effect of adequate sedation & body shivering**

Shivering can occur as a natural reflex from discomfort, pain, or cold — including therapeutic hypothermia — in most patients [84,91]. Shivering increases metabolic rate, oxygen consumption, and sympathetic tone, which increase heart rate and cardiac output. In particular, shivering is more likely to occur during hypothermia induction at temperatures between 35°C and 37°C and less likely at target temperatures for mild hypothermia between 32°C and 34°C; thus shivering may delay reaching the target temperature [84]. These effects may offset the therapeutic effects of hypothermia for I/R injury. Therefore, adequate management of shivering with sedatives, analgesics, and other interventions is required.

It is known that low skin temperature is responsible for about 20% of shivering, so an application of counter-warming with a forced-air warmer on the body surface, especially in areas where cutaneous temperature sensors are concentrated, such as the face and hands, may help inhibit shivering [84,91]. However, counter-warming alone is not sufficient and simultaneous rapid pharmacologic suppression of shivering is required during the induction of hypothermia. Because the target temperature should be reached rapidly, it is recommended to prevent shivering with the most effective combination of treatments.

According to previous clinical trials [71–74], shivering prophylaxis using various pharmacological agents that lower the shivering threshold is recommended (Table 3). If shivering prophylaxis is unsuccessful with routine pharmacological agents, sedation with propofol or midazolam or analgesic with additional opioids such as fentanyl or hydromorphone can be used, but caution is required for respiratory depression [84]. In the case of refractory shivering, neuromuscular blockers can be used with mechanical ventilation after intubation, but sedation and analgesia are mandatory.

**Localized myocardial hypothermia**

Recently, a new method for localized myocardial hypothermia in AMI has been introduced, although it has already been used in various cardiac surgeries in the surgical field. As mentioned above, disappointing results of mild hypothermia in human clinical trials are thought to be due to inadequate core temperature for I/R injury prevention, slow cooling rate, prolonged infarct duration during systemic cooling, the actual difference between tissue and core temperature, and adverse effects of cooling such as shivering.

A modified technique using selective intracoronary hypothermia can rapidly achieve target region hypothermia by infusion of cold saline at 4°C for 10 min during reperfusion. This method can induce hypothermia during coronary angiography by injecting a small amount of saline of only several hundred milliliters to avoid

| Table 3. Pharmacological Agents for Reducing the Shivering |
|-----------------|---------|---------|-----------------|-------------|
| **Agent**       | **Route** | **Dosage** | **Mechanisms** | **Cautions** |
| Buspirone       | Oral    | 30–60 mg  | Partial 5HT₁₅ agonist | Sedation, dizziness, nausea |
| Meperidine      | Intravenous | Loading: 1 mg/kg (or 0.5 mg/kg in case of other opioid use) over 15 to 20 min | Agonist at opioid receptors (μ and κ) and α₂β₃ receptors | Sedation, respiratory depression, seizure |
| Magnesium       | Intravenous | Loading: 2–4 g bolus over 4 h | Antagonist at N-methyl-D-aspartate receptor | |
| Dexmedetomidine | Intravenous | 0.2–0.7 μg/kg/h | α-2 receptor agonist | Hypotension, bradycardia, sedation |
volume overload and detained control of temperature, infusion rate, and pressure with sensors of the intracoronary catheter that provide safety [87,92,93]. Although there have been several reports of the feasibility and reproducibility of selective intracoronary hypothermia [87,92,93], clinical data on its effectiveness in reducing I/R injury, infarct size, ventricular dysfunction, or MACE compared with prior techniques are unknown, and more evidence is required.

**Therapeutic hypothermia in anesthesia and critical care**

For anesthesiologists, hypothermia is associated with complications such as myocardial ischemia, coagulopathy, wound infection, shivering, or long-term recovery from anesthesia [94,95]. However, they are also becoming accustomed to hypothermia and rewarming in the fields of cardiac anesthesia, neurosurgery, or various critical cares [94,95]. For example, it is known that hypothermia during cardiopulmonary bypass (CPB) is primarily suitable for protecting neurological functions, including the prevention of brain damage and vital organs.

Although there is endless debate about the benefits of hypothermia on neurologic function and mortality during CPB, hypothermia may reduce oxygen demand and myocardial damage [96,97]. In addition, as mentioned above, adequate sedation and protection of body shivering required for anesthetic procedures during therapeutic hypothermia have become essential. Therefore, anesthesiologists should be familiar with metabolic changes in anesthetics for the safety of patients as long as hypothermic technique is used [95,97,98].

Hypothermia impairs temperature-sensitive enzymes, leading to changes in distribution volume and decreased drug metabolism [97]. A 3°C decrease in core body temperature results in a 28% increase in propofol concentrations due to decreased inter-compartmental clearance, decreased metabolism due to reduced hepatic blood flow, and changes in the cytochrome enzyme (cytochrome P450 2B6) system [97,99,100]. The clearance of midazolam decreases by 11.1% for each 1°C decrease in temperature below 36.5°C [101]. Fentanyl is metabolized primarily by cytochrome P450 3A4, similar to midazolam, but due to its high distribution and high clearance properties, clearance is dependent on hepatic blood flow [100]. During hypothermia, plasma concentrations of fentanyl increase due to decreased clearance [102]. Remifentanil has a short half-life due to its rapid hydrolysis by nonspecific esterase [100]. The clearance of remifentanil decreases by 6.37% for a 1°C decrease in temperature below 37°C, and a 30% decrease in infusion rate is recommended for a 5°C decrease in temperature [103].

Hypothermia also affects the duration of action and recovery time of muscle relaxants. A 3°C lower core temperature due to changes in Hofmann degradation or ester hydrolysis increases the duration of atracurium by approximately 60% [99]. In the case of mild hypothermia, vecuronium recovery time is increased about 2.2 times compared to normal body temperature [104]. Similarly, hypothermia may increase the duration of action of rocuronium [105]. Interestingly, after reversal using sugammadex, the recovery time of rocuronium also increased about 1.4-fold compared to normothermia [106]. The long-term effects of these neuromuscular blockers are due to changes in pharmacokinetics, primarily clearance, rather than pharmacodynamics [105]. Also, neuromuscular monitoring may not be possible in hypothermic conditions [107].

**Conclusion**

Available evidence suggests that therapeutic hypothermia has the potential to reduce myocardial ischemic injury in humans. However, randomized clinical trials have not reproduced the promising results seen in preclinical studies. Compared to many studies regarding the role of therapeutic hypothermia on post-resuscitation brain injury or myocardial protection for surgery, limited studies have focused on improving myocardial reperfusion injury. There are many questions left to be answered, which include: (1) the optimal target temperature for STEMI; (2) the optimal therapeutic hypothermia method; (3) the need for a target temperature to be achieved prior to reperfusion; (4) optimal duration of hypothermia; (5) myocardial protective mechanisms; (6) optimal target patient population; and (7) optimal protocol for rewarming. The emergence of new devices that allow for faster cooling may help to better define some of these questions and lead to positive results in future clinical trials.

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**Conflicts of Interest**

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

**Author Contributions**

Ki Tae Jung (Visualization; Writing – original draft; Writing – re-
References

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Introduction

The use of video-assisted thoracic surgery (VATS), a minimally invasive alternative to open thoracotomy, has increased over the years, which has led to a significant reduction in postoperative pain and shorter hospital stays [1,2]. However, some patients continue to suffer from moderate-to-severe pain after VATS and postoperative pain control remains challenging [3,4]. Although thoracic epidural analgesia (TEA) has been regarded as the gold standard for postoperative pain management in thoracic surgery [5–8], complica-
tions such as epidural hemorrhage, hypotension, and postoperative urinary retention can be fatal in high-risk patients [9–11]. Considering the risks and benefits, it is necessary to use an appropriate regional analgesia technique suitable for minimally invasive thoracic surgery.

Thoracic paravertebral block (TPVB) provides unilateral thoracic analgesia comparable to TEA. Additionally, not only is it less invasive than TEA, but it can also maintain hemodynamic stability and carries lower risk of complications due to anticoagulation therapy associated with anticoagulation [9,12]. According to the Enhanced Recovery After Surgery (ERAS) guidelines and the Procedure-specific postoperative pain Management (PROSPECT) group, TPVB is recommended as the primary method of regional analgesia for thoracic surgery [13,14].

Recently, however, various regional analgesia techniques, such as the erector spinae plane block (ESPB) and the serratus plane block (SPB), have superseded the traditional TPVB through their comparable analgesic effect along with reduced associated complications [15,16]. Although many studies have reported the efficacy of each of these regional analgesia techniques and have compared their effectiveness in VATS, the relative efficacy of these techniques has not been compared using network meta-analysis (NMA).

Therefore, we identified and reviewed all the articles that investigated the effects of various techniques used for postoperative analgesia for VATS, and performed an NMA to the rank order of the regional analgesia in terms of effectiveness for VATS. Our primary outcome was opioid consumption during the first 24 h postoperative period, and we also evaluated pain severity during three different postoperative periods (the early, middle, and late periods).

Materials and Methods

This study was conducted in accordance with the recommended Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [17] and was registered with the International Prospective Register of Systematic Reviews (PROSPERO, CRD42021252062).

Data source and search strategy

The literature search was conducted to identify eligible studies for this systematic review and meta-analysis. Two researchers (S.P. and B.H.) independently searched the following electronic databases: Medline, EMBASE, Cochrane Controlled Trial Register, Web of Science, and Google Scholar for relevant studies published in English. Articles published between September 2005 and December 2020 in peer-reviewed journals were included. The primary search was conducted on January 28, 2021; however, an additional search was conducted on February 28, 2021 to include more recent studies. In addition, the studies referenced in the selected articles were searched manually.

The search strategy was as follows: (“Video assisted thoracoscopy surgery” or VATS) and (“Thoracic paravertebral block” or TPVB) or (“paravertebral block” or PVB) or (“Serratus plane block” or “Serratus anterior plane block” or “Serratus interfascial plane block” or SPB) or (“Erector spinae plane block” or ESPB) or (“Intercostal nerve block” or INB)).

Inclusion and exclusion criteria

Studies were considered eligible if they were randomized controlled trials (RCTs) published in English that reported postoperative pain scores or total postoperative opioid consumption in both the experimental and control groups as outcomes. Non-RCTs (quasi-experimental designs), abstracts, conference proceedings, unpublished gray literature, and review studies were excluded. Among the regional analgesia techniques, continuous blocks via catheterization were also excluded.

Review procedure

We performed six steps to select the studies. First, two researchers (S.P. and B.H.) imported the titles and abstracts of the articles identified in the searches into reference management software (EndNote 20, ClarivateTM) and performed a preliminary review. Second, duplicate papers were identified and eliminated using the reference management software. Third, two researchers (S.P. and B.H.) independently reviewed the imported studies. We excluded all of the imported studies that did not clearly meet the inclusion criteria (due to the study design, participants, types of intervention, and comparison groups). Fourth, they also independently screened the titles, abstracts, and methodology sections of the studies that appeared to meet the inclusion criteria. Fifth, we retrieved the full texts of the papers that met all the inclusion criteria for data extraction and linked multiple reports of the same study. Finally, the studies included in the final selection were confirmed and coded for analysis by two researchers (B.H. and Y.J.). These coding sheets were independently checked for accuracy by researchers who were not involved in the review process. If there were any differences between the codes provided by the two reviewers, the discrepancies were resolved by consulting a third independent reviewer (C.O.).
Data extraction

The information from the included articles was independently extracted by two reviewers (B.H. and Y.J.), and each selected article was reviewed twice by both reviewers. To determine the outcomes of individual studies, pain scores and opioid consumption were determined for each group and recorded as the means and standard deviations (SDs). Medians and interquartile ranges (IQRs), as approximations of the mean and SDs, were determined using the estimation method proposed by Wan et al. [18]. When outcome data were available only as a graph, a virtual ruler was used to extract the value by matching the interval between the basic unit of the plot and the ruler. The effect sizes and standard errors were calculated. Additional data, including the location, sample size, characteristics of individual study populations, and the intervention design, were extracted using a predetermined data extraction table.

Outcome definitions

The primary outcome was cumulative opioid consumption during the first 24 h postoperative period. All opioids were converted to equianalgesic intravenous (IV) morphine doses (IV morphine 1 mg = IV fentanyl 10 µg = IV sufentanil 2 µg = IV tramadol 10 mg). The secondary outcome was pain scores assessed during three different periods in the first 24 h, namely, the early (0–6 h), middle (6–18 h), and late (18–24 h) periods. For studies that included several time points within each time period, pain scores close to 0–6 h, close to 12 h for middle, and close to 24 h for late were used. In the one study that timetable was expressed as an interval (ex. 6 a.m. to 2 p.m.), a similar period expected to include the interval was used. Pain scores that were assessed using visual analogue scales (VAS) were converted to a 0–10 analogue scale to allow for statistical evaluation.

Data synthesis and statistical analysis

A random-effects NMA within a frequentist framework was performed using the R software version 4.0.3 (R Foundation for Statistical Computing, Austria) and the “netmeta” package for frequentist NMA [19,20]. A network plot was constructed to evaluate the direct and indirect comparisons of network structures, including studies. Heterogeneity was evaluated using $I^2$ statistics. The Q statistic based on the full design-by-treatment interaction random-effects model was calculated to evaluate the global inconsistency [21]. We also evaluated the local inconsistencies between the direct and indirect effects using the net splitting technique. If the P value of the net splitting was < 0.05, we presumed there was a significant disagreement (inconsistency) between the direct and indirect estimates. We visualized the net split results using forest plots and direct evidence plots, which showed the percentage of direct and indirect evidence used for each estimated comparison. A mean path length > 2 indicated that the comparison estimate should be interpreted with caution. Additionally, a net heat plot was constructed to determine the importance of each comparison and the inconsistency of the design. Network league tables and forest plots were produced to show details of the results of the comparisons between the interventions. Outcomes are presented as mean differences with a 95% CI. To rank the analgesic interventions in order, we reported the P score, which measures the level of certainty that an intervention is better than the competing interventions [22]. In this study, the P score ranged from 0 to 1, with 1 indicating that the treatment option was statistically best and 0, the worst. Potential publication bias was assessed using comparison-adjusted funnel plots and Egger’s test. The confidence for every outcome was rated according to the grading of recommendations assessment, development, and evaluation (GRADE) system with the support of the CINeMA (Confidence in Network Meta-Analysis, https://cinema.ispm.unibe.ch/) web application (Institute of Social and Preventative Medicine, University of Bern, Switzerland) [23]. This is based on a methodological framework that considers six domains: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence [24]. The minimal clinically important difference was set at 1 out of 10 for postoperative pain and 10 mg for IV morphine-equivalent consumption.

Results

Baseline characteristics of the included studies

The literature screening process and results are shown in Fig. 1. The screening sequence of the PRISMA 2009 flow diagram identified 21 studies that compared the analgesic efficacy of TPVB, ESPB, SPB, intercostal nerve block (INB) and against control (no block) [25–45] with a total of 1,391 patients included. Table 1 shows the characteristics of the included studies. Table 2 shows the number of included studies and enrolled patients sorted by outcomes.

Methodological quality and risk of bias

Individual studies were assessed using the Cochrane Collaboration’s Risk of Bias tool [46] and ranked according to a low/high/
unclear grading scale (Fig. 2). The overall quality of the 21 included studies was moderate. Some of the studies showed possible patient selection bias and bias in methodology, with 70% showing an unclear or high risk of bias in performance concealment, 25% in blinding of participants and personnel, and 55% in blinding of the outcome assessment. A comparison-adjusted funnel plot showed evidence of a visually symmetric plot of opioid consumption and pain scores during the three time periods. The results of Egger’s regression test showed no significant publication bias (P > 0.05) (page 14 of each Supplementary Materials 1 to 4). The quality of evidence was rated as very-low-to-low in nature according to the GRADE system (Table 2), and the confidence rating of each comparison using CINeMA is described in the supplement file (Supplementary Material 3).

Heterogeneity and consistency test results

The results of the I² and Q statistics (based on the full design-by-treatment interaction random-effects model) indicated that a random-effects model may be suitable for revealing any inconsistency or heterogeneity in our network model (Table 2). Additionally, according to the colored background of the net heat plot, the random-effects model appeared to be suitable for our data (pages 10 and 11 of each Supplementary Materials 1 to 4). A direct evidence plot (page 5 to 6 of each Supplementary Materials 1 to 4) and forest plot of the net splitting results (page 11 to 12 of each Supplementary Materials 1 to 4) were used to evaluate local inconsistency.

Efficacy outcomes (network meta-analysis)

Of the included studies, 17 [25–28,30,31,33,35,37–45] RCTs reported opioid consumption and 18 [25,26,28,30–36,38–45], 16 [25,26,28–35,38–44], and 17 [25–27,29,30,33–36,38–45] RCTs reported pain scores for each of the three postoperative time periods (early, middle, and late, respectively). The networks for the TPVB and control were greater than the networks for other blocks, followed by the ESPB and control. As shown in Fig. 3, TPVB had the best analgesic effect on opioid consumption compared with the control (mean difference [MD]: −13.2 mg, 95% CI [−16.2, −10.1]), followed by INB (MD: −9.55 mg, 95% CI [−13.2, −5.9]), ESPB (MD: −8.7 mg, 95% CI [−11.4, −6.1]), and SPB (MD: −5.9 mg, 95% CI [−9.4, −2.5]). In terms of pain scores in the early period, ESPB had the greatest effect compared with the control (MD: −1.6, 95% CI [−2.3, −0.9]), followed by TPVB, INB and SPB. In the middle and late periods, TPVB, ESPB and INB showed superior analgesic effects in reducing pain scores compared to the control, whereas SPB did not have a significant effect. The local inconsistency in ESPB and control was significant in the early and middle periods (Table 2). The two studies by Ciftci et al. [34,35] had effect sizes that tended to be higher than those measured in the other studies. Table 3 shows the network league table that displays the direct comparison and full model results separately.

Results of the ranking hierarchy

Table 4 shows the P-scores of analgesic efficacy and the ranking of the five groups. TPVB ranked highest for opioid consumption in the first 24 h (0.996) and for middle- and late-period pain scores (0.793 and 0.831, respectively). However, ESPB ranked first for pain scores in the early period (0.792). INB ranked second for opioid consumption and third for pain scores in all three periods. SPB ranked fourth for all the outcomes.

Additional analysis after removal of retracted article

During proofreading, we noticed that the article which included our analysis had been retracted from its journal [37]. Thus, we performed an additional analysis after removing the retracted article. That retracted paper only had information on the 24 hours opioid consumption, and there was no significant change in effect

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Fig. 1. Study flow diagram.
<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Country</th>
<th>Surgery</th>
<th>Port</th>
<th>Group(s) (n)</th>
<th>Block level</th>
<th>Localization</th>
<th>Local anesthetics</th>
<th>Block timing</th>
<th>Opioid data</th>
<th>Plot/Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu, 2021</td>
<td>China</td>
<td>Lobectomy, wedge resection, segmentectomy</td>
<td>1</td>
<td>ESPB (40); control (40)</td>
<td>T5</td>
<td>Ultrasound</td>
<td>25 ml of 0.4% ropivacaine</td>
<td>Before induction</td>
<td>Sufentanil</td>
<td>Table (2, 8, 24)</td>
</tr>
<tr>
<td>Hu, 2021</td>
<td>China</td>
<td>Wedge resection</td>
<td>1</td>
<td>TPVB (30); control (30)</td>
<td>T4, intrathoracic approach</td>
<td>Thoracosopic-assisted</td>
<td>20 ml of 0.375% ropivacaine</td>
<td>End of surgery</td>
<td>Sufentanil</td>
<td>Table (6, 12, 24)</td>
</tr>
<tr>
<td>Zhao, 2020</td>
<td>China</td>
<td>Lobectomy, wedge resection, segmentectomy</td>
<td>NA</td>
<td>ESPB (33); TPVB (33)</td>
<td>ESPB: T4 and T6</td>
<td>Ultrasound</td>
<td>30 ml of 0.4% ropivacaine</td>
<td>Before induction</td>
<td>Oxycodone</td>
<td>Table (NA, NA, 24)</td>
</tr>
<tr>
<td>Yao, 2020</td>
<td>China</td>
<td>Lobectomy, segmentectomy</td>
<td>NA</td>
<td>ESPB (37); control (38)</td>
<td>T5</td>
<td>Ultrasound</td>
<td>25 ml of 0.5% ropivacaine</td>
<td>Before induction</td>
<td>Sufentanil</td>
<td>Table (1, 8, 24)</td>
</tr>
<tr>
<td>Viti, 2020</td>
<td>Italy</td>
<td>Lobectomy, segmentectomy</td>
<td>3</td>
<td>SPB (46); control (44)</td>
<td>Fifth rib</td>
<td>Ultrasound</td>
<td>30 ml of 0.3% ropivacaine</td>
<td>After induction</td>
<td>No data</td>
<td>Plot (NA, 6 a.m. to 2 p.m. POD 1, 2 p.m. to 10 p.m. POD 1)</td>
</tr>
<tr>
<td>Turhan, 2020</td>
<td>Turkey</td>
<td>Lobectomy, segmentectomy</td>
<td>2</td>
<td>ESPB (35); TPVB (35); INB (36)</td>
<td>ESPB, TPVB: fibr rib INB: T4–T7</td>
<td>Ultrasound</td>
<td>20 ml of 0.5% ropivacaine</td>
<td>TPVB, ESPB: before induction INB: after induction</td>
<td>Morphine mg equivalent</td>
<td>Table (1, 12, 24)</td>
</tr>
<tr>
<td>Lee, 2020</td>
<td>Korea</td>
<td>Lobectomy</td>
<td>3</td>
<td>INB (23); SPB (23)</td>
<td>Fifth rib</td>
<td>Ultrasound</td>
<td>20 ml of 0.375% ropivacaine</td>
<td>INB: end of the surgery</td>
<td>Fentanyl</td>
<td>Table (2, 12, 24)</td>
</tr>
<tr>
<td>Kim, 2020</td>
<td>Korea</td>
<td>Wedge resection for primary spontaneous pneumothorax</td>
<td>1</td>
<td>INB (25); SPB (25)</td>
<td>Fifth rib</td>
<td>Ultrasound</td>
<td>20 ml of 0.375% ropivacaine</td>
<td>INB: end of the surgery</td>
<td>Fentanyl, no standard time (chest tube removal)</td>
<td>Table (3, 12, NA)</td>
</tr>
<tr>
<td>Finnerty, 2020</td>
<td>Ireland</td>
<td>Wedge resection, pleurodesis, pleurectomy, lobectomy, decortication, bullectomy, or pleural biopsy</td>
<td>NA</td>
<td>ESPB (30); SPB (30)</td>
<td>T5, fifth rib</td>
<td>Ultrasound</td>
<td>30 ml of 0.25% levobupivacaine</td>
<td>After induction</td>
<td>Oxycodone</td>
<td>Plot (1, 12, 24)</td>
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<tr>
<td>Ciftci, 2020</td>
<td>Turkey</td>
<td>Lobectomy, wedge resection</td>
<td>3</td>
<td>ESPB (30); TPVB (30); control (30)</td>
<td>T5</td>
<td>Ultrasound</td>
<td>20 ml of 0.25% bupivacaine</td>
<td>Before induction</td>
<td>Fentanyl, 48 h of data only</td>
<td>Plot (1, 8, 24)</td>
</tr>
<tr>
<td>Ciftci, 2020</td>
<td>Turkey</td>
<td>Lobectomy</td>
<td>NA</td>
<td>ESPB (30); control (30)</td>
<td>T5</td>
<td>Ultrasound</td>
<td>20 ml of 0.25% bupivacaine</td>
<td>Before induction</td>
<td>Fentanyl</td>
<td>Table (2, 8, 24)</td>
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</table>

(Continued to the next page)
<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Country</th>
<th>Surgery</th>
<th>Port</th>
<th>Group(s) (n)</th>
<th>Block level</th>
<th>Localization</th>
<th>Local anesthetics</th>
<th>Block timing</th>
<th>Opioid data</th>
<th>Pain score data representation method (early, middle, late period [h])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chu, 2020</td>
<td>China</td>
<td>Lobectomy, wedge resection, segmentectomy</td>
<td>NA</td>
<td>TPVB (25); control (24)</td>
<td>T4, T7</td>
<td>Ultrasound</td>
<td>20 ml of 0.375% ropivacaine</td>
<td>Unknown</td>
<td>Sufentanil, no data</td>
<td>Table (1, NA, 24)</td>
</tr>
<tr>
<td>Cheng, 2020</td>
<td>China</td>
<td>Lobectomy</td>
<td>1</td>
<td>SPB (25) (modified intercostal nerve block); control (25)</td>
<td>Fourth and fifth rib</td>
<td>Ultrasound</td>
<td>10 ml of 0.35% ropivacaine</td>
<td>After induction</td>
<td>Sufentanil</td>
<td>NA</td>
</tr>
<tr>
<td>Chen, 2020</td>
<td>China</td>
<td>Lobectomy, wedge resection, segmentectomy</td>
<td>2</td>
<td>TPVB (24); INB (24); ESPB (24)</td>
<td>TPVB: T5, T6, T7 INB: T4–T9 ESPB: T5</td>
<td>Ultrasound</td>
<td>20 ml of 0.375% ropivacaine</td>
<td>After induction</td>
<td>Morphine mg equivalent</td>
<td>Plot (2, 8, 24)</td>
</tr>
<tr>
<td>Gaballah, 2019</td>
<td>Egypt</td>
<td>Wedge resection, decortication, bullectomy, pleural biopsy, pleurodesis, repair of bronchopleural fistula, diaphragmatic plication</td>
<td>NA</td>
<td>ESPB (30); SPB (30)</td>
<td>ESP: T5 SPB: T7</td>
<td>Ultrasound</td>
<td>20 ml of 0.25% bupivacaine</td>
<td>After induction</td>
<td>Pethidine</td>
<td>Plot (1, 12, 24)</td>
</tr>
<tr>
<td>Wu, 2018</td>
<td>China</td>
<td>Wedge resection, lobectomy, bullectomy, pneumonectomy</td>
<td>NA</td>
<td>TPVB (34); INB (32)</td>
<td>TPVB: T5 INB: fourth and seventh intercostal space</td>
<td>Ultrasound</td>
<td>0.3 ml/kg of 0.5% ropivacaine</td>
<td>Before induction</td>
<td>Sufentanil</td>
<td>Plot (1, 10, 24)</td>
</tr>
<tr>
<td>Okmen, 2018</td>
<td>Turkey</td>
<td>Wedge resection, lobectomy</td>
<td>NA</td>
<td>SPB (20); control (20)</td>
<td>Fifth rib</td>
<td>Ultrasound</td>
<td>20 ml of 0.25% bupivacaine</td>
<td>End of surgery</td>
<td>Tramadol</td>
<td>Table (2, 12, 24)</td>
</tr>
<tr>
<td>Kim, 2018</td>
<td>Korea</td>
<td>Lobectomy, wedge resection, segmentectomy</td>
<td>2 or 3</td>
<td>SPB (42); control (43)</td>
<td>Fifth rib</td>
<td>Ultrasound</td>
<td>0.4 ml/kg of 0.375% ropivacaine</td>
<td>After induction</td>
<td>Morphine mg equivalent</td>
<td>Plot (NA, 12, 24)</td>
</tr>
<tr>
<td>Ahmed, 2017</td>
<td>Pakistan</td>
<td>Elective diagnostic VATS</td>
<td>NA</td>
<td>INB (30); control (30)</td>
<td>5 level</td>
<td>Bone landmark</td>
<td>20 ml of 0.25% bupivacaine</td>
<td>End of surgery</td>
<td>Morphine</td>
<td>Plot (1, 12, 24)</td>
</tr>
<tr>
<td>Kaya, 2006</td>
<td>Turkey</td>
<td>Wedge resection, lung biopsy, pleural biopsy</td>
<td>NA</td>
<td>TPVB (25); control (22)</td>
<td>T4–T8, 5 level</td>
<td>Bone landmark</td>
<td>20 ml of 0.5% bupivacaine</td>
<td>Before induction</td>
<td>Morphine</td>
<td>Table (1, 8, 24)</td>
</tr>
<tr>
<td>Vogt, 2005</td>
<td>Switzerland</td>
<td>Biopsy, lung resection, pleurodeses, resection of intrathoracic tumor</td>
<td>NA</td>
<td>TPVB; control (T6)</td>
<td>Bone landmark</td>
<td>0.4 ml/kg of 0.375% bupivacaine</td>
<td>After induction</td>
<td>Morphine</td>
<td>Plot (1, NA, 24)</td>
<td></td>
</tr>
</tbody>
</table>

ESPB: erector spinae plane block, INB: intercostal nerve block, SPB: serratus plane block, TPVB: thoracic paravertebral block, NA: not applicable.
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No. of studies</th>
<th>No. of patients</th>
<th>No. of pairwise comparisons</th>
<th>No. of designs</th>
<th>I² (%)</th>
<th>Global p value</th>
<th>Local p value</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid consumption</td>
<td>17</td>
<td>1073</td>
<td>21</td>
<td>9</td>
<td>86.9</td>
<td>0.833</td>
<td>All comparisons were insignificant</td>
<td></td>
</tr>
<tr>
<td>Early postoperative period (up to 6 h) pain scores</td>
<td>18</td>
<td>1146</td>
<td>24</td>
<td>9</td>
<td>35.3</td>
<td>0.353</td>
<td>ESPB vs. control significant (P = 0.014), other comparisons insignificant</td>
<td></td>
</tr>
<tr>
<td>Middle postoperative period (6 to 18 h) pain scores</td>
<td>16</td>
<td>1062</td>
<td>22</td>
<td>9</td>
<td>26.6</td>
<td>0.159</td>
<td>ESPB vs. control significant (P = 0.004), other comparisons insignificant</td>
<td></td>
</tr>
<tr>
<td>Late postoperative period (18 to 24 h) pain scores</td>
<td>17</td>
<td>1250</td>
<td>23</td>
<td>9</td>
<td>39.5</td>
<td>0.935</td>
<td>All comparisons were insignificant</td>
<td></td>
</tr>
</tbody>
</table>

Fig. 2. Assessment of risk of bias of included studies. The overall quality of the included studies were deemed satisfactory.
Fig. 3. Network plots and forest plots for the network meta-analysis. (A) opioid consumption in the first 24 h post-operation, (B) early postoperative period (up to 6 h) pain scores, (C) middle postoperative period (6–18 h) pain scores, and (D) late postoperative period (18–24 h) pain scores. The mean difference (MD) and 95% CI are shown. ESPB: erector spinae plane block, INB: intercostal nerve block, SPB: serratus plane block, TPVB: thoracic paravertebral block.

Discussion

Various regional analgesia techniques are used in clinical set-
tings to improve postoperative pain management in VATS, and our NMA not only demonstrated the potential benefits of these but also ranked them based on efficacy. When compared with mere systemic analgesia, all four regional analgesic techniques significantly reduced cumulative opioid consumption during the first 24 h postoperative period. In particular, TPVB showed remarkable effectiveness in reducing opioid consumption. Additionally, ESPB ranked highest for lowering the pain score in the early postoperative period, while the effect size of TPVB was clinically similar to that of ESPBs. In the case of SPB, however, even though the statistical significance of opioid consumption was clear, the effect size was approximately half that of the other meth-
ods. Moreover, the pain scores measured in the middle and late periods were not significantly different compared to control.

Statistically significant differences are not always clinically significant—e.g., a difference of 10 mg or more in parenteral morphine [47], and a change of 10 mm in a 100 mm visual analog scale are regarded as clinically significant [48]. In our opinion, changes of about 1–2 points in the pain score for patients who had initially addressed moderate-to-severe pain should be considered a clinically significant difference. In addition, changes in the pain score from initial values of 4–5 points to values < 3 were considered to be a clinically significant difference. In fact, a score < 33 points on a 100-point VAS is accepted as a state of well-controlled pain in a clinical setting [48].

TPVB showed a reduction of 13.2 mg in opioid consumption along with a reduction of more than 1 point in the pain score, which were viewed as clinically significant. For ESPB, the reduction in opioid consumption was 8.71 mg, which was less than 10 mg, but the decrease in the pain score was 1.6, showing the best results in the early postoperative period. However, this result had direct and indirect inconsistencies; therefore, caution should be taken when interpreting these results. Two studies, which were performed by Ciftci et al. [34,35] and included in our NMA, compared ESPB to control with a very large effect size compared to the others, which may have led to this inconsistency.

ESPB is an emerging technique that has been widely applied in multiple fields. Importantly, it can be easily administered even by trainees [15]. Its analgesic effect has been verified in various studies [49–51]. However, its mechanism is not well understood. The most convincing hypothesis is that the local anesthetic physically spreads to the thoracic paravertebral space and the associated neural structures [52]. Penetration via diffusion into the paravertebral space through the intertransverse connective tissue complex may continue over a prolonged period. Therefore, if anterior spreading to the thoracic paravertebral space is sufficient, ESPB should provide an effect similar to that of TPVB. However, studies that have compared ESPB and TPVB have found a significant difference in analgesic effect between the two blocks [38,49]. Improvement in postoperative pain scores and a reduction in opioid consumption were found to be better with TPVB than with ESPB. Interestingly, in contrast to results with single ESPB, a comparison of continuous infusion through a catheter showed that ESPB was noninferior to TPVB [53]. In both groups, a continuous infusion of 8 ml/h following a 20 ml bolus injection was performed. In the early postoperative period, TPVBs presented favorable results with regard to pain scores compared to ESPBs, but in the long term, the effects of the two blocks were similar, and thus no difference in opioid consumption was observed. If the mechanism of action involves anterior spreading to the thoracic paravertebral space by gradual diffusion, continuous infusions may be more effective than a single injection. However, to reduce heterogeneity, we only included RCTs using the single-block technique. Continuous TPVB using a catheter is still recommended for thoracotomy by the PROSPECT group [14], but it is questionable whether continuous blocks are necessary in VATS, as it is a minimally invasive surgical technique. In most of the RCTs included in this NMA, pain scores during the middle and late periods were mild (NRS < 3) in the control group. Therefore, multimodal analgesia, including regular acetaminophen, NSAIDs, and adjuvants to prolong the blocks may be sufficient for VATS [54,55].

According to a recent Cochrane review, while TPVB was as effective as TEA for controlling acute pain, TPVB was associated with fewer complications, such as hypotension, urinary retention, nausea, and vomiting [56]. Owing to these advantages, TPVB has recently been preferred to TEA for thoracic surgery. For other surgeries (e.g., breast surgery), the excellent analgesic effect of TPVB is offset by concerns about the potential risk of pneumothorax [57]. However, concerns about pneumothorax are greatly reduced in VATS, which allows for the administration of TPVB without concern for this complication.

INB is a well-known traditional technique for pain management after thoracic surgery. INB can be performed easily using various techniques, such as ultrasonography or blind techniques. In addition, a thoracic surgeon can directly inject inside the thorax [30]. INB only result in a segmental somatic nerve blockade, and thus multiple injections are necessary for appropriate pain control. Therefore, one might expect that the effect size of INB would be similar to that of SPB. Although only two direct comparisons between INB and SPB were included in this NMA, no differences in analgesic effect was found.

SPB can be easily performed in the lateral decubitus position, which is the surgical position for thoracic surgery [58]. Although the analgesic effect of SPBs was comparable to that of TEA in a previous study [59], our NMA results showed only a limited effect in the early postoperative period. The reduction in opioid consumption was less than half that found with TPVB. Among the four block techniques, only SPB was adequate to block the long thoracic nerve, which controls pain derived from damage to the serratus muscle and strain on surrounding structures [60]. Blockades of the long thoracic nerve have been found to reduce postoperative pain after VATS [61]. In addition, there is growing evidence that motor nerves are also involved in afferent nociception via sensory innervation and connection with other nerves [62,63]. However, the clinical effects of long thoracic nerve blockade do not meet expectations and this is attributed to trivial muscle dam-

https://doi.org/10.4097/kja.21330
age due to VATS, which does not significantly affect postoperative pain.

This study has several limitations. First, the included studies were highly heterogeneous. Although the present study included only RCTs in patients who underwent VATS, the concentrations of drugs and technical details were not consistent. In addition, various drugs were used for multimodal analgesia. Second, the time points at which pain scores were measured were not consistent between studies and were not always presented as accurate values. To reduce any bias, we divided the time period into three intervals and used the values corresponding to each interval as representative values. Third, the sample size was insufficient to draw definitive conclusions. Lastly, ESPB and SPB are currently developing techniques, which may lead to possible publication bias. In conclusion, in this study, NMA was conducted to compare regional analgesia techniques in terms of their efficacy at improving postoperative pain control after VATS. TPVB showed outstanding analgesic effects and ESPB led to the greatest reduction in pain scores during the early postoperative period. However, given the significant reduction in opioid consumption seen with all the four regional analgesic techniques evaluated, using any of these regional blocks after VATS seems reasonable. Further and more refined studies are needed to determine the optimal regional analgesia technique to improve postoperative pain control after VATS.

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Conflicts of Interest

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

Author Contributions

Yumin Jo (Writing – original draft; Writing – review & editing)
Seyeon Park (Data curation; Formal analysis; Methodology; Visualization)
Chahyun Oh (Investigation; Software; Validation)
Yujin Pak (Methodology; Project administration; Resources)
Kuhee Jeong (Visualization; Writing – review & editing)
Sangwon Yun (Visualization; Writing – review & editing)
Chan Noh (Formal analysis; Resources; Validation)
Woosuk Chung (Conceptualization; Writing – review & editing)

Yoon-Hee Kim (Resources; Supervision; Writing – review & editing)
Young Kwon Ko (Conceptualization; Supervision; Writing – review & editing)
Boohwi Hong (Conceptualization; Data curation; Supervision; Writing – original draft; Writing – review & editing)

Supplementary Materials

Supplementary Material 1. 24 hours opioid consumption.
Supplementary Material 2. Pain score at postoperative early (up to 6 hours) period.
Supplementary Material 3. Pain score at postoperative middle (6 to 18 hours) period.
Supplementary Material 4. Pain score at postoperative late (18 to 24 hours) period.
Supplementary Material 5. Confidence rating of each outcomes.
Supplementary Material 6. 24 hours opioid consumption after removal of retracted article.

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erva Anesthesiol 2021; 87: 903-14.
Preoperative dexmedetomidine and intraoperative bradycardia in laparoscopic cholecystectomy: a meta-analysis with trial sequential analysis

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Background: While laparoscopic surgical procedures have various advantages over traditional open techniques, artificial pneumoperitoneum is associated with severe bradycardia and cardiac arrest. Dexmedetomidine, an imidazole derivative that selectively binds to α²-receptors and has sedative and analgesic properties, can cause hypotension and bradycardia. Our primary aim was to assess the association between dexmedetomidine use and intraoperative bradycardia during laparoscopic cholecystectomy.

Methods: We performed a systematic review with a meta-analysis and trial sequential analysis using the following PICOS: adult patients undergoing endotracheal intubation for laparoscopic cholecystectomy (P); intravenous dexmedetomidine before tracheal intubation (I); no intervention or placebo administration (C); intraoperative bradycardia (primary outcome), intraoperative hypotension, hemodynamics at intubation (systolic blood pressure, mean arterial pressure, heart rate), dose needed for induction of anesthesia, total anesthesia requirements (both hypnotics and opioids) throughout the procedure, and percentage of patients requiring postoperative analgesics and experiencing postoperative nausea and vomiting (O); randomized controlled trials (S).

Results: Fifteen studies were included in the meta-analysis (980 patients). Compared to patients that did not receive dexmedetomidine, those who did had a higher risk of developing intraoperative bradycardia (RR: 2.81, 95% CI [1.34, 5.91]) and hypotension (1.66 [0.92, 2.98]); however, they required a lower dose of intraoperative anesthetics and had a lower incidence of postoperative nausea and vomiting. In the trial sequential analysis for bradycardia, the cumulative z-score crossed the monitoring boundary for harm at the tenth trial.

Conclusions: Patients undergoing laparoscopic cholecystectomy who receive dexmedetomidine during tracheal intubation are more likely to develop intraoperative bradycardia and hypotension.

Keywords: Bradycardia; Cholecystectomy; Dexmedetomidine; Laparoscopy; Meta-analysis; Review.
Introduction

Laparoscopic surgical procedures have various advantages over traditional open techniques, particularly in terms of early ambulation, decreased need for analgesia, and reduced hospital stay [1]. However, pneumoperitoneum induction is associated with the release of vasopressin and catecholamines and a subsequent increase in heart rate (HR), systemic vascular resistance, and mean arterial pressure (MAP) [2]. Furthermore, artificial abdominal gas insufflation during laparoscopy might cause severe bradycardia and cardiac arrest related to the uncontrolled increase in vagal tone caused by peritoneal stretch [3].

Several strategies have been employed to control this sympathetic response to pneumoperitoneum; among them, dexmedetomidine has shown promising results [4]. Dexmedetomidine is an imidazole derivative that highly selectively binds to \( \alpha_2 \)-receptors, thus inhibiting norepinephrine release at the level of sympathetic terminals, leading to hypotension and bradycardia and promoting analgesia in spinal cord receptors [5].

Therefore, we may infer that although dexmedetomidine could be useful for controlling sympathetic stimulation, administering it along with peritoneal insufflation could lead to severe intraoperative bradycardia.

It has been shown that compared with no dexmedetomidine or placebo, the use of dexmedetomidine for tracheal intubation is associated with an increased risk for intraoperative bradycardia in the general surgical population [6]. However, no information on patients undergoing laparoscopic procedures has been reported. Therefore, we performed a meta-analysis of randomized controlled trials (RCTs) comparing dexmedetomidine versus placebo or no intervention in patients undergoing laparoscopic cholecystectomy with respect to the occurrence of intraoperative bradycardia. To prevent bias related to different surgical procedures, we focused our investigation on laparoscopic cholecystectomies only.

The secondary objectives of this study were to assess the association between dexmedetomidine use and hemodynamics at intubation (HR, MAP, systolic blood pressure [SBP]), the occurrence of intraoperative hypotension, intraoperative hypnotics and opioid consumption, and the occurrence of postoperative side effects (postoperative nausea and vomiting [PONV], shivering, and analgesic requirements).

Materials and Methods

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) statement guidelines to prepare this manuscript [7]. The review protocol was registered in PROSPERO (CRD42021249799) on April 18, 2021.

Search strategy

We performed a systematic review of the medical literature to screen for relevant articles. The search was performed in the following databases from inception until April 18, 2021 with no language restrictions: PubMed, Scopus, the Cochrane Central Register of Controlled Trials, EMBASE, and Google Scholar. The reference lists of the included studies were also examined. Details regarding the search strategy are available in Supplemental Data S1. The search strategy was developed to include all RCTs employing dexmedetomidine in general surgery.

Study selection

Two researchers (A.D.C. and F.G.) independently screened the titles and abstracts of the identified studies for inclusion. Each citation was reviewed, and the full text of any potentially relevant study was retrieved. All studies meeting the following PICO5 (Population, Intervention, Comparison, Outcome) criteria were included in our analysis: adult (aged ≥ 18 years) patients undergoing endotracheal intubation for laparoscopic cholecystectomy (P); who received intravenous dexmedetomidine before tracheal intubation (I); compared to no intervention or any placebo (C); with data on the following: intraoperative bradycardia (primary outcome), intraoperative hypotension, hemodynamics at intubation (SBP, MAP, HR), dose needed for induction of anesthesia, total anesthesia requirements (both hypnotics and opioids) throughout the procedure, percentage of patients requiring postoperative analgesics, and percentage of patients experiencing PONV and postoperative shivering (O); and only RCTs were included (S).

Data extraction and data retrieval

After identifying those studies that met the inclusion criteria, two members of our team (M.I. and G.Z.) independently reviewed and assessed each of the included studies. Any disagreement regarding study selection or data extraction was resolved by discussion with a third author (A.D.C.). The following information was collected: first author; year; total number of patients per group; occurrence of intraoperative bradycardia (percent of patients) and hypotension (percent of patients); SBP, MAP, and HR at tracheal intubation; induction and intraoperative anesthetic type and dosage; analgesic requirement in the first 24 h; and...
PONV and shivering (percent of patients). If data were missing, a request was sent by e-mail to the corresponding author of the study. If no response was received after our initial request, a second request was sent seven days later. A third and last request was sent one week after the second request.

Quality assessment and certainty of evidence assessment

Two researchers (E.P. and N.R.) independently evaluated the quality of the included RCTs using the Risk of Bias (RoB) 2 Tool [8]. Disagreements were resolved by discussion with a third researcher (A.B.). We used the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach to assess the certainty of evidence related to each of the key outcomes [9]. We defined the following as key outcomes: intraoperative bradycardia; intraoperative hypotension; and HR, SBP, and MAP at tracheal intubation. Starting from a high quality of evidence, the certainty of evidence quality for each outcome is downgraded by one level for serious or by two levels for very serious study limitations, such as risk of bias, indirectness of evidence, inconsistencies, imprecision of effect estimates or other considerations (which include publication bias, large effect, plausible confounders, and dose response gradient).

Statistical methods

A meta-analysis of the data was performed using RevMan version 5.3 (The Cochrane Collaboration, 2020). The treatment effect for continuous outcomes is expressed as standardized mean difference (SMD) with 95% CIs when the outcome was expressed with different measurement techniques, or mean difference (MD) with 95% CIs when the outcome was derived from the same measurement technique. The treatment effect for dichotomous outcomes was expressed as risk ratios (RRs) with 95% CIs. Zero events were treated by applying a continuity correction adding one to each value.

Heterogeneity and publication bias analysis

To assess study heterogeneity, the chi-squared test and I²-statistic were used (considering I² values as follows: low heterogeneity: < 25%, moderate heterogeneity: 25% to 50%, and high heterogeneity: > 50%) [10]. A random-effects model was preferred when I² was > 25%. Publication bias was evaluated by visual inspection of the funnel plots. The Egger test (P < 0.05 indicating a possible publication bias) was used for outcomes based on more than ten studies [11].

Subgroup and sensitivity analysis

We performed the following pre-planned subgroup analyses on the main outcome.

Dexmedetomidine dose

We arbitrarily subdivided the dose of dexmedetomidine into a high dose (≥ 0.70 µg/kg), medium dose (0.40–0.69 µg/kg), and low dose (< 0.40 µg/kg) and evaluated the effects of these different dosing regimens on intraoperative bradycardia.

Intraoperative dexmedetomidine infusion

We evaluated whether the intraoperative use of dexmedetomidine continuous infusion affects the primary outcome.

Anticholinergic premedication

We evaluated the effects of anticholinergic premedication on intraoperative bradycardia.

To investigate the robustness of our findings, we planned to perform the following sensitivity analyses: 1) only low risk of bias studies and 2) outcomes with a low heterogeneity (from 0 to 25%) with a random-effect model and by removing continuity correction.

Trial sequential analysis

A pre-specified trial sequential analysis (TSA) [12] was performed on the main outcome using TSA software (Copenhagen Trial Unit, Center for Clinical Intervention Research, Copenhagen). We estimated the required sample size on the calculated minimal intervention effect, considering a type I error of 5% and a power of 90%. Statistical significance was set at P < 0.05 for all analyses.

Results

Study selection and data retrieval

The search results are summarized in the PRISMA diagram (Fig. 1). We retrieved a total of 3,841 studies, 15 of which (980 patients) were included in the qualitative and quantitative analyses [4,13–26].

Study characteristics

The 15 included studies had a total of 519 patients randomized to the dexmedetomidine group and 461 randomized to the no in-
One study [16] included patients aged > 65 years, while all the other studies included only younger patients. All the studies included patients with an American Society of Anesthesiologists Physical Status (ASA-PS) I-II, while only one study [26] included patients with an ASA-PS of III. One study [20] did not include any information regarding either the ASA-PS or the age of the included patients.

The dexmedetomidine bolus administered for tracheal intubation ranged from 1 µg/kg [4,17,19,21,22] to 0.01 µg/kg [15]. Five studies used a bolus dose > 0.7 µg/kg (dexmedetomidine group: 137 patients; placebo/no intervention group: 139 patients) [4,17,19,21,22], five studies used a dose between 0.7 µg/kg and 0.4 µg/kg (dexmedetomidine and placebo/no intervention groups: 177 patients each) [13,14,20,24,26], four studies used a dose < 0.4 µg/kg (dexmedetomidine and placebo/no intervention groups: 115 patients each) [15,16,18,23], and one study [25] used both medium and high bolus doses of dexmedetomidine (dexmedetomidine group: 90 patients; placebo/no intervention group: 30 patients). The characteristics of the included studies are available in Supplemental Data S2.
Two studies [17,25] were evaluated as having a low risk of bias, while all the remaining studies had some potential risk of bias. However, no study was evaluated as having a high risk of bias (Fig. 2). Further details regarding the risk of bias assessments are available in Supplemental Data S3.

The primary and secondary outcomes are summarized in Table 1. All forest plots and funnel plots are available as supplementary materials (Supplemental Data S4 and S5).

### Primary outcome

Ten studies described the occurrence of intraoperative bradycardia [4,14–17,19,21,23–25]. Patients receiving dexmedetomidine had a higher risk of developing intraoperative bradycardia (RR: 2.81, 95% CI [1.34, 5.91], P = 0.006, I² = 0%) (Fig. 3). We calculated a number needed to harm (NNH) of 17.4 (95% CI [13.3, 107.1]). The certainty of evidence was evaluated as very low due to high heterogeneity (Supplemental Data S6).

### Secondary outcomes

#### Intraoperative hypotension

Nine studies reported the incidence of intraoperative hypotension [4,14–19,23,25]. This complication occurred more frequently in patients receiving dexmedetomidine than in those receiving placebo or no intervention (Table 1). The calculated NNH was 24 (95% CI [13.3, 107.1]). The certainty of evidence was evaluated as moderate (Supplemental Data S6).

#### Hemodynamics at intubation

The MAP, SBP, and HR were reported in 11 [4,13–19,21,22,26], 5 [4,19,22,24,25], and 13 [4,13,19,21,22,24–26] studies, respectively. Patients who received dexmedetomidine at intubation had lower MAP, SBP, and HR values (Table 1). The certainty of evidence for these three outcomes was evaluated as very low due to high heterogeneity (Supplemental Data S4).

### Table 1. Primary and Secondary Outcomes of the Studies Involved

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>N study</th>
<th>Mean (95% CI)</th>
<th>P value</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative bradycardia</td>
<td>10</td>
<td>RR 2.81 (1.34, 5.91)</td>
<td>0.006</td>
<td>0%</td>
</tr>
<tr>
<td>Intraoperative hypotension</td>
<td>9</td>
<td>RR 1.66 (0.92, 2.98)</td>
<td>0.09</td>
<td>98%</td>
</tr>
<tr>
<td>SBP</td>
<td>5</td>
<td>MD −18.54 (−34.01, −3.08)</td>
<td>0.02</td>
<td>95%</td>
</tr>
<tr>
<td>MAP</td>
<td>11</td>
<td>MD −9.42 (−14.30, −4.55)</td>
<td>&lt; 0.001</td>
<td>95%</td>
</tr>
<tr>
<td>HR</td>
<td>13</td>
<td>MD −16.30 (−21.48, −11.13)</td>
<td>&lt; 0.001</td>
<td>95%</td>
</tr>
<tr>
<td>Induction agents</td>
<td>6</td>
<td>SMD −2.68 (−4.06, −1.30)</td>
<td>&lt; 0.001</td>
<td>96%</td>
</tr>
<tr>
<td>Postoperative nausea/vomiting</td>
<td>5</td>
<td>RR 0.55 (0.38, 0.79)</td>
<td>&lt; 0.001</td>
<td>21%</td>
</tr>
</tbody>
</table>

SBP: systolic blood pressure, MAP: mean arterial pressure, HR: heart rate. RR: relative risk, MD: mean difference, SMD: standardized mean difference.

#### Supplemental Data S6

In the TSA, the cumulative z-score crossed the monitoring boundary for harm at the tenth trial, yielding an effect that was both statistically and clinically significant (Fig. 4). The certainty of evidence was evaluated as moderate (Supplemental Data S6). Notably, no patient included in this study experienced either cardiac arrest or myocardial ischemia.

### Fig. 3. Intraoperative bradycardia forest plot. Forest plot of intraoperative bradycardia.
Anesthetics

Six studies reported the anesthesia requirements at anesthesia induction \[4,13,18,20,21,24\]. The use of dexmedetomidine as an adjuvant allowed for a lower total dose of anesthetics for intubation (Table 1).

Only a few of the studies described the intraoperative opioid requirements \[20,23\] and hypnotics \[23\] and therefore a meta-analysis was not performed. Both of these studies employed a continuous infusion of dexmedetomidine during surgery and found a significant association between dexmedetomidine use and lower opioid and hypnotic intraoperative consumption.

Postoperative analgesics and side-effects

We performed a meta-analysis of the five studies evaluating PONV, which revealed a lower risk of PONV for patients receiving dexmedetomidine (Table 1). Two studies evaluated shivering and found a statistically significant difference in favor of dexmedetomidine (Chilkoti et al. [18]: 0% vs. 12.5% and Bielka et al. [16]: 3.3% vs. 13.2%). Postoperative rescue analgesics were evaluated in two studies with different results. Park et al. [23] found no differences in the use of analgesics, while Khanduja et al. [20] reported a lower need for analgesics in the postoperative period for those who received dexmedetomidine.

Sensitivity analysis

Excluding the continuity correction did not change the effect estimation for any of the outcomes where the correction was applied (intraoperative bradycardia: RR 5.70, 95% CI [1.84, 17.76], \(P = 0.003\), \(\eta^2 = 0\%\); intraoperative hypotension: RR 1.96, 95% CI [0.99, 3.86], \(P = 0.05\), \(\eta^2 = 21\%\)). Given that no meta-analysis with low heterogeneity was found and only two studies \[17,25\] were at low risk of bias, the other two preplanned sensitivity analyses were not performed.

Publication bias

The Egger test was performed for intraoperative bradycardia HR and MAP outcomes, both of which included at least ten studies. Publication bias was not evident for any of the examined outcomes: intraoperative bradycardia (\(P = 0.755\)), MAP at intubation (\(P = 0.635\)), or HR outcomes (\(P = 0.124\)). For the other outcomes, notwithstanding the lack of clear asymmetry on visual inspection, a definite interpretation of the funnel plots was not possible due to the paucity of studies (Supplemental Data S5).

Subgroup analyses

Subgroup analysis forest plots are available as supplementary material (Supplemental Data S7).

Dexmedetomidine dose

Five studies used a dexmedetomidine dose ≥ 0.70 µg/kg [4,14,17,19,21], one study used a dose between 0.70 and 0.40 µg/
kg [24], and three studies used a low dose regimen (< 0.40 µg/kg) [15,16,23], while one study [25] used all three regimens. There were no differences regarding the occurrence of intraoperative bradycardia when considering the three different dose regimens (P = 0.47, $I^2 = 0\%$ for subgroup differences).

**Intraoperative dexmedetomidine infusion**

All studies except two [19,25] used a dexmedetomidine continuous infusion protocol during surgery. There were no statistically significant differences among the subgroups associated with the intraoperative dexmedetomidine infusion (P = 0.23, $I^2 = 29.6\%$ for subgroup differences).

**Anticholinergic premedication**

None of the patients that received an anticholinergic drug at anesthesia induction developed bradycardia (RR: 1.86, 95% CI [0.52, 6.66], P = 0.34, $I^2 = 0\%$); however, the difference was not statistically significant among the groups (P = 0.46).

**Discussion**

Our meta-analysis shows that premedication with dexmedetomidine for endotracheal intubation during laparoscopic cholecystectomy is associated with a higher risk of intraoperative bradycardia than placebo or no intervention. Moreover, patients receiving dexmedetomidine, despite requiring less anesthetics at anesthesia induction, developed lower blood pressure and HR during tracheal intubation, and experienced more frequent intraoperative hypotension but less frequent PONV.

Although laparoscopy is commonly considered a minimally invasive surgical approach, pneumoperitoneum is responsible for extensive perturbations of the patient's physiology due to increased intra-abdominal pressure, cephalic displacement of the diaphragm with alterations in intrathoracic pressure, carbon dioxide accumulation, and marked hemodynamic response [27]. On the one hand, laparoscopic surgery is associated with a profound sympathetic stimulus with an increase in HR and blood pressure due to catecholamine release [27], while on the other hand, peritoneal stretch secondary to intra-abdominal gas insufflation may lead to an increase in the vagal tone with subsequent bradycardia [3].

Given its potential impact on postoperative outcomes, sympathetic stimulus control during anesthesia is of paramount importance. Particularly, uncontrolled intraoperative tachycardia is associated with an increased risk of perioperative myocardial infarction [28] and mortality [29]. Dexmedetomidine is employed for sedation in different care settings and has been shown to reduce the plasma levels of catecholamines even at low concentrations [30]. Our meta-analysis suggests that the administration of dexmedetomidine before endotracheal intubation compared to no dexmedetomidine or placebo may be associated with a lower HR and BP. These findings confirm the results of a previous meta-analysis, which showed that dexmedetomidine use was associated with a reduction in the adrenergic response at induction, surgical incision, and extubation [6].

However, blunting of the adrenergic response should be weighed against potential perioperative complications, such as bradycardia and hypotension. Our work suggests that dexmedetomidine administration may be associated with the occurrence of these hemodynamic alterations in approximately 5 out of every 100 patients.

While two previous meta-analyses evaluated the effects of dexmedetomidine administered during tracheal intubation [5,6], our group [6] investigated the effect of dexmedetomidine during all surgical procedures (laparoscopic, robotic, and open surgeries). We found an association between bradycardia and dexmedetomidine administration (one in every 12 patients) and concluded that it therefore should be administered with caution in daily practice.

Of note, Demiri et al. [5] recently studied the incidence of perioperative adverse events after the administration of α₂-agonist where 31% of the patients also received clonidine. These authors highlighted the finding that patients receiving dexmedetomidine but not clonidine were at a higher risk for intraoperative bradycardia than those who received both medications.

While the aforementioned studies were based on all surgical procedures (open or laparoscopic) [5,6], the present study focused on laparoscopic cholecystectomy. Our study findings suggest that caution should be taken regarding routine dexmedetomidine use during laparoscopic surgery. Indeed, dexmedetomidine should not be used as a first choice in patients undergoing cholecystectomy, given the hemodynamic alterations discussed above. Rather, its use should be reserved and considered along with a risk-benefit analysis for patients with a strict need for sympathetic response control, even if data regarding this specific population are still insufficient for strong recommendations. If dexmedetomidine is administered, a dose of 0.5 µg/kg is preferable to a higher dose (e.g., 1.0 µg/kg) given the lower incidence of bradycardia associated with this dose in the general population [6]. As an additional note, the present study confirms the potential benefit of dexmedetomidine in reducing PONV [6].

Our study has a few limitations. First, although we focused only on laparoscopic cholecystectomy, which decreased clinical heterogeneity, we recognize that the heterogeneity associated with dif-
Dexmedetomidine and cholecystectomy

ferent anesthesia protocols and cut-off values for identifying some complications limits our conclusions. Second, to avoid increasing type I errors, we did not consider other potentially interesting outcomes (such as intraoperative hemodynamics).

In conclusion, patients undergoing laparoscopic cholecystectomy that receive dexmedetomidine during tracheal intubation are more likely to develop intraoperative bradycardia and hypotension. This effect may be attenuated by the administration of an anticholinergic agent.

Funding

None.

Conflicts of Interest

PN received royalties from Intersurgical for Helmet Next invention and speaking fees from Draeger, Intersurgical, Getinge, Philips, Resmed, MSD, Gilead and Novartis. The other authors have no other competing interests to declare.

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Paolo Navalesi (Conceptualization; Supervision; Writing – review & editing)
Annalisa Boscolo (Conceptualization; Supervision; Writing – review & editing)

Supplementary Materials

Supplemental Data S1. Search Strategy
Supplemental Data S2. Study characteristics
Supplemental Data S3. ROB2
Supplemental Data S4. Forest Plot
Supplemental Data S5. Funnel Plot
Supplemental Data S6. Grade
Supplemental Data S7. Subgroup+sensitivity

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Efficacy of perineural versus intravenous dexamethasone in prolonging the duration of analgesia when administered with peripheral nerve blocks: a systematic review and meta-analysis

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Background: Perineural dexamethasone has been regarded as a promising adjunct for prolonging the duration of nerve blocks. However, it is uncertain whether its effects are due to local effects on the nerves or from systemic absorption. This systematic review aimed to compare the duration of postoperative analgesia associated with perineural versus intravenous dexamethasone as an adjunct to peripheral nerve blocks.

Methods: A total of 2,216 relevant academic articles were identified after a comprehensive search of PubMed, Embase, Scopus, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from 1967 until 2020. All randomized controlled trials that compared perineural and intravenous dexamethasone as adjuncts to peripheral nerve limb blocks were included.

Results: Fifteen randomized controlled trials (1,467 cases; 738 perineural dexamethasone, 729 intravenous dexamethasone) were eligible. The primary outcome (duration of analgesia) was significantly longer in the perineural than in the intravenous dexamethasone group (mean difference [MD]: 2.72 h, 95% CI [1.42, 4.01], P < 0.001). Perineural dexamethasone was also found to prolong the sensory block (MD: 3.45 h, 95% CI [1.36, 5.54], P = 0.001) and lower 24 h postoperative pain scores (MD: −0.74 h, 95% CI [−1.40, −0.07], P = 0.03).

Conclusions: This review confirms the greater efficacy of perineural compared to intravenous dexamethasone in prolonging the analgesic duration of peripheral nerve blocks. However, the extent of prolongation was small and may not represent a clinically meaningful difference.

Keywords: Acute pain; Conduction anesthesia; Enhanced recovery after surgery; Nerve block; Pharmaceutical adjuvants; Postoperative pain.

Introduction

Moderate-to-severe pain is common after orthopedic surgery. Peripheral nerve blocks are thus frequently employed during these surgeries to improve perioperative pain control and reduce opioid consumption and opioid-related side effects [1].

One of the major problems with single-shot peripheral nerve blocks is the relatively short duration of action of the local anesthetics currently available. Consequently, pa-
Patients may experience significant pain after the block has worn off [2]. Perineural catheters have thus been used to extend the duration of analgesia. However, these catheters can be challenging to perform, time- and labor-intensive to manage, and also carry the risk of block failure. They are also susceptible to a number of complications, such as catheter dislodgement, pump-related issues [3] and catheter site infections [4]. Furthermore, given the increasing pressure on hospitals to discharge patients early, the use of perineural catheters may become less relevant in the future.

Consequently, an adjuvant that can prolong the duration of a peripheral nerve block is highly desirable. Several systematic reviews and meta-analyses have established the superiority of perineural dexamethasone in extending the duration of the block effects [5–7]. In 2017, a meta-analysis conducted by Pehora et al. [6] estimated that perineural dexamethasone prolonged the duration of peripheral nerve blocks by 6.7 hours compared to placebo. However, the mechanism of action underlying this phenomenon is unclear. Some possible explanations include the systemic absorption of dexamethasone leading to anti-inflammatory effects [8] and local effects, such as the modulation of C-fibers and local vasoconstriction [9,10]. Previous meta-analyses, which have included studies conducted up to 2018, have shown that perineural dexamethasone results in a longer duration of action compared to similar doses of intravenous dexamethasone, ranging from 0.48 to 3.96 h [11–13].

More recent randomized controlled trials (RCTs) examining the effects of perineural versus intravenous dexamethasone have been conducted [14–17]. This review thus aims to provide an update with the current literature pertaining to the efficacy of perineural compared with intravenous dexamethasone in prolonging the analgesic duration of peripheral nerve blocks for upper and lower limb surgeries.

Materials and Methods

This systematic review and meta-analysis followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO registration number CRD420 20210257).

Search methods

An electronic search was conducted using the following data-bases from January 1967 until November 2020: PubMed, Embase, Scopus, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov. The following search terms were used: (“Perineural Dexamethasone” OR “Perineural Steroid” OR “Dexamethasone” OR “Steroid”) AND (“Nerve block” OR “Peripheral nerve block” OR “Regional anaesthesia” OR “Regional anesthesia”).

Two reviewers (E.T. and Y.T.) independently reviewed the titles and abstracts of all search entries to exclude irrelevant studies. The full texts of the remaining studies were further examined for inclusion according to the inclusion and exclusion criteria. Disagreements regarding study eligibility were arbitrated by a third reviewer (C.L.).

Selection criteria

The inclusion criteria were as follows: RCTs (published or unpublished) involving adult patients undergoing upper or lower limb surgeries that compared the duration of analgesia (defined as time to first analgesia request or time to first pain sensation) following perineural versus intravenous dexamethasone. All RCTs that fulfilled the criteria were included in the analysis, without language restrictions.

Studies that involved any ongoing trials, children or animals, surgeries with truncal blocks, drug preparations with other additives combined with dexamethasone, and studies that included different doses for each route were excluded.

Quality assessment

Two reviewers (E.T. and Y.T.) independently assessed the validity of each included study using the revised Cochrane Collaboration risk-of-bias tool [19]. This tool addresses seven domains of possible bias in each study, including appropriate randomization process, adequate allocation concealment, blinding of the participants and personnel involved, outcome assessment process, missing outcome data, selective reporting of results, and any other types of biases [19]. The quality of evidence for each outcome in our review was evaluated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach [20]. For this approach, the grade of a study is decreased based on the degree of risk of bias, indirectness of the evidence, inconsistency and imprecision of effect estimates across studies, and the presence of possible publication or reporting biases. All discrepancies were resolved through a consensus process involving a third author (C.L.).
Data extraction

Two reviewers (E.T. and Y.T.) independently extracted the data onto a standardized form using Microsoft Excel version 2016 (Microsoft Corp., Redmond, 2015). The following data were collected from each study: authors’ names; publication year; sample size; type of surgery; type of peripheral nerve block performed; local anesthetic used (type of local anesthetic, concentration, and volume); dose of dexamethasone administered; time to first analgesia request; time to first pain sensation; duration of sensory block; duration of motor block; postoperative cumulative opioid requirement; postoperative pain scores at various time points; and incidence of adverse events including postoperative nausea and vomiting, hyperglycemia, and prolonged paresthesia or motor block. If additional data were required, attempts were made to contact the authors of the studies to obtain the missing information. Any disagreements were resolved through discussion with a third reviewer (C.L.).

Data analysis and statistical methods

To standardize the data for analysis, the outcomes assessing the duration of effect were converted to hours. Opioid use was converted to oral morphine analgesic equivalent doses using the Faculty of Pain Medicine of the Australian and New Zealand College of Anesthetists Opioid Calculator [21]. Data that were measured as median and interquartile range (IQR) were converted to approximate mean and standard deviation values using Hozo’s validated formula [22].


Random-effects modelling was used for all pooled data. Continuous data were compared using means and 95% CIs. Dichotomous data were pooled and analyzed using the Mantel-Haenszel odds ratio with 95% CIs. The I² test was used to estimate the degree of statistical heterogeneity. Sensitivity analysis was performed to assess the robustness of the results. Subgroup analyses were performed to detect any significant heterogeneity. Funnel plots and Egger’s test were performed to evaluate the risk of publication bias. A trial sequential analysis for the primary outcome was performed using Trial Sequential Analysis Viewer (TSA Viewer) software version 0.9.5.10 Beta, Copenhagen: Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet 2016.

Results

Study selection and characteristics

A total of 2,198 articles were identified during the initial search, after which the 232 duplicates were removed (Fig. 1). After screening the titles and abstracts, 58 studies were identified for full-text review, of which 43 were excluded because they did not fulfill the inclusion criteria. Of note, two studies [23,24] were excluded because different doses of dexamethasone were used for the perineural and intravenous routes, and one study [25] was excluded because no surgery was performed. Finally, fifteen RCTs were included in this systematic review and meta-analysis. These 15 studies [14–17,26–36] included a total of 1,467 participants, of which 738 were in the perineural dexamethasone group and 729 were in the intravenous dexamethasone group.

The study conducted by Holland et al. [15] was a two-by-two factorial design study comparing both 4 mg and 8 mg of perineural dexamethasone with equivalent doses of intravenous dexamethasone. We therefore analyzed the data separately and labeled them Holland 2018 (Dexa 4 mg) and Holland 2018 (Dexa 8 mg), respectively.

Identification of studies via databases and registers

<table>
<thead>
<tr>
<th>Identification of studies via databases and registers</th>
</tr>
</thead>
</table>
| Records identified from  
  • Databases (n = 2,198)  
  • Registers (n = 18) |
| Records removed before screening  
  Duplicate records removed (n = 232) |
| Records screened (n = 1,384) |
| Records excluded (n = 1,926) |
| Reports sought for retrieval (n = 58) |
| Reports not retrieval (n = 0) |
| Reports assessed for eligibility (n = 58) |
| Reports excluded  
  • Non-RCT (n = 1)  
  • Blocks performed for surgery other than limb surgery (n = 7)  
  • No surgery performed (n = 1)  
  • Did not compare against intravenous dexamethasone (n = 32)  
  • Dexamethasone doses used between intervention group and comparator group were different (n = 2) |

Studies included in review (n = 15)

Fig. 1. PRISMA flow diagram.
For the upper limb surgery studies [14–17,29–36], the brachial plexus blocks were administered using different approaches. Nine of these studies used the interscalene approach [14–17,24,29,30,33,35,36], two used the supraclavicular approach [14,31], one the infracavicular approach [34], and one used the axillary approach [32]. For the lower limb surgery studies [26–28], one performed femoral nerve blocks [26], and two performed sciatic nerve blocks [27,28]. Regarding the dose of dexamethasone, five studies used a range between 1 and 4 mg [15–17,30,36], ten used a range between 5 and 10 mg [15,26–29,31–35], and one study used a weight-calculated dose of 0.05 mg/kg [14]. For the anesthetic, five studies used ropivacaine 0.5% [16,29–31,33,35], three used ropivacaine 0.75% [27,30,36], four used bupivacaine 0.5% alone [15,17,31], one used bupivacaine 0.5% with lignocaine 2% and adrenaline [14], two used bupivacaine 0.25% with lignocaine 1% and adrenaline [32,34], and one used bupivacaine 0.5% with adrenaline [28]. The volume of the local anesthetic administered ranged from 5 to 30 ml. Specific details regarding the included studies and their block characteristics are summarized in Table 1.

### Risk of bias assessment

The risk of bias assessment results are shown in Fig. 2. No significant publication bias was detected according to the funnel plots or Egger's test ($P = 0.386$). As per the inclusion criteria, all studies included in the meta-analysis were RCTs.

### Primary outcome

#### Duration of analgesia

The primary outcome (the duration of analgesia) was reported in thirteen studies [14–17,26,27,29–32,34,35], with a total of 641 patients in the perineural dexamethasone group and 634 patients in the intravenous dexamethasone group. The duration of action was assessed either as the time to first pain sensation [15–17,27,31,32,34] or the time to first analgesia request [14,16,26,29,30,35]. Significant heterogeneity was observed among the studies. Overall, patients in the perineural dexamethasone group had a significantly longer duration of analgesia compared to the intravenous dexamethasone group (mean difference [MD]: 2.72 h, 95% CI [1.42, 4.01], moderate quality evidence, $I^2 = 86\%$, $P < 0.001$) (Fig. 3). When analyzed separately, subgroup analyses still demonstrated a statistically significant prolongation of both time to first pain sensation (MD: 2.58 h, 95% CI [1.13, 4.03], $I^2 = 74\%$, $P < 0.001$) and time to first analgesic request (MD: 2.69 h, 95% CI [0.26, 5.11], $I^2 = 92\%$, $P = 0.03$) in the perineural dexamethasone group (Figs. 4 and 5). The trial sequential analysis indicated strong evi-

### Table 1. Main Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study &amp; Year</th>
<th>Type of nerve block</th>
<th>Type of surgery</th>
<th>Dose of dexamethasone (mg)</th>
<th>Type of local anesthetic (<em>mg</em>)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Godbole, 2019 [14]</td>
<td>Interscalene</td>
<td>Shoulder arthroscopy</td>
<td>4</td>
<td>Ropivacaine 0.5%, 5 ml</td>
</tr>
<tr>
<td>Holland, 2018 [15]</td>
<td>Interscalene</td>
<td>Shoulder arthroscopy</td>
<td>8</td>
<td>Ropivacaine 0.5%, 30 ml</td>
</tr>
<tr>
<td>Kahn, 2018 [16]</td>
<td>Interscalene</td>
<td>Shoulder arthroscopy</td>
<td>8</td>
<td>Ropivacaine 0.5%, 30 ml</td>
</tr>
<tr>
<td>Sakae, 2017 [17]</td>
<td>Interscalene</td>
<td>Shoulder arthroscopy</td>
<td>8</td>
<td>Ropivacaine 0.5%, 30 ml</td>
</tr>
<tr>
<td>Leurcharusmee, 2016 [18]</td>
<td>Interscalene</td>
<td>Shoulder arthroscopy</td>
<td>10</td>
<td>Ropivacaine 0.5%, 30 ml</td>
</tr>
<tr>
<td>Rahangdale, 2014 [19]</td>
<td>Interscalene</td>
<td>Shoulder arthroscopy</td>
<td>10</td>
<td>Ropivacaine 0.5%, 30 ml</td>
</tr>
<tr>
<td>Chun, 2016 [20]</td>
<td>Interscalene</td>
<td>Shoulder arthroscopy</td>
<td>10</td>
<td>Ropivacaine 0.5%, 30 ml</td>
</tr>
<tr>
<td>Kawanishi, 2014 [21]</td>
<td>Interscalene</td>
<td>Shoulder arthroscopy</td>
<td>12</td>
<td>Ropivacaine 0.5%, 30 ml</td>
</tr>
<tr>
<td>Alfarah, 2016 [22]</td>
<td>Interscalene</td>
<td>Shoulder arthroscopy</td>
<td>14</td>
<td>Ropivacaine 0.5%, 30 ml</td>
</tr>
<tr>
<td>Susanto, 2016 [23]</td>
<td>Interscalene</td>
<td>Shoulder arthroscopy</td>
<td>14</td>
<td>Ropivacaine 0.5%, 30 ml</td>
</tr>
<tr>
<td>Chung, 2016 [24]</td>
<td>Interscalene</td>
<td>Shoulder arthroscopy</td>
<td>15</td>
<td>Ropivacaine 0.5%, 30 ml</td>
</tr>
<tr>
<td>Abdallah, 2015 [25]</td>
<td>Interscalene</td>
<td>Shoulder arthroscopy</td>
<td>17</td>
<td>Ropivacaine 0.5%, 30 ml</td>
</tr>
<tr>
<td>Desai, 2013 [26]</td>
<td>Interscalene</td>
<td>Shoulder arthroscopy</td>
<td>17</td>
<td>Ropivacaine 0.5%, 30 ml</td>
</tr>
<tr>
<td>Dawson, 2015 [27]</td>
<td>Interscalene</td>
<td>Shoulder arthroscopy</td>
<td>17</td>
<td>Ropivacaine 0.5%, 30 ml</td>
</tr>
<tr>
<td>Rahangdale, 2014 [28]</td>
<td>Interscalene</td>
<td>Shoulder arthroscopy</td>
<td>17</td>
<td>Ropivacaine 0.5%, 30 ml</td>
</tr>
</tbody>
</table>

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https://doi.org/10.4097/kja.21390
have artificially skewed the results towards favoring perineural dexamethasone, a sensitivity analysis was performed with this study excluded. However, this did not result in a significant decrease in the overall heterogeneity of the studies or outcomes (MD: 2.32 h, 95% CI [1.12, 3.52], I² = 84%, P < 0.001).

Several subgroup analyses were performed to account for the significant heterogeneity of the results. When the studies involving upper limb blocks were analyzed separately, the duration of analgesia with perineural dexamethasone remained significantly longer than that with intravenous dexamethasone (MD: 2.27 h, 95% CI [1.03, 3.51], P < 0.001). Another subgroup analysis was performed that included only those studies that used interscalene blocks, which is the most common approach. However, significant differences were still not found between the groups (MD: 1.56 h, 95% CI [−0.15, 3.28], P = 0.07). A trial sequential analysis was then performed, which indicated that data were insufficient to refute a possible effect with interscalene blocks.

To determine whether dexamethasone had a dose-dependent effect, the studies using dexamethasone doses ≤ 4 mg were analyzed separately from studies using dexamethasone doses > 4 mg. Both subgroup analyses showed a significantly prolonged analgesic duration, with a mean difference of 3.01 h in the ≤ 4 mg dose group (P < 0.001) and a mean difference of 2.81 h in the > 4 mg dose group (P = 0.02).

Secondary outcomes

Postoperative pain scores

The study conducted by Kahn et al. [17] reported pain scores in the post-anesthesia care unit, and the one conducted by Chun et al. [33] reported 6-h postoperative pain scores. In the study by Kahn et al. [17], no significant differences in pain scores were seen in the post-anesthesia care unit between the two groups (MD: 0.1, 95% CI [−0.6, 0.7], P = 0.999). Similarly, the study by Chun et al. [33] also did not find a significant difference in pain scores at 6 h post-operation (median [IQR]: perineural dexamethasone: 1 [0–2], intravenous dexamethasone: 1 [0–2]; P = 0.39).

A meta-analysis was performed for both the 12 and 24 h postoperative pain scores. Four trials [16,33,35,36] analyzed pain scores at 12 h post-operation, showing significantly lower pain scores in the perineural dexamethasone group (MD: −0.68, 95% CI [−1.05, −0.31]; low quality evidence, I² = 19%, P < 0.001) (Fig. 6).

Ten trials [15,16,26,28,30,31,33,35,36] compared 24 h postoperative pain scores, revealing a statistically significant reduction in pain in the perineural compared with the intravenous dexamethasone group (MD: −0.74, 95% CI [−1.40, −0.07]; low quality evi-
Fig. 3. Forest plot of perineural vs. intravenous dexamethasone; duration of analgesia in hours.

Fig. 4. Forest plot of subgroup analysis of time to first pain sensation in hours for perineural vs. intravenous dexamethasone.

Fig. 5. Forest plot of subgroup analysis of time to first analgesic request in hours for perineural vs. intravenous dexamethasone.

Fig. 6. Forest plot of 12-h postoperative pain scores for perineural vs. intravenous dexamethasone.

dence, $I^2 = 83\%$, $P = 0.03$). However, the mean differences at both 12 and 24 h post-operation were small and not considered clinically relevant [37] (Fig. 7).

24 h opioid consumption

Eight trials [15,16,26–28,31,35] examined 24 h oral morphine equivalent requirements. No significant difference was found between the groups (MD: $−1.05$ mg, 95% CI $[−2.71, 0.61]$; low quality evidence, $I^2 = 76\%$, $P = 0.21$) (Fig. 8).
Duration of sensory and motor block

Six studies [14,27,32,34–36] reported on the sensory block duration. The perineural dexamethasone group showed a longer duration compared to the intravenous dexamethasone group (MD: 3.45 h, 95% CI [1.36, 5.54]; moderate quality evidence, $I^2 = 82\%$, $P = 0.001$).

Additionally, six trials [14,16,31,32,34,36] analyzed the motor block duration; however, no significant difference between the groups was found (MD: 2.01 h, 95% CI [−0.92, 4.94]; low quality evidence, $I^2 = 93\%$, $P = 0.18$).

Postoperative nausea and vomiting

Six studies [16,26,27,30,31,36] compared the incidence rates of postoperative nausea and vomiting. No significant differences were observed between the groups, with a pooled incidence of 17.15% in the perineural dexamethasone group and 20.4% in the intravenous dexamethasone group (odds ratio: 0.78, 95% CI [0.46, 1.34], $I^2 = 0\%$, $P = 0.37$).

Postoperative blood glucose levels

Postoperative blood glucose levels were reported in three studies. Both Desmet et al. [29] and McHardy et al. [16] reported a statistically (but not clinically) significantly higher mean postoperative blood glucose level in the intravenous dexamethasone group than in the perineural dexamethasone group. Desmet et al. showed a mean increase of 0.3 mmol/L in the intravenous group and 0.2 mmol/L in the perineural group ($P < 0.05$), while McHardy et al. demonstrated a mean difference of 0.34 mmol/L ($P = 0.02$) in the intravenous group compared to the perineural group. Another study, conducted by Chun et al. [33], reported no significant differences between the two groups (mean [95% CI] 0.5 mmol/L [0.2, 0.8] vs. 0.4 mmol/L [0.2, 0.6], $P = 0.55$).

Neurological complications

Six studies [15,28,29,32–34] reported the neurological outcomes of the participants. The studies conducted by Desmet et al. [29], Aliste et al. [32], Chun et al. [33] and Rahangdale et al. [28] found no significant short-term or long-term neurological deficits. However, two studies [15,34] reported longer-lasting neurological outcomes in their participants. Leurcharumsie et al. [34] reported paresthesia in one patient in the perineural dexamethasone group that resolved within a week, while no neurological complications were reported in the intravenous dexamethasone group. The study conducted by Holland et al. [15] reported a higher incidence of neurological issues in the perineural dexamethasone group. In that study, the incidence of paresthesia was 13% and 14% in the 4 mg and 8 mg perineural dexamethasone groups, respectively, while for the intravenous dexamethasone groups, the incidence was 6% (4 mg group) and 11% (8 mg group). These differences, however, were not statistically significant, and an in-depth review of the cas-
es resulted in the conclusion that paresthesia was unlikely to be related to the use of dexamethasone.

Satisfaction scores
Satisfaction scores were recorded in seven studies [17,26,28-31,35], of which five [17,28,29,31,35] reported similar mean satisfaction scores between the groups, one [26] reported better patient satisfaction scores with perineural dexamethasone, and another [30] showed better satisfaction scores with intravenous dexamethasone.

Discussion

Compared to placebo, perineural dexamethasone as an adjunct to local anesthetics has been estimated to increase the duration of analgesia by 6.7 h [6]. However, it is unclear whether this is a result of systemic dexamethasone absorption. This meta-analysis, which included 15 RCTs and at total of 1,467 patients, suggests that local effects might explain this difference, considering that the duration of analgesia was longer in the perineural dexamethasone group compared to the intravenous dexamethasone group. The results of this study are similar to those of a previous meta-analysis performed in 2017 [11]. However, the impact of perineural dexamethasone on the duration of analgesia was found to be more modest than previously estimated [11].

Compared with intravenous dexamethasone, perineural dexamethasone was found to only increase the duration of analgesia by 2.72 h. The study conducted by Morales-Muñoz et al. [26] thus appears to be an outlier. Although efforts were made to determine why their results differed so considerably from those of the rest of the studies, no reasonable explanation was found. After this study was excluded from the analysis, an even more modest difference of 2.32 h was found. We believe that 2.32 h is likely to be closer to the true effect size.

Although the subgroup analysis that included only those patients undergoing interscalene blocks demonstrated no statistically significant differences between the perineural and intravenous dexamethasone groups, there was a trend towards a longer duration of analgesia in the perineural group. A trial sequential analysis confirmed that this may have been due to an inadequate sample size. Importantly, there were no clinically relevant differences in the 24 h postoperative pain scores, 24 h opioid consumption, or satisfaction scores.

A potential concern regarding the use of perineural dexamethasone is neurotoxicity. Animal studies have raised concerns regarding the potential neurotoxic effects of dexamethasone [38]. Despite this, we caution against labelling dexamethasone as neurotoxic based on animal cell culture studies with methodological flaws. Perineural dexamethasone has been used in the past for many causes of acute and chronic pain with no indication of increased neurotoxicity [39,40]. Consistent with other meta-analyses examining perineural steroids [16,33], no concerns linking the use of perineural steroids with poor neurological outcomes were found in our study.

This study has certain limitations. The most significant limitation was the heterogeneity of the included studies. Although the primary outcome (duration of analgesia) was assessed in all the studies, there was a lack of standardization regarding how this was defined or assessed. For example, some studies defined it as the time to the first pain sensation, while others defined it as the time to the first analgesia request. Furthermore, the methods of collecting the data were different between the studies; for example, some utilized retrospective telephone interviews, while others utilized patient self-report diaries. Heterogeneity may have also resulted from differences in the exact nature of the surgery as well as differences in surgical techniques.

Another limitation of this study was the lack of clarity on how researchers handled the time to first analgesia for the patients who did not require rescue analgesia. Apart from the study by Desmet et al. [29], which reported no significant differences in the number of patients who did not require rescue analgesia at 48 h post-surgery (4 out of 49 patients in the perineural dexamethasone group compared to 5 out of 49 in the intravenous dexamethasone group), the remaining studies did not report the number of patients who did not require rescue analgesia and did not discuss how these data were handled.

Taken together, this systematic review and meta-analysis offers a weak recommendation that perineural dexamethasone not be routinely administered as an adjunct to local anesthetics. Rather, intravenous dexamethasone should be considered, as it may be able to extend the duration of analgesia and can also be used to prevent postoperative nausea and vomiting [41]. The basis for this recommendation is that an increase in the duration of analgesia of 2.32 h is unlikely to be clinically relevant. Furthermore, perineural dexamethasone did not improve other pain-related parameters, such as pain scores or opioid consumption. The lack of standardization regarding how the primary outcome was defined and assessed in many of the studies also affects the reliability of the pooled results. Nevertheless, this review does not recommend further studies be conducted on this topic, given that they are unlikely to drastically change the results of this meta-analysis or lead to a change in the recommendations.

In conclusion, this systematic review and meta-analysis showed that perineural dexamethasone, when used as an adjunct to local

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anesthetics, results in a longer duration of analgesia than intravenous dexamethasone. However, the effect size was small and may not be clinically meaningful. Perineural dexamethasone was also not associated with a clinically significant reduction in 24 h pain scores or opioid consumption. We therefore make a weak recommendation that perineural dexamethasone not be routinely administered to patients to prolong the duration of analgesia following peripheral nerve blocks. Instead, intravenous dexamethasone should be considered.

Funding

None.

Conflicts of Interest

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

Author Contributions

Elizabeth Sein Jieh Tan (Conceptualization; Formal analysis; Investigation; Methodology; Writing – original draft)
Yan Ru Tan (Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft)
Christopher Wei Yang Liu (Conceptualization; Formal analysis; Methodology; Supervision; Writing – review & editing)

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References


33. Chun EH, Kim YJ, Woo JH. Which is your choice for prolonging the analgesic duration of single-shot interscalene brachial blocks for arthroscopic shoulder surgery? intravenous dexamethasone 5mg vs. perineural dexamethasone 5mg randomized, controlled, clinical trial. Medicine (Baltimore) 2016; 95: e3828.


Introduction

Supraglottic airway (SGA) devices have increasingly been used to maintain the airway during anesthesia. The American Society of Anesthesiologists has recommended the use of SGA devices in the practice guidelines for management of difficult airways [1, 2]. Various SGA devices have been developed and introduced, such as the Classic™ laryngeal mask airway (LMA) (Laryngeal Mask Airway Co. Ltd., UK), Proseal™ LMA (Laryngeal Mask Co. Ltd., Seychelles), LMA flexible™ (Teleflex Co., Ireland), and i-gel™ (Intersurgical, UK).

Prompt insertion and placement of the SGA device in the correct position are import-
ant during induction of anesthesia or emergency airway management. Conventionally, the standard digit-based technique involves using the index finger for SGA device insertion. However, this technique is somewhat difficult [3], and thus it requires certain training and some degree of skill [4]. Consequently, standard digit-based technique does not always ensure successful insertion and optimal placement of the SGA device. The first-attempt success rate of standard digit-based technique is reported to be 67–90% [5,6].

Various techniques have been investigated to increase the success rate of SGA device insertion in the first attempt, including the 90° rotation technique, 180° rotation technique, head elevation, or rotation and guidance technique [7–12]. Among these approaches, the 90° rotation technique was first introduced by Hwang et al. [7] in 2009. Thereafter, this technique has been investigated with a variety of SGA devices in several studies [8,11–13]. The 90° rotation technique has shown favorable results in increasing the success rate of SGA device insertion in several studies [8,12]. In contrast, it was unclear whether the 90° rotation technique could improve the success rate of SGA insertion compared to the standard digit-based technique [11,13].

Given the conflicting reports of previous studies, this meta-analysis was designed to verify the superiority of the 90° rotation technique over the standard digit-based technique in terms of insertion success rate and postoperative complications in anesthetized patients undergoing surgery.

Materials and Methods

Literature search

This study was performed in accordance with the Preferred Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines [14]. The protocol was registered in the International Prospective Register of Systematic Reviews (CRD42021 271253). In this study, we searched studies comparing the 90° rotation and the standard digit-based techniques for the insertion of SGA devices in patients undergoing general anesthesia. Eligible studies published until July 26, 2021, were searched on electronic databases, such as PubMed, EMBASE, CENTRAL, CINAHL, Scopus, and Web of Science. The search terms consisted of Medical Subject Headings (MeSH) terms and keywords, such as ‘Laryngeal Masks,’ ‘laryngeal mask,’ ‘LMA,’ or ‘rotation.’ Terms were combined with the Boolean operators ‘AND’ or ‘OR.’ The detailed search strategies for each database are shown in Supplemental digital content 1. The search was conducted without limitations on publication period, language, journal, or region.

Study selection

Two authors (C.-H.K. and J.-H.R.) independently screened papers and selected eligible studies according to predefined inclusion and exclusion criteria. The inclusion criteria were: (1) randomized controlled trials (RCTs), (2) studies including patients with SGA device insertion under general anesthesia, (3) studies comparing the 90° rotation technique with the standard digit-based technique for insertion of the SGA device, (4) studies reporting outcomes regarding insertion success rate and complication rate. Exclusion criteria were: (1) animal studies, (2) non-randomized studies (e.g., observational studies, retrospective studies, or case reports), (3) incomplete papers (e.g., conference abstracts, protocols, letters, or editorials). The results obtained by searching each database were combined, and the title and abstract of each paper was examined to screen for relevant studies. Subsequently, we found and reviewed the full text of the relevant studies and included RCTs that met the inclusion criteria in the final analysis. If any disagreement occurred during study selection, a third author (J.-W.H.) participated in the study selection and made the final decision.

Data extraction

The RCTs included in the final analysis were reviewed, and data were extracted and summarized into Excel sheets (Microsoft Inc., USA). The data extracted were the following: (1) name of the first author, (2) publication year, (3) sample size, (4) age of participants, (5) type and size of SGA device, (6) cuff pressure of SGA device before insertion, (7) allowance of manipulation during SGA device insertion, (8) types of neuromuscular blocking agents (NMBA) used, (9) success rates for SGA device insertion, (10) insertion time, and (11) postoperative complications regarding SGA device placement. If the result in a study was only plotted as a graph, we extracted the numerical data using the GetData Graph Digitizer 2.26 (http://www.getdata-graph-digitizer.com). The primary outcome was the first-attempt success rate for SGA device insertion. Secondary outcomes included the overall success rate for insertion, insertion time, and postoperative complications regarding SGA device insertion. The definitions of success of SGA placement and insertion time in each RCT are summarized in Supplemental digital content 2. Complications were defined as postoperative sore throat and pharyngeal injury assessed by blood stains on the surface of the SGA device.

The risk-of-bias (RoB) of each RCT was assessed using the revised Cochrane RoB tool (RoB 2) [15]. Two authors (C.-H.K. and J.-H.R.) independently reviewed the full text of each RCT and
graded the level of the RoB. The RoB 2 has five domains (randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result) and each domain is graded as ‘low risk,’ ‘some concerns,’ or ‘high risk.’ Subsequently, the overall RoB in each RCT was determined according to the RoB for each domain. When all domains were graded ‘low risk,’ the overall RoB was considered ‘low risk.’ If there were ‘some concerns’ without ‘high risk,’ the overall RoB was determined to be ‘some concerns.’ If at least one domain was graded ‘high risk,’ the overall RoB was considered ‘high risk.’ Any disagreements were resolved by participation of the third author (Y.-T.J.).

The level of evidence for each outcome was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system [16]. It has five domains including RoB, inconsistency, indirectness, imprecision, and publication bias.

Statistical analysis

To determine the degree of agreement between two authors for the study selection and data extraction, we calculated the kappa value and interpreted the value as follows according to the Cochrane Handbook [17]: 0.4–0.59, fair agreement; 0.6–0.75, good agreement; 0.75–1.0, excellent agreement.

We used R statistical software version 3.6.1. (R Foundation for Statistical Computing, Austria) with the ‘meta’ and ‘metafor’ package to conduct data synthesis and meta-analyses [18–20]. We calculated the risk ratio (RR) for categorical variables, such as success rates and the incidence of postoperative complications. We calculated the mean differences (MDs) for the insertion time (a continuous variable). In addition, sensitivity analysis was performed by using the leave-one-out approach to assess the robustness of our findings. The level of heterogeneity across studies was determined by calculating the inconsistency index ($I^2$). If $I^2 < 50\%$, a fixed-effects model was used; otherwise, a random-effects model was used to estimate effect size. To explore the potential sources of heterogeneity, we planned to perform subgroup analysis according to the age of participants (adults vs. children), use of NMBAs, allowance of manipulation during SGA device placement, and cuff pressure before insertion. Additionally, we also conducted meta-regression analysis in case significant heterogeneity was observed. All subgroup-, sensitivity-, and meta-regression analyses were restricted to the primary outcome. We constructed funnel plots and conducted Egger’s linear regression analysis to detect publication bias. A $P$ value $<0.05$ was considered statistically significant.

Results

Included and excluded studies

The literature search yielded 589 papers, of which 300 were duplicate. The remaining 289 papers were screened, and of these, 275 irrelevant papers were excluded. A review of the remaining 14 papers led to the exclusion of four papers based on the exclusion criteria: incomplete papers (n = 3) and a non-randomized study design (n = 1). Therefore, 10 RCTs, with 1,286 patients, were included in the final meta-analysis (Fig. 1) [7,8,11–13,21–25]. In the study selection, the kappa value between two authors was 0.811, indicating excellent agreement.

Among the participants, 644 patients were allocated to the 90° rotation group and 642 patients were allocated to the standard group. The characteristics of each RCT are shown in Table 1. Since nine of the 10 RCTs included adult patients, we decided not to conduct subgroup analysis according to age. The Proseal™ LMA device was used in half of the included RCTs [7,8,12,22,24] and the i-gel™ device was used in two RCTs [21,25]. The Clas-

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Fig. 1. PRISMA flow diagram for the included and excluded studies. A total of 589 papers were searched through databases. We excluded 300 duplicate papers and 275 irrelevant papers. The full texts of 14 eligible studies were reviewed, and four studies were excluded. Finally, a total of 10 RCTs were included in the final analysis. RCT: randomized controlled trial.
Characteristics of Included RCTs (n = 10)

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Sample size (standard/rotation)</th>
<th>Age</th>
<th>Type and size of SGA device</th>
<th>Cuff pressure</th>
<th>Allowance of manipulation</th>
<th>Type and doses of NMBA</th>
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</thead>
<tbody>
<tr>
<td>Bhardwaj, 2020 [21]</td>
<td>45/45</td>
<td>34.9 ± 10.9</td>
<td>i-gel™ (3/4/5)</td>
<td>No cuff</td>
<td>Yes</td>
<td>Vecuronium 0.1 mg/kg</td>
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<tr>
<td>Dhuilkhed, 2017 [22]</td>
<td>60/60</td>
<td>28.8 ± 9.6</td>
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<tr>
<td>Hwang, 2009 [7]</td>
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<td>43.0 ± 11.1</td>
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<td>No</td>
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<tr>
<td>Jeon, 2010 [8]</td>
<td>60/60</td>
<td>49.0 ± 12.0</td>
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<td>Deflated</td>
<td>No</td>
<td>Rocuronium 0.6 mg/kg</td>
</tr>
<tr>
<td>Kim, 2014 [25]</td>
<td>90/91</td>
<td>65.9 ± 9.9</td>
<td>i-gel™ (3/4)</td>
<td>No cuff</td>
<td>Yes</td>
<td>Rocuronium 0.6 mg/kg</td>
</tr>
<tr>
<td>Koo, 2019 [13]</td>
<td>66/63</td>
<td>44.8 ± 11.1</td>
<td>Flexible™ (3/4)</td>
<td>Deflated</td>
<td>Yes</td>
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<tr>
<td>Mahmoodpoor, 2015 [23]</td>
<td>50/50</td>
<td>62.5 ± 9.4</td>
<td>Classic™</td>
<td>Inflated</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Nalini, 2016 [24]</td>
<td>70/70</td>
<td>38.9 ± 13.8</td>
<td>Proseal™ (3/4)</td>
<td>Deflated</td>
<td>Yes</td>
<td>Atracurium 0.5 mg/kg</td>
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<tr>
<td>Shyam, 2021 [11]</td>
<td>60/60</td>
<td>35.5 ± 12.0</td>
<td>Unique™ (3/4)</td>
<td>Deflated</td>
<td>Yes</td>
<td>Atracurium 0.05 mg/kg</td>
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<tr>
<td>Yun, 2011 [12]</td>
<td>63/63</td>
<td>6.0 ± 2.0</td>
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<td>Deflated</td>
<td>No</td>
<td>Rocuronium 0.6 mg/kg</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD. RCT: randomized controlled trial, SGA: supraglottic airway, NMBA: neuromuscular blocking agent.

Overall success rate

The overall success rate was reported in seven RCTs, with a total of 917 patients [7,8,11–13,21–25]. It was 98.7% in the 90° rotation group and 93.0% in the standard group. An RR of 1.06 indicated that the 90° rotation technique significantly improved the overall success rate of SGA device insertion as compared to the standard technique (RR: 1.06, 95% CI [1.03, 1.09], P < 0.001, I² 0%, fixed-effects model; Fig. 2B). The funnel plot is shown in Supplemental digital content 7. The results of Egger’s linear regression analysis proved that there was no significant publication bias (P = 0.662).

Insertion time

Insertion time was reported in all 10 RCTs [7,8,11–13,21–25]. Mahmoodpoor et al. [23] showed the time for SGA device insertion as a graph, and the unit of time in the figure was ‘minutes’. However, according to the main text of their paper, the unit of time was ‘seconds.’ We contacted the study author and confirmed that the unit of time was ‘seconds.’ In addition, we regarded that the error bar represented the standard error of mean. The results...
of our meta-analysis demonstrated that the 90° rotation technique required less time for SGA device placement than the standard technique (MD: $-4.42$ s, 95% CI $[-6.70, -2.15]$ s, $P < 0.001$, $I^2 = 91\%$, random-effects model; Fig. 3). The funnel plot is shown in Supplemental digital content 8. The results of Egger’s linear regression analysis confirmed that there was no significant publication bias ($P = 0.173$).

### Postoperative complications

Postoperative sore throat was reported in nine RCTs [7,8,11–13,21,22,24,25]. A total of 75 patients (12.7%) in the 90° rotation group experienced sore throat after surgery, while 118 patients (20.1%) in the standard group experienced sore throat after surgery. The meta-analysis confirmed that fewer patients in the 90° rotation group had postoperative sore throat than those in the standard group (RR: 0.63, 95% CI [0.49, 0.83], $P < 0.001$, $I^2 = 47\%$, fixed-effects model; Fig. 4A).

Blood staining on the SGA device surface was reported in all 10 RCTs [7,8,11–13,21–25]. The incidence of blood staining was 6.2% in the 90° rotation group and 22.3% in the standard group. An RR of 0.28 implied that the 90° rotation technique significantly decreased the incidence of blood staining on the SGA device surface as compared to the standard technique (RR: 0.28, 95% CI [0.20, 0.39], $P < 0.001$, $I^2 = 17\%$, fixed-effects model; Fig. 4B).

Given the symmetrical funnel plots and results of Egger’s linear regression analysis of funnel plot asymmetry ($P = 0.968$ and 0.95 respectively), publication biases for postoperative complications were considered insignificant (Supplemental digital content 9).

### Risk of bias

As shown in Supplemental digital content 10, the overall RoB was rated as ‘low risk’ in four RCTs and ‘some concerns’ in five RCTs. The reason for ‘some concerns’ was the absence of descrip-

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### Table: Comparing SGA insertion techniques

<table>
<thead>
<tr>
<th>Study</th>
<th>90° rotation</th>
<th>Standard</th>
<th>RR</th>
<th>95% CI</th>
<th>Weight</th>
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<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Total</td>
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<tr>
<td>Bhardwaj, 2020</td>
<td>38</td>
<td>45</td>
<td>37</td>
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<tr>
<td>Hwang, 2009</td>
<td>80</td>
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<td>68</td>
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<td>Kim, 2014</td>
<td>87</td>
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<td>Koo, 2019</td>
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<td>Mahmoodpoor, 2015</td>
<td>48</td>
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<td>69</td>
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<td>57</td>
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Random effects model

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<th>Study</th>
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<th>Standard</th>
<th>RR</th>
<th>95% CI</th>
<th>Weight</th>
</tr>
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<td>Yun, 2011</td>
<td>63</td>
<td>36</td>
<td>60</td>
<td>63</td>
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</table>

Fixed effects model

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**Fig. 2.** Forest plots for success rates of SGA insertion. (A) First attempt success rate, (B) overall success rate. Both first attempt success rate and overall success rate were significantly higher in the 90° rotation group than in the standard group ($P < 0.001$, respectively). SGA: supraglottic airway, RR: risk ratio.
**Fig. 3.** Forest plot for insertion time for SGA insertion. Insertion time was significantly lower in the 90° rotation group than in the standard group (P < 0.001). SGA: supraglottic airway, MD: mean difference, SD: standard deviation.

**Fig. 4.** Forest plots for postoperative complications. (A) postoperative sore throat, (B) blood staining. The 90° rotation technique was associated with a significantly decreased incidence of postoperative sore throat and blood staining (P < 0.001, respectively). RR: risk ratio.
tions of allocation concealment [4,10,16–18,20]. Due to the design of the studies, it was impossible to blind the anesthesiologists who inserted the SGA device in all studies. However, objective approaches, for example, a square wave of capnograph or a blinded observer were used to determine the success rate of SGA insertion. Therefore, we judged that the awareness of the allocated group may not have affected the assessment of outcome.

**Level of evidence**

The level of evidence for each outcome was shown in Supplemental digital content 11. The level of evidence was moderate for first-attempt success rate and postoperative complications, high for overall success rate, and low for insertion time.

**Discussion**

The present meta-analysis showed that the 90° rotation technique increased both the first-attempt success and overall success rate as compared to the standard digit-based technique during the insertion of SGA devices in anesthetized patients. The 90° rotation technique also reduced SGA device insertion time. In addition, it was associated with less postoperative complications, in that the incidence of postoperative sore throat and mucosal bleeding was lower in patients intubated using the 90° rotation technique than in those intubated with the standard digit-based technique.

Insertion success rate is the most critical outcome in terms of SGA device insertion. The 90° rotation technique increased both the first attempt and overall success rate as compared with the standard digit-based technique in SGA device insertion. Park et al. [26] conducted meta-analysis with 13 RCTs and concluded that rotation technique provided higher first-attempt and overall success rate. However, they included both 90° and 180° rotation techniques. Among the included studies, there are only four studies that compared the 90° rotation to standard technique. Given that our results are based on more RCTs that validated the 90° rotation technique solely, our study may provide further evidence for the usefulness of the 90° rotation technique. During the advancement of the SGA device by means of the standard digit-based technique, impaction and friction at the back of the mouth are often encountered, which are the main causes of failed insertion [27]. Furthermore, some types of SGA device have soft bowl, large cuff, or flexible shaft [28,29]. These features may disturb the insertion of the SGA device. In the 90° rotation technique, the SGA device is inserted until the cuff is inside the mouth; then, it is rotated 90° and advanced until resistance from the hypopharynx is felt; and finally, it is straightened out in the hypopharynx [7]. Therefore, the 90° rotation technique may reduce the resistance between the SGA and the posterior pharyngeal wall at the lateral edge of the oral cavity, making advancement of the SGA device easier. The reduced insertion time of the 90° rotation technique may be explained by the same oral cavity anatomical factors mentioned above.

This meta-analysis included studies that used various SGA devices including the Classic™, Proseal™, Flexible™, Unique™, and i-gel™ devices. Hence, a moderate degree of heterogeneity may be shown for the first-attempt success rate. We performed subgroup, sensitivity, and meta-regression analyses to explore the potential sources of heterogeneity. We found that the allowance for manipulations of SGA device insertion accounted for the heterogeneity. It is reasonable to infer that manipulation could facilitate SGA device insertion and affect the success rate. It is notable in this study that the 90° rotation technique improved the first-attempt success rate for device placement, irrespective of whether NMBA was administered, whether manipulation for placement was allowed, or whether the cuff was inflated or deflated. We believe that the results of subgroup analyses emphasize the validity of the 90° rotation technique in various circumstances. There was a high degree of heterogeneity in the insertion time. We recognized that definitions of success and insertion time were slightly inconsistent among the studies, and that these discrepancies might cause heterogeneity in the first-attempt success rate and insertion time. Nevertheless, it is interesting to note that there was no heterogeneity in the overall success rate.

Postoperative complications related to SGA device insertion results in postoperative sore throat and mucosal bleeding, which is manifested by blood staining on the surface of the removed SGA device. The 90° rotation technique was associated with a significantly reduced incidence of sore throat and mucosal bleeding as compared with the standard digit-based technique. This result may also be due to the reduced resistance and friction between the shaft of the SGA and the pharyngeal wall at the lateral edge of the oral cavity [7].

This study had several limitations. First, generally, SGA insertion requires certain training and sufficient experience. The SGA could be skillfully inserted only after mastering the correct method. Therefore, the professional title and experience of the researcher may be important factors for the success rate of SGA placement. Second, this study included electively anesthetized pa-
tients, and thus, it is difficult to extrapolate our findings to other fields, such as the emergency department. Third, RCTs included in this study used five types of SGA devices. However, there are various types of SGA devices which are not included in this study, for example, SoftSeal LMA. Given that our findings are based on five types of SGA devices, the results from this analysis should be treated with caution and are hardly to be generalized to all types of SGA devices.

In conclusion, this meta-analysis of 10 RCTs demonstrated that the 90° rotation technique was superior to the standard digit-based technique during insertion of the SGA device in anesthetized patients in that it was associated with increased first-attempt and overall success rate of device insertion, decreased insertion time, and decreased postoperative complications than the standard digit-based technique. Further research is needed in un-anesthetized patients with difficult airways in emergency airway management situations.

**Funding**

None.

**Conflicts of Interest**

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

**Author Contributions**

Chang-Hoon Koo (Data curation; Investigation; Methodology; Software; Visualization; Writing – original draft)
Ah-Young Oh (Conceptualization; Investigation; Methodology; Visualization; Writing – original draft)
Young-Tae Jeon (Conceptualization; Investigation; Methodology; Resources; Writing – review & editing)
Jung-Won Hwang (Conceptualization; Investigation; Methodology; Resources; Validation; Writing – review & editing)
Jung-Hee Ryu (Conceptualization; Formal analysis; Investigation; Methodology; Supervision; Writing – review & editing)

**Supplementary Materials**

Supplementary Digital Content 1. Search strategies for each database.
Supplementary Digital Content 2. Definitions of success and insertion time for supraglottic airway (SGA) device placement in each study.
Supplementary Digital Content 3. Forest plot for sensitivity analysis for first-attempt success rate. Omitting each study in turn did not skew the pooled effect size.
Supplementary Digital Content 4. Forest plots for subgroup analyses of first-attempt success rate. Subgroup analysis was performed according to (A) the use of neuromuscular blocking agents (NMBA), (B) allowance for manipulation of supraglottic airway (SGA) placement, and (C) cuff pressure before insertion. The first-attempt success rate remained significantly higher in the 90° rotation group than in the standard group in the NMBA (P = 0.004), no NMBA (P < 0.001), manipulation (P = 0.008), no manipulation (P < 0.001), no cuff (P = 0.016), inflated cuff (P = 0.001), and deflated cuff (P = 0.003) subgroups.
Supplementary Digital Content 5. Meta-regression analysis for the potential sources of heterogeneity.
Supplementary Digital Content 6. Funnel plot for first-attempt success rate. Egger's linear regression analysis of the funnel plot asymmetry revealed that publication bias was insignificant (P = 0.300).
Supplementary Digital Content 7. Funnel plot for overall success rate. Egger's linear regression analysis of the funnel plot asymmetry revealed that publication bias was insignificant (P = 0.662).
Supplementary Digital Content 8. Funnel plot for insertion time. Egger's linear regression analysis of the funnel plot asymmetry revealed that publication bias was insignificant (P = 0.173).
Supplementary Digital Content 9. Funnel plots for postoperative complications. (A) Postoperative sore throat, (B) Blood staining on supraglottic airway (SGA) device surface. Egger's linear regression analysis of the funnel plot asymmetry revealed that publication bias was insignificant (P = 0.968, 0.806, respectively).
Supplementary Digital Content 10. Risk-of-bias graph. D1: bias arising from the randomization process, D2: bias due to deviations from the intended intervention, D3: bias due to missing outcome data, D4: bias in measurement of the outcome, D5: bias in the selection of the reported results. Green circle: low risk, yellow circle: some concerns.
Supplementary Digital Content 11. Level of evidence for each outcomes.

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Koo et al. · Comparing of SGA insertion techniques

References


The effect of ultrasound-guided bilateral thoracic retrolaminar block on analgesia after pediatric open cardiac surgery: a randomized controlled double-blind study

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Department of Anesthesia and Surgical Intensive Care, Faculty of Medicine, ¹Mansoura University, Mansoura, ²Portsaid University, Portsaid, ³Damietta University, Damietta, Egypt

Background: The thoracic retrolaminar block (TRLB) is a relatively new regional analgesia technique that can be used as an alternative to the thoracic paravertebral block. This study aimed to evaluate the postoperative analgesic effects of ultrasound-guided TRLB in children undergoing open cardiac surgery via median sternotomy incision.

Methods: Sixty-six patients aged 2–8 years were recruited. In the TRLB group, 0.25% bupivacaine 0.4 ml/kg was injected into the retrolaminar space on both sides at the level of the T4 lamina. Patients in the control group were injected with 0.9% saline. The primary outcome measure was fentanyl consumption in the first 24 h post-extubation. The secondary outcome measures were the total intraoperative fentanyl consumption, postoperative modified objective pain score (MOPS), and time to extubation.

Results: The total intraoperative fentanyl requirements and fentanyl consumption in the first 24 h post-extubation were significantly lower (P < 0.001) in the TRLB group (9.3 ± 1.2; 6.9 ± 2.1 μg/kg, respectively) than in the control group (12.5 ± 1.4; 16.6 ± 2.8, respectively). The median (Q1, Q3) time to extubation was significantly shorter (P < 0.001) in the TRLB group (2 [1, 3] h) than in the control group (6 [4.5, 6] h). The MOPS was significantly lower (P < 0.05) in the TRLB group than in the control group at 0, 2, 4, 8, 12 and 16 h post-extubation.

Conclusions: Bilateral ultrasound-guided TRLB is effective in providing postoperative analgesia in children undergoing open cardiac surgery via median sternotomy incision.

Keywords: Analgesia; Cardiac surgical procedures; Child; Fentanyl; Nerve block; Sternotomy; Ultrasonography.

Introduction

Cardiac surgery via a median sternotomy incision causes moderate to severe postoperative pain that can be prevented using an appropriate multimodal analgesic regimen [1]. Regional analgesia is an essential component of postoperative multimodal analgesia for all surgical patients, including children undergoing cardiac surgery. The use of ultrasound guidance in anesthesia increases the safety and efficacy of various regional anesthesia techniques [2]. Currently, the use of neuraxial analgesia, including epidural, caudal, and spinal analgesia, has been gradually replaced by safer ultrasound-guided fascial plane...
blocks, especially in cardiac surgery, to avoid the potential risk of epidural hematoma in fully anticoagulated patients [3,4].

Ultrasound-guided thoracic retrolaminar block (TRLB) is a relatively new regional analgesic block that can be used as an alternative to the thoracic paravertebral block as a component of multimodal analgesia to control postoperative pain [5]. In adults, the analgesic efficacy of TRLB has been reported for rib fractures [6], breast surgery [7,8], and video-assisted thoracoscopic surgery [9].

Injecting a local anesthetic in the retrolaminar space blocks the ventral and dorsal rami of the thoracic spinal nerves and spreads laterally in the fascial plane to block the lateral cutaneous branch of the intercostal nerve and the small branches arising from it [5].

The only pediatric randomized study on the use of TRLB for postoperative analgesia was conducted in patients undergoing inguinal hernia repair [10]. To the best of our knowledge, this is the first clinical trial to evaluate the analgesic efficacy of TRLB after open cardiac surgery via median sternotomy.

This prospective randomized controlled study was designed to demonstrate the postoperative analgesic effects of single-shot bilateral TRLB in terms of 24 h postoperative fentanyl consumption and pain scores. We hypothesized that the bilateral TRLB would decrease the postoperative fentanyl consumption and pain scores. The primary outcome measured was 24 h post-extubation fentanyl consumption, and the secondary outcomes were postoperative pain scores, time to first rescue analgesia, time to extubation, and the incidence of TRLB-related complications.

**Materials and Methods**

This was a single-center, prospective, randomized, double-blind, superiority study with two parallel arms. The study protocol was approved by the Institutional Review Board of Mansoura Faculty of Medicine, Mansoura, Egypt (IRB code: R 20.11.1073) on December 3, 2020, and registered in the African clinical trial registry (PACTR202012621958228) before patient recruitment. Written informed consent to perform the retrolaminar block and publish this study was obtained from the patients’ legal guardians before surgery. This study was conducted in accordance with the ethical principles of the Helsinki Declaration-2013 and followed good clinical practice guidelines.

This study was conducted at the cardiac division of Mansoura University Children’s Hospital between December 2020 and September 2021. A total of 66 patients aged 2–8 years (both male and female) with American Society of Anesthesiologists physical status classification I and II who were scheduled to undergo cardiac surgery via midline sternotomy by cardiopulmonary bypass (CPB) for the repair of simple congenital heart diseases were recruited. The exclusion criteria were as follows: history of multiple cardiac surgeries, history of emergency surgery, intubated patients, patients receiving inotropic support, and those with pulmonary hypertension, bleeding disorders, or an allergy to amide local anesthetics.

The patients were randomized to either the TRLB or control group using random computer-generated numbers with an allocation ratio of 1 : 1. The patient group assignment was kept in a sealed opaque envelope that was delivered to the operating room on the day of surgery and opened just before the induction of anesthesia. The anesthesiologist who prepared the local anesthetic and placebo was not involved in the study. The anesthesia residents who collected the data and the nursing staff who provided postoperative care were all blinded to patient group allocation.

Patients were premedicated with 0.5 mg/kg oral midazolam 30 min before separation from their parents. Patients were monitored before induction of anesthesia using 5-lead electrocardiography, pulse oximetry, and a non-invasive blood pressure cuff. Induction of anesthesia was performed either through inhaled sevoflurane or intravenous propofol 1.5 mg/kg depending on the presence or absence of an intravenous line and the patient's age. Rocuronium 0.9 mg/kg and fentanyl 2 μg/kg were administered before tracheal intubation. A capnography was then connected to the endotracheal tube to monitor end-tidal CO\textsubscript{2}. A 3 Fr Leadercath (Vygon, France) was inserted into the femoral artery for invasive arterial pressure monitoring, a 5–5.5 Fr central venous catheter was inserted into the right internal jugular vein to monitor the central venous pressure, and a temperature probe was inserted into the nasopharynx to monitor the patient's temperature.

Anesthesia was maintained with sevoflurane (1–2%) in a mixture of air-oxygen at a ratio of 1 : 1, fentanyl 1 μg/kg/h, and rocuronium 0.5 mg/kg/h. Additional 1 μg/kg boluses of fentanyl were administered before skin incision, before the sternotomy, and when the mean arterial blood pressure and/or heart rate increased by 20% above baseline.

After anesthesia induction, the patient was placed in a prone position with a pillow under the chest to perform a retrolaminar block on both sides. The spinous process of the fourth thoracic vertebra was identified and marked. Ultrasound-guided TRLB was performed under complete sterilization using Sterillium® sterile drapes, and the ultrasound probe was placed in a sterile sheath. A GE Vivid S5 high-frequency ultrasound linear transducer (General Electric Ving Med Systems, Horten, Norway) was placed in a parasagittal position just lateral to the spinous processes of the thoracic vertebra to identify the trapezius, rhomboid major, erector spinae, and paraspinal muscles and the vertebral lamina (Fig. 1). A 50-mm 22 gauge sonographic needle (Stimuplex®,
Braun Medical, USA) was inserted using the in-plane technique in the cephalad-to-caudal direction and advanced until the lamina of the fourth thoracic vertebra was touched, after which 0.25% bupivacaine 0.4 ml/kg was injected on each side (Fig. 1). In the control group, 0.9% normal saline 0.4 ml/kg was injected instead of 0.25% bupivacaine.

All surgeries were performed via midline sternotomy incision (Fig. 2A). Before initiation of CPB, each patient received 3–4 mg/kg heparin through the central venous catheter to increase the activated clotting time above 480 s. The presence of mild hypothermia was considered acceptable. After the cardiac defect was repaired, the patient was rewarmed, separated from CPB, and protamine was administered to antagonize the heparin. After the surgery was completed and the drainage tubes were placed (Fig. 2B), the patient was transferred to the intensive care unit (ICU).

The patients were monitored in the ICU using the same parameters as those used during surgery. Extubation was performed once the patient fulfilled the extubation criteria (adequate level of consciousness, normothermia, hemodynamic stability, minimal inotropic support, absence of significant bleeding, adequate spontaneous respiration, and acceptable arterial blood gas levels). Postoperative pain was assessed for the first 24 h after extubation using a 10-point modified objective pain score (MOPS) [11]. All patients received a standard protocol of multimodal analgesia in the form of paracetamol 15 mg/kg every 8 h and intravenous ibuprofen 10 mg/kg every 6 h. Fentanyl 1 μg/kg was administered as a rescue analgesic when the MOPS was > 3.

The primary outcome measure was fentanyl consumption in the first 24 h post-extubation. The secondary outcome measures were total intraoperative fentanyl consumption, postoperative pain scores at rest, time to extubation measured after arrival in the ICU, time to the first rescue analgesia measured after extubation, ICU length of stay, and the incidence of TRLB-related complications (e.g., hypotension, pneumothorax, vascular or neurological injury, or local anesthetic toxicity). The incidence of other complications (vomiting and pruritus) were also reported. Postoperative pain (according to the MOPS) was assessed at rest at 0, 2, 4, 8, 12, 16, and 24 h post-extubation.

Sample size and statistical analysis

The sample size was calculated using PASS version 15.0.5 software for Windows (PASS, LLC, USA), and a superiority test was conducted to determine the difference between two means. This study was designed as a superiority trial. Since no similar study has been conducted previously, we calculated the sample size using the results of our pilot study, which included six patients in each group (these patients are not included in this study). The mean ± SD fentanyl consumption in the first 24 h post-extubation in our pilot study was 7.5 ± 2.4 μg/kg in the TRLB group and 13 ± 4.3 μg/kg in the control group. Group sample sizes of 25 patients achieved 80% power to detect superiority using a one-sided two-sample t-test. The margin of superiority was 3 μg/kg. The true difference between the means was assumed to be 5.5 μg/kg. The significance level (α) of the test was 0.05. The data were drawn from populations with standard deviations of 2.4 and 4.3. The final sample size was increased to 32 patients per group to compensate for an estimated dropout rate of 20%.

Statistical analysis was performed using IBM SPSS (version 21.0; IBM Corp., USA) for Windows. The Shapiro-Wilk test was used to determine the normality of the data distribution. Normally distributed quantitative data are represented as the mean ± SD and were analyzed using the independent t-test. Non-parametric variables are reported as median (interquartile range [Q1, Q3]) and were analyzed using the Mann-Whitney U test. Categorical variables are expressed as numbers and were analyzed using the
chi-square test. Statistical analyses were performed by comparing the TRLB and control groups. P < 0.05 was used to indicate statistical significance with a 95% CI.

Results

Sixty-six patients were recruited, of whom eight were excluded either due to refusal by their legal guardians (n = 3) or failing to meet the inclusion criteria (n = 5) (Fig. 3). One patient in the control group was lost to follow-up owing to re-exploration after developing postoperative surgical bleeding. Fifty-seven patients completed the final analysis, 29 in the TRLB group and 28 in the control group (Fig. 3).

There were no significant differences between the TRLB and control groups in terms of the patient and surgical characteristics (Table 1).

The analgesic profiles of the two study groups are compared in Table 2. The mean ± SD total intraoperative fentanyl consumption and fentanyl consumption in the first 24 h post-extubation were significantly lower (P < 0.001) in the TRLB group (9.3 ± 1.2 and 6.9 ± 2.1 μg/kg, respectively) than in the control group (12.5 ± 1.4 and 16.6 ± 2.8 μg/kg, respectively). The median (Q1, Q3) time to first rescue analgesia was significantly longer (P < 0.001) in the TRLB group (7 [5, 8] h) than in the control group (2 [1, 2] h). The median (Q1, Q3) time to extubation and the mean ± SD ICU length of stay were significantly shorter (P < 0.001) in the TRLB group (2 [1, 3] h and 23.8 ± 3.2 h, respectively) than in the control group (6 [4.5, 6] h and 30.3 ± 3.2 h, respectively) (Table 2). There were no TRLB-related complications reported (hypotension, pneumothorax, vascular or neurological injury, or local anesthetic toxicity) (Table 2). There was also no significant difference in the incidence of vomiting or pruritus between the control and TRLB groups.

Fig. 4 shows a comparison of the MOPS between the TRLB and control groups. The MOPS was significantly lower (P < 0.05) in the TRLB group than in the control group at 0, 2, 4, 8, 12 and 16 h post-extubation. At 24 h post-extubation, however, the MOPS was similar between the groups.

Discussion

In this randomized controlled superiority study, 66 patients

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**Table 1. Patients and Surgical Characteristics**

<table>
<thead>
<tr>
<th>Variable</th>
<th>TRLB group (n = 29)</th>
<th>Control group (n = 28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>4.2 (2.9, 6.7)</td>
<td>3.9 (3.2, 5.7)</td>
<td>0.481</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>13/16</td>
<td>12/16</td>
<td>0.881</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>14.5 ± 3.2</td>
<td>13.7 ± 3.1</td>
<td>0.380</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>105 ± 13</td>
<td>101 ± 12</td>
<td>0.343</td>
</tr>
<tr>
<td>BSA (m²)</td>
<td>0.60 ± 0.08</td>
<td>0.56 ± 0.08</td>
<td>0.146</td>
</tr>
<tr>
<td>Aortic clamp time (min)</td>
<td>35 (22, 43)</td>
<td>34 (23, 40)</td>
<td>0.987</td>
</tr>
<tr>
<td>CPB time (min)</td>
<td>56 ± 11</td>
<td>58 ± 8</td>
<td>0.423</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>194 ± 21</td>
<td>196 ± 19</td>
<td>0.615</td>
</tr>
<tr>
<td>Surgical procedure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VSD repair</td>
<td>12</td>
<td>9</td>
<td>0.765</td>
</tr>
<tr>
<td>ASD repair</td>
<td>15</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>CAVC repair</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

Values are presented as median (Q1, Q3), number of patients, or mean ± SD. TRLB: thoracic retrolaminar block, BSA: body surface area, CPB: cardiopulmonary bypass, VSD: ventricular septal defect, ASD: atrial septal defect, CAVC: common atrioventricular canal.
were examined for eligibility, nine of whom were excluded or lost to follow-up, leaving a total of 57 patients in the final analysis (n = 29 in the TRLB group and n = 28 in the control group). The main results of our study demonstrated that bilateral ultrasound-guided TRLB is associated with decreased perioperative fentanyl consumption, post-extubation pain scores, time to first analgesia request, time to extubation, and ICU length of stay.

Pediatric open cardiac surgery causes moderate to severe postoperative pain that arises mainly from the median sternotomy incision and, to a lesser extent, the drainage tube sites [12]. An appropriate multimodal analgesic regimen, including the use of a regional anesthetic technique, is usually used to control pain after cardiac surgery. Currently, most anesthetists prefer to use ultrasound-guided muscle plane blocks instead of spinal, caudal, epidural, or paravertebral analgesia due to the associated risk of epidural hematoma after full heparinization [3,4]. Bilateral ultrasound-guided erector spinae plane blocks [13−15] and transversus thoracis muscle plane blocks [16,17] are associated with effective postoperative analgesia after pediatric cardiac surgery. The present study is the first to use bilateral TRLB for analgesia after cardiac surgery via midline sternotomy incision.

The retrolaminar block is a simple and easy to perform fascial plane block that involves the deposition of local anesthetics between the posterior surface of the thoracic vertebral lamina and overlying paraspinal muscles [18]. In this study, we injected a relatively large volume of 0.25% bupivacaine (0.4 ml/kg) because the distribution of local anesthetics and the analgesic efficacy of TRLB are volume-dependent [19]. The injectate increases the pressure in the non-compliant retrolaminar space, allowing for the ventral spread of local anesthetics into the paravertebral and epidural spaces to block the dorsal and ventral rami of the spinal nerves. The injectate also spreads laterally in the fascial plane along the ventral surface of the erector spinae muscle to block the cutaneous and small branches of the intercostal nerves, producing analgesia in the hemithorax [5]. Currently, the exact mechanism of TRLB analgesia is not completely understood. We postulated that the principal mechanism is the spread of the injected local anesthetic to the paravertebral and epidural spaces, producing analgesia similar to or somewhat inferior to that of paravertebral blocks.

### Table 2. Intraoperative Fentanyl Consumption and Postoperative Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>TRLB group (n = 29)</th>
<th>Control group (n = 28)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraoperative fentanyl consumption (μg/kg)</td>
<td>9.3 ± 1.2</td>
<td>12.5 ± 1.4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Time to extubation (h)</td>
<td>2 (1, 3)</td>
<td>6 (4.5, 6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Time to first rescue analgesia after extubation (h)</td>
<td>7 (5, 8)</td>
<td>2 (1, 2)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>First 24 h post-extubation fentanyl consumption (μg/kg)</td>
<td>6.9 ± 2.1</td>
<td>16.6 ± 2.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>ICU length of stay (h)</td>
<td>23.8 ± 3.2</td>
<td>30.3 ± 3.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>TRLB complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vascular/neurological injury</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Local anesthetic toxicity</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>6 (20.6)</td>
<td>8 (28.2)</td>
<td>0.550</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7 (24.1)</td>
<td>8 (28.5)</td>
<td>0.770</td>
</tr>
</tbody>
</table>

Values are presented as mean ± SD, median (Q1, Q3), or number (%) of patients. TRLB: thoracic retrolaminar block, ICU: intensive care unit.

**Fig. 4.** Postoperative modified objective pain score (MOPS). Values are presented as median (Q1, Q3). The thick black line in the boxplot represents the median, the upper border represents Q3 and the lower border represents Q1. *P < 0.05 and †P < 0.001 vs. TRLB group.
Several studies have demonstrated the analgesic efficacy of TRLB. Nobukuni et al. [20] compared the postoperative efficacy of TRLB and thoracic epidural analgesia after video-assisted thoracoscopic surgery and found that TRLB was as effective as epidural analgesia in controlling postoperative pain in terms of pain scores and opioid consumption. Sotome et al. [21] found that the postoperative analgesic effects of TRLB were equivalent to those of erector spinae plane blocks after breast surgery. Zhao et al. [22] found that the analgesic effects of TRLB were superior to those of erector spinae blocks in patients with multiple rib fractures. Wang et al. [9] compared ultrasound-guided TRLBs and paravertebral blocks for postoperative analgesia in patients undergoing video-assisted thoracoscopic surgery and found that the paravertebral block resulted in better analgesia than the TRLB. In contrast, Hwang et al. [23] conducted a randomized placebo study that aimed to assess the analgesic efficacy of a single injection of ultrasound-guided TRLB after breast surgery and reported that TRLB did not reduce postoperative analgesic consumption. We postulate that the lack of efficacy of TRLB in reducing opioid consumption after radical mastectomy could be attributed to the complexity of the surgery, which includes axillary lymphadenectomy.

In our study, TRLB was associated with a reduced time to extubation and ICU length of stay. This is consistent with other chest wall fascial plane blocks, including the bilateral erector spinae plane block [13–15] and the transversus thoracis muscle plane block [16,17]. These findings could be explained by the reduction in perioperative opioid consumption. Decreasing the time to extubation and ICU length of stay allows for fast-track cardiac surgery, decreases costs, and saves resources.

In this study, TRLB complications (hypotension, pneumothorax, vascular or neurological injury, and local anesthetic toxicity) were not reported. Ultrasound-guided TRLB is simple, easy to perform, and theoretically safer than thoracic epidural analgesia and paravertebral blocks since the block needle is inserted towards the vertebral lamina and thus away from any important vessels, the pleura, and the dura. Additionally, sonographic visualization of the block needle is better in children than in adults.

Our study had several limitations. First, the sample size was small in this single-center study, and we could thus not determine the actual incidence of TRLB complications. Future multicenter studies with larger sample sizes are recommended. Second, we did not assess the dermatomal spread of the TRLB because we performed TRLBs in children after anesthesia induction. Further studies in conscious adults are necessary. Third, the smallest effective volume of local anesthetics is unknown; we used a relatively large volume (0.4 ml/kg) of 0.25% bupivacaine to ensure the efficacy of the block. Fourth, a single injection of a local anesthetic was used in this study, which resulted in a limited duration of analgesia. Therefore, continuous infusions of local anesthetics is recommended in future studies to obtain more prolonged analgesia. Finally, we did not measure the serum concentration of bupivacaine because of the unavailability of the above technology in our institutional hospital.

Based on the findings of this study, we conclude that ultrasound-guided bilateral TRLB performed at the level of the fourth thoracic vertebra is effective in providing postoperative analgesia in terms of opioid consumption and postoperative pain scores in children undergoing open cardiac surgery via median sternotomy incision. Additionally, TRLB is associated with early tracheal extubation and a short ICU length of stay.


Methotrexate (MTX) is an immunosuppressive agent indicated for malignant and chronic inflammatory states [1,2]. It is used as a disease-modifying agent in patients with rheumatoid arthritis to halt disease progression and provide symptomatic relief. Low-dose MTX (15–25 mg per week) is usually effective for rheumatoid arthritis. Toxic effects can be seen if the daily dose exceeds 500 mg/m² of the body surface area, which manifests as mucocutaneous lesions and life-threatening multiorgan dysfunction [3]. We report a case of severe MTX toxicity leading to fatal multiorgan failure and death following repeated contrast imaging with intravenous iohexol.

Background: Methotrexate is an antimetabolite drug that blocks dihydrofolate reductase and impairs cellular DNA synthesis. Administration of intravenous iodinated radiocontrast agents can cause life-threatening toxicity in patients receiving methotrexate.

Case: A 60-year-old female patient with rheumatoid arthritis underwent a craniotomy and clipping of a distal anterior cerebral artery aneurysm. The patient had been on low-dose oral methotrexate for the previous 5 years, which was discontinued two days before surgery. The patient received the first intravenous contrast agent injection (iohexol) during diagnostic cerebral angiography one day prior to surgery (50 ml) and the second contrast dose on the first postoperative day (60 ml). The patient developed severe methotrexate toxicity, leading to fatal multiorgan failure and death following repeated contrast imaging with intravenous iohexol.

Conclusions: Even though low-dose oral methotrexate has minor adverse effects, life-threatening toxicity can be precipitated in the presence of iodinated contrast agents.

Keywords: Anesthesia; Iohexol; Leucovorin; Methotrexate; Rheumatoid arthritis; Toxicity.

Methotrexate (MTX) is an immunosuppressive agent indicated for malignant and chronic inflammatory states [1,2]. It is used as a disease-modifying agent in patients with rheumatoid arthritis to halt disease progression and provide symptomatic relief. Low-dose MTX (15–25 mg per week) is usually effective for rheumatoid arthritis. Toxic effects can be seen if the daily dose exceeds 500 mg/m² of the body surface area, which manifests as mucocutaneous lesions and life-threatening multiorgan dysfunction [3]. We report a case of severe MTX toxicity leading to fatal multiorgan dysfunction in a patient on low-dose oral MTX who received two doses of an iodinated contrast agent.

Case Report

The authors certify that written informed consent for publication was obtained from the patient or guardian.

A 60-year-old woman diagnosed with a distal anterior cerebral artery aneurysm was scheduled for a craniotomy and clipping of the aneurysm. The patient was known to have rheumatoid arthritis and to be taking 15 mg of oral MTX per week for the previous five years, the last dose of which was taken two days prior to admission. A diagnostic cerebral
angiogram was performed on admission with 50 ml of intravenous iohexol (Omnipaque, 350 mg iodine/ml, GE Healthcare Pvt. Ltd, India) before surgery. Preoperative blood test results were unremarkable, and echocardiography revealed normal contractility, with an ejection fraction of 60%. The patient successfully underwent aneurysm clipping the day after admission, and the trachea was extubated following an uneventful intraoperative course. The patient was monitored in the neurocritical care unit in the immediate postoperative period and was treated with intravenous levetiracetam, mannitol, and paracetamol.

Gross abdominal distension was noted on the first postoperative day. Her blood test results were normal, except for a serum potassium level of 2 mmol/L. Emergent contrast-enhanced computed tomography (CECT) of the abdomen was performed with 60 ml of intravenous iohexol to rule out other possibilities. As the CECT of the abdomen was unremarkable, a diagnosis of postoperative paralytic ileus was considered, and intravenous potassium correction was initiated. The patient developed diffuse erythematous skin rashes 24 h after the CECT of the abdomen was conducted (Fig. 1). Suspecting an adverse drug event, antibiotics and anticonvulsants were temporarily withheld. On the third postoperative day, an increase in liver enzymes and doubling of creatinine levels were noted. The blood counts revealed severe pancytopenia with hemoglobin, leukocyte, and platelet counts of 6.6 g/dl, 3.4 × 10^9/L, and 42 × 10^9/L, respectively. MTX toxicity due to repeated contrast agent exposure was suspected, and the patient was hydrated with intravenous fluids to maintain a positive balance. As per the rheumatologist’s advice, leucovorin rescue was initiated at 75 mg/day in divided doses. However, in the subsequent days, the patient suffered a progressive decline in cell counts with worsening hepatic and renal parameters. On the fifth postoperative day, the patient required trachea intubation and lung ventilation owing to her deteriorated sensorium. An emergent plain computed tomography (CT) brain scan was performed, which did not reveal any apparent detectable pathology. The patient developed severe hypotension on the same day (postoperative day 5) and bedside echocardiography revealed global hypokinesia with mild pericardial effusion. Stabilization of the patient’s hemodynamics required supramaximal doses of intravenous noradrenaline and dobutamine. The patient developed severe bradycardia and cardiac arrest within a few hours, with no return of spontaneous circulation, despite cardiopulmonary resuscitation.

**Discussion**

The clinical manifestations of severe MTX toxicity include pancytopenia due to bone marrow suppression, skin rashes, acute renal tubular failure due to crystallization of MTX in the renal tubules, intracranial bleeding, leukoencephalopathy, and cardiac failure, leading to multiorgan dysfunction and rapid progression to death. In patients receiving high-dose intravenous MTX, toxicity can be triggered by an intravenous iodinated contrast agent [4,5]. Non-steroidal anti-inflammatory drugs can induce similar adverse reactions in patients taking low-dose MTX [6]. However, fatal MTX toxicity following radiocontrast administration in patients receiving low-dose oral MTX has not been described previously. The differential diagnoses for the initial mucocutaneous lesions included toxic epidermal necrolysis, pemphigus vulgaris, and severe systemic lupus erythematosus. This patient had a long history of MTX ingestion, and the symptoms were temporally associated with contrast drug administration. The mucocutaneous lesions also preceded organ dysfunction. All of these findings suggested MTX toxicity and helped to rule out other possibilities. The patient received the first contrast injection 18 h prior to the surgery and the second dose 24 h after the surgery. The administration of mannitol (nephrotoxic agent) was the key precipitating event. Intravenous hydration, alkalinization of the urine, and leucovorin rescue are the standard treatment protocols for MTX toxicity. However, despite these measures, the patient could not be saved.

MTX-induced cerebral leukoencephalopathy can result in stroke-like symptoms or a sudden decrease in sensorium levels [7]. The sensorium of our patient deteriorated in the late stages.

**Fig. 1.** Erythematous skin lesion due to methotrexate toxicity.
despite a normal brain CT, which can be attributed to the above factors. Following oral ingestion, MTX undergoes rapid intracellular uptake in various tissues and is transformed to methotrexate polyglutamate, which inhibits the dihydrofolate reductase enzyme [8]. Even though the red blood cell concentration of methotrexate polyglutamate falls rapidly following oral cessation, there can be a slow and sustained release of the molecules from various tissue storage sites into the circulation, which can predispose a patient to toxicity by factors such as dehydration and renal dysfunction by delaying drug clearance. Glucarpidase is an MTX antidote that reduces extracellular MTX and facilitates its elimination [9]. Owing to its unavailability, this agent was not administered to the patient. To avoid dangerous drug interactions, it is recommended that the administration of contrast agents be delayed until the plasma MTX concentration falls below 0.05 mmol/L; therefore, waiting a minimum of 3–7 days between the last dose of MTX and the administration of a contrast agent is imperative [4]. However, as ruptured intracranial aneurysms require urgent treatment, as in this case, surgery cannot always be delayed and serum level estimations are not routinely available.

In conclusion, fatal multiorgan dysfunction can occur in patients receiving low-dose oral MTX who undergo contrast imaging; thus, extreme vigilance is necessary.

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None.

**Conflicts of Interest**

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

**Author Contributions**

Balaji Vaithialingam (Conceptualization; Data curation; Investigation; Writing – original draft; Writing - review & editing)

Radhakrishnan Muthuchellappan (Writing – review & editing)

Mouleeswaran Sundaram (Writing – original draft)

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**References**


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Ultrasound-guided regional anesthesia (USGRA) is commonly performed with B-mode (2D) imaging using high-frequency linear array and low-frequency curved array transducers. With biplane imaging (BI), phased array and high-frequency curved array (endocavity) transducers are available to evaluate cardiac and fetal anatomy and for needle guidance during transrectal procedures. BI capabilities have recently been incorporated into high-frequency linear transducers, making BI technology available for USGRA. During a peripheral nerve block (PNB), real-time BI eliminates the need to rotate the transducer to obtain both short-and long-axis views of the nerves, vessels, bones, muscles, or fascial planes. In addition, the needle is displayed in-plane and out-of-plane, and the spread of the local anesthetic can be visualized in two orthogonal planes simultaneously. Using BI for USGRA can decrease procedure time and the number of attempts and needle passes, improve block success and quality, and maximize safety by mitigating the risk of unintended intraneural, intrapleural, and intravascular injection. We report the novel use of BI for USGRA of the thorax, abdomen, and upper and lower extremities.

This technical report was exempt from internal review board approval since patient identifiable information were removed per institutional policies at the University of Texas Health Science Center at Houston and Memorial Hermann Hospital System, USA. Deidentified images were obtained from a regional anesthesia image bank. The highest quality images from each major region of the body were selected. Upper extremity biplane USGRA images, which are shown in Figs. 1A–1C, include interscalene, infraclavicular, and axillary brachial plexus blocks. Images of truncal fascial plane blocks are presented in Figs. 1D–1F, which include the superficial parasternal block, deep serratus plane block, and rectus sheath block. Figs. 1G and 1H highlight the high thoracic paravertebral block and the low thoracic erector spinae plane block. Finally, lower extremity biplane USGRA images of the femoral nerve block, distal femoral triangle block and popliteal sciatic nerve block are depicted in Figs. 1I–1K.

The Butterfly IQ+ (Butterfly Network, Inc., USA) ultrasound attached to either an iPhone 11 (iPhone 11 Pro-Butterfly iQ app) or a fifth generation iPad mini (iPad Butterfly iQ app) was utilized to perform biplane USGRA. The standard B-mode image (reference plane) is displayed at the bottom of the screen, while the orthogonal plane that correlates to the curser (perpendicular plane) is shown at the top of the screen. The transducer was positioned to be simultaneously perpendicular to the object of interest in the short axis and parallel in the long axis to ensure optimal BI. A 20–22 gauge blunt-tip 50–100 mm echogenic block needle (B Braun Ultraplex 360, USA) or 18-gauge SonoTAP Tuohy needle (PAJUNK GmbH Medizintechnologie, Germany) was advanced to the target location for each block using the reference plane and an in-plane technique. The biplane cursor

The novel use of biplane imaging for ultrasound-guided regional anesthesia

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Ultrasound-guided regional anesthesia (USGRA) is commonly performed with B-mode (2D) imaging using high-frequency linear array and low-frequency curved array transducers. With biplane imaging (BI), phased array and high-frequency curved array (endocavity) transducers are available to evaluate cardiac and fetal anatomy and for needle guidance during transrectal procedures. BI capabilities have recently been incorporated into high-frequency linear transducers, making BI technology available for USGRA. During a peripheral nerve block (PNB), real-time BI eliminates the need to rotate the transducer to obtain both short-and long-axis views of the nerves, vessels, bones, muscles, or fascial planes. In addition, the needle is displayed in-plane and out-of-plane, and the spread of the local anesthetic can be visualized in two orthogonal planes simultaneously. Using BI for USGRA can decrease procedure time and the number of attempts and needle passes, improve block success and quality, and maximize safety by mitigating the risk of unintended intraneural, intrapleural, and intravascular injection. We report the novel use of BI for USGRA of the thorax, abdomen, and upper and lower extremities.

This technical report was exempt from internal review board approval since patient identifiable information were removed per institutional policies at the University of Texas Health Science Center at Houston and Memorial Hermann Hospital System, USA. Deidentified images were obtained from a regional anesthesia image bank. The highest quality images from each major region of the body were selected. Upper extremity biplane USGRA images, which are shown in Figs. 1A–1C, include interscalene, infraclavicular, and axillary brachial plexus blocks. Images of truncal fascial plane blocks are presented in Figs. 1D–1F, which include the superficial parasternal block, deep serratus plane block, and rectus sheath block. Figs. 1G and 1H highlight the high thoracic paravertebral block and the low thoracic erector spinae plane block. Finally, lower extremity biplane USGRA images of the femoral nerve block, distal femoral triangle block and popliteal sciatic nerve block are depicted in Figs. 1I–1K.

The Butterfly IQ+ (Butterfly Network, Inc., USA) ultrasound attached to either an iPhone 11 (iPhone 11 Pro-Butterfly iQ app) or a fifth generation iPad mini (iPad Butterfly iQ app) was utilized to perform biplane USGRA. The standard B-mode image (reference plane) is displayed at the bottom of the screen, while the orthogonal plane that correlates to the curser (perpendicular plane) is shown at the top of the screen. The transducer was positioned to be simultaneously perpendicular to the object of interest in the short axis and parallel in the long axis to ensure optimal BI. A 20–22 gauge blunt-tip 50–100 mm echogenic block needle (B Braun Ultraplex 360, USA) or 18-gauge SonoTAP Tuohy needle (PAJUNK GmbH Medizintechnologie, Germany) was advanced to the target location for each block using the reference plane and an in-plane technique. The biplane cursor
Fig. 1. (A) Interscalene brachial plexus block. The ultrasound was placed over the clavicle in a transverse orientation. In the reference plane, the orientation marker (OM) is lateral, and the brachial plexus, ASM, MSM, VA, and the SCM are displayed in the short-axis view, while the seventh cervical transverse process is seen in the long-axis view. The needle trajectory is in-plane lateral to medial. The biplane cursor is over the C5 and C6 nerve roots. In the perpendicular plane, the icon is caudal. The needle trajectory is out-of-plane, and the tip can be seen between C5 & C6 in long-axis. The craniocaudal spread of the local anesthetic (LA) within the brachial plexus is visualized. In all images, the white arrow represents the needle shaft on the ultrasound and the white arrowhead represents the needle tip on the ultrasound. (B) Infraclavicular brachial plexus block. The ultrasound was placed over the lateral chest in a sagittal orientation. In the reference plane, the OM is cranial with the brachial plexus and AxA are displayed in short-axis. The needle trajectory is in-plane with the biplane cursor directly over the AxA. In the perpendicular plane, the icon is lateral. The needle trajectory is out-of-plane. The AxA and the mediolateral spread of LA are visualized in long-axis. (C) Axillary brachial plexus block. The ultrasound was placed over the axilla in a sagittal orientation. In the reference plane, the OM is superior, and the branches of the brachial plexus, AxA, and vein are displayed in short-axis. The needle trajectory is in-plane in the superior-inferior direction. The needle reverberation artifact makes it challenging to identify the MN and McN in this image. The biplane cursor is located directly over the AxA. In the perpendicular plane, the icon is lateral. The needle trajectory is out-of-plane. The AxA and mediolateral spread of LA within the brachial plexus are visualized in long-axis. The needle is not seen on the long axis view in this image as the biplane sector is distal to the needle tip. (D) Superficial parasternal block. The ultrasound transducer is placed over CC4 in a sagittal orientation. In the reference plane, the OM is medial, CC4 and CC5 are displayed in short-axis, while the IMV is seen in long-axis. The needle trajectory is in-plane. The biplane cursor is directly over the fourth intercostal space. The needle trajectory is out-of-plane, and the shaft of the needle can be seen traversing the PMM. The internal mammary vessels and the mediolateral spread of LA between the PMM and ICM are seen in short-axis. (E) Deep serratus plane block. The ultrasound was placed over the posterior axillary line in a sagittal orientation. In the reference plane, the OM is cranial, the fifth rib is displayed in short-axis. The needle trajectory is in-plane. The biplane cursor is directly over the fifth rib. In the perpendicular plane, the icon is anterior. The needle trajectory is out-of-plane with the needle tip visible deep to the SAM. The fifth rib and the anteroposterior spread of the LA are visualized in long-axis. (F) Rectus sheath block. The ultrasound was placed over the mid-abdomen in a sagittal orientation. In the reference plane, the OM is cranial, and the fifth rib is displayed in short-axis. The needle trajectory is in-plane. The biplane cursor is directly over the tip of the needle. In the perpendicular plane, the icon is cranial. The craniocaudal spread of the LA and the tip of the needle are visualized in short-axis. The white arrow represents the needle on the ultrasound. The white arrowhead represents the needle tip on the ultrasound. (G) Thoracic paravertebral block. The ultrasound was placed over the 4TP in a transverse orientation. In the reference plane, the OM is lateral, and the 4TP is displayed in long-axis. The needle trajectory is in-plane. The biplane cursor is directly over the paravertebral space. In the perpendicular plane, the icon is caudal. 5TP and the craniocaudal spread of the LA are visualized in short-axis.
The white arrow represents the needle on the ultrasound. (H) Erector spinae plane block. The ultrasound was placed over the tenth TP in a sagittal orientation at an approximately 20-degree clockwise rotation. In the reference plane, the OM is caudal, and the TP is displayed in short-axis. The needle trajectory is in-plane. The bplane cursor is directly over the TP. In the perpendicular plane, the icon is lateral. The TP and the mediolateral spread of the local anesthetic are visualized in long-axis. The white arrow represents the needle on the ultrasound. The white arrowhead represents the needle tip on the ultrasound. (I) Femoral nerve block. The ultrasound is placed over the inguinal ligament in a transverse orientation to identify the femoral nerve, artery, and vein. In the reference plane, the OM is medial, and the SFA, SN, and NVM are displayed in short-axis. The circumferential spread of the LA around the SFA is noted in this plane. The biplane cursor is located over the SFA. The icon is superior in the perpendicular plane. The SFA and craniocaudal spread of the LA are visualized in long-axis. (J) Saphenous nerve block. The ultrasound was placed over the long saphenous artery in a transverse orientation. In the reference plane, the OM is lateral, and the SN and CP nerve are displayed in short-axis after a popliteal sciatic block. The circumferential spread of the local anesthetic is visualized in this plane. The biplane cursor is located over the OM and PA. The icon is superior in the perpendicular plane. Superficially, the SN is visualized in long-axis. Inferiorly, the OM, PA, and craniocaudal spread of the local anesthetic are visualized in long-axis. SCV: sternocleidomastoid muscle, ASM: anterior scalene muscle, MSM: middle scalene muscle, C: vertebral artery, C5: fifth cervical nerve root, C6: sixth cervical nerve root, C7: seventh cervical nerve root, PMM: pectoralis major muscle, PmM: pectoralis minor muscle, AxA: axillary artery, PC: posterior cord, AxV: axillary vein, MC: medial cord, LC: lateral cord, AT: adipose tissue, CT: conjoint tendon, TM: triceps muscle (C), BBM: biceps brachii muscle, CBM: coracobrachialis muscle, MCN: musculocutaneous nerve, MN: medial nerve, RN: radial nerve, UN: ulnar nerve, SCM: intercostal muscles, IMV: internal mammary vein, IMA: internal mammary artery, CC4: fourth costal cartilage, LDM: latissimus dorsi muscle, SAM: serratus anterior muscle, RAM: rectus abdominis muscle, RS: rectus sheath, TM: trapezius muscle (G&H), RM: rhomboid muscle, ESM: erector spinae muscle, 5TP: fifth transverse process, 4TP: fourth transverse process, TP: transverse process, FL: fascia lata, FI: fascia iliaca, FN: femoral nerve, IM: iliacus muscle, SM: sartorius muscle, SFA: superficial femoral artery, VM: vastus medialis muscle, AL: adductor longus muscle, NVM: nerv to vastus medialis, SN: saphenous nerve (J), BFMM: biceps femoris muscle, SMM: semimembranosus muscle, SN: sciatic nerve (K), TN: tibial nerve, PA: popliteal artery, CP: common peroneal nerve, PV: popliteal vein.

was placed over the needle tip for visualization in the short-axis view, on the neurovascular structures to obtain images of the entire nerve or artery in the long-axis view, and/or bone, muscle, or fascial planes of interest to obtain an orthogonal view. The biplane spread of the local anesthetic was observed upon injection.

BI can be activated at any time; however, due to the reduced screen size and image quality, we recommend timing it on a case-by-case basis. For superficial blocks, where needle visualization is less challenging, BI can be activated when the optimal monoplane view is obtained in B-mode. For deeper blocks, where needle localization is more difficult to confirm sonographically, we recommend advancing the needle in B-mode and activating BI once the needle tip is in the desired location to improve the accuracy and visualization of the local anesthetic injectate as it spreads orthogonally through the tissue planes.

The use of BI for superficial ultrasound-guided (USG) vascular access has been reported using low- and high-frequency matrix transducers. One study concluded that the enhanced visualization of structures and needles leads to improved performance and feasibility. For internal jugular vein (IJV) cannulation using the short-axis approach, applying BI with a low-frequency matrix transducer resulted in fewer puncture attempts and needle redirections, a lower incidence of posterior wall punctures, and successful puncture of the IJV on the first attempt in 90% of cases vs. 50% with B-mode [1]. The low-frequency transducer used in this study, which is designed for imaging large, superficial vascular structures, is acceptable for IJV cannulation; however, it provides suboptimal visualization of small superficial structures, such as nerve roots for USGRA [2]. For the case presented by Convissar et al. [3], a semiconductor-based ultrasound with a high-frequency setting (vascular) was used to perform radial artery cannulation with BI. To date, this case is the only report of BI needle guidance for high-frequency ultrasound. The use of BI for USGRA has not previously been reported. Therefore, in this study, we included images of the USG PNB and fascial plane blocks using the novel application of a high-frequency ultrasound transducer (Figs. 1A–1K).

The spread of injectate following the PNB was studied through cadaveric dissection after dye or radiologic contrast injections. However, this type of study has been criticized since postmortem alterations in tissue integrity could affect the patterns of injectate spread and may not accurately represent clinical situations. In the clinical setting, arterial pulsations, muscle contractions, respiration, and differences in tissue resistance can influence the spread of local anesthetics [4]. Although BI technology is not currently available in the most common ultrasound systems used for USGRA, enhanced imaging may improve our understanding of sonoanatomy and the spread of local anesthesia. In 2019, a high-frequency matrix linear array piezoelectric transducer was introduced into the market for vascular applications (Philips XL
14-3 mMatrix, Netherlands). In 2020, BI for a high-frequency handheld ultrasound became commercially available (Butterfly Network, Inc., USA). Rapid technological advances in ultrasound coupled with the potential for enhanced superficial imaging might lead to a future where matrix 3- and 4-dimensional imaging for USGRA is the standard.

BI is a new feature in high-frequency matrix ultrasound transducers that can improve needle localization and enhance visualization of local anesthetic spread during USGRA. We reported on the novel application of BI for USGRA. More studies are needed to assess the utility of BI in USGRA and evaluate its impact on the safety and delivery of regional anesthesia.

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Conflicts of Interest

No potential conflict of interest relevant to this article was reported. Nadia Hernandez and Amit Pawa have received honoraria from Butterfly Network, Inc. for educational activities unrelated to this article.

Author Contributions

Nadia Hernandez (Conceptualization; Visualization; Writing – original draft; Writing – review & editing)
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References

We read the recent original article by Abdelbaser et al. [1] outlining the efficacy of a bilateral thoracic retrolaminar block (TRLB) for perioperative analgesia in pediatric open-heart surgery with great interest. We would like to congratulate the authors on their novel study, which employed a meticulous randomized double-blinded approach that involved the administration of a local anesthetic block after anesthesia induction in the study group and saline in the control group, after which both underwent surgical interventions of a comparable duration of approximately 3 h [1]. Nonetheless, the index study findings must be interpreted cautiously in consideration of the following observations.

The authors found significant statistical differences between the TRLB (n = 29) and the control (n = 28) groups with regard to the first 24 h post-extubation fentanyl consumption and postoperative modified objective pain scores (MOPS), measured at 0, 2, 4, 8, 12, and 16 h post-extubation [1]. Importantly, the median (Q1, Q3) time (h) of extubation was significantly lower in the TRLB group (2 [1, 3]) than in the control group (6 [4.5, 6]) [1]. This significant difference in time-to-extubation complicates a sound comparison of the postoperative MOPS between the two groups. Since strictly referenced time periods after extubation were used [1], the MOPS evaluations were likely quite variable in relation to the actual time the single block injections were administered between the two groups. Using the quoted figures from the study by Abdelbaser et al. [1], a patient in the TRLB group was likely first assessed for MOPS-0 between 4 and 6 h after the block administration compared to a much later MOPS-0 evaluation between 7.5 and 9 h after the block for the control group.

Drawing on our research experience, we also acknowledge the practicalities of postoperative MOPS assessments [2]. Therefore, any perioperative analgesia study of inter-dependent objectives needs to closely account for inconsistencies resulting from the practicalities. In this context, it could have been more appropriate to evaluate the time to first postoperative rescue analgesia starting from admission to the intensive care unit rather than highlighting the inter-group differences in the time to rescue analgesia by measuring this parameter from extubation, as was the case in the study by Abdelbaser et al. [1]. Needless to say, these differences could result in the misinterpretation of the “true” analgesic potential of novel modalities, which is particularly relevant for studies with small sample sizes [3,4].

However, the study by Abdelbaser et al. demonstrated the role of TRLB in reducing the intraoperative fentanyl requirement, which is noteworthy and resonates well with the paradigm shift towards opioid-sparing cardiac anesthesia [1,5]. We were equally intrigued by the analgesic management of cardiopulmonary bypass in their study, as they...
discussed the administration of prophylactic doses of fentanyl prior to skin incision and sternotomy and supplemental doses of fentanyl in the event of a $\geq 20\%$ increase in the mean arterial blood pressure and/or heart rate above baseline [1].

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**References**

Notice

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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.⁵ 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.⁶

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], Mg⁺⁺ [X], Mg⁺⁺ [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 emphasized 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 be exceed 50. For exceeding the number of references, it should be negotiated with the Editorial Board. References should be numbered consecutively in the order in which they are first mentioned in the text. Provide footnotes in the body text section. All of the references should be stated in English, including author, title, name of journal, etc.

- If necessary, the editorial board may request original documents of the references.


- Six authors can be listed. If more than 6 authors are listed, only list 6 names with ‘et al.’

- Provide the start and final page numbers of the cited reference.

- Abstracts of conferences are not allowed to be included in the references. The American Society of Anesthesiologists (ASA) refresher course lecture is not acceptable as a reference.

- Description format

A. Regular journal

Author name. Title of journal Name of journal published
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).

3) 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.

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

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

6) Figures (line drawings) should be clearly printed in black and white.

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

8) 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.

9) 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.

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.

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 kept. If necessary, the editor or reviewers may request copies of these documents. Rarity of a disease condition is itself not an acceptable justification for a case report.

1) Title page: Same as clinical and experimental studies.
2) Manuscript
   ① Title and Running title.
   ② Abstract: All case reports should contain a structured abstract that is written only in English. Provide an abstract of no more than 150 words. It should contain 3 subsections: Background, Case, and Conclusions. A list of keywords, with a minimum of 6 and maximum of 10 items, should be included at the end of the abstract. The selection of keywords should be from MeSH (http://www.ncbi.nlm.nih.gov/mesh) and should be written in small alphabetic letters with the first letter in capital letter. Separate each word by a semicolon (;), and mark a period (.) at the end of the last word.
   ③ Introduction: Should not be separately divided. Briefly describe the case and background without a title.
   ④ Case report: Describe only the clinical statement that is directly related to diagnosis and anesthetic management.
   ⑤ Discussion: Briefly discuss the case, and state conclusions at the end of the case. Do not structure the conclusion section separately.
   ⑥ References: Do not exceed 15 references. For exceeding the number of references, it should be negotiated with the Editorial Board. 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.
   ⑦ Tables and figures: Proportional to clinical and experimental studies.

4) Reviews
Review articles synthesize previously published material into an integrated presentation of our current understanding of a topic. Review articles should describe aspects of a topic in which scientific consensus exists, as well as aspects that remain controversial and are the subject of ongoing scientific disagreement and research. Review articles should include unstructured abstracts equal to or less than 250 words in English. Figures and tables should be provided in English. References should be obviously related to documents and should not be exceed 100. For exceeding the number of references, it should be negotiated with the Editorial Board. Body text should not exceed 30 A4 pages, and the number of figures and tables should be equal to or less than 6.

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

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

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

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