Special Issue: Systematic review and Meta-analysis

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Aims and Scope

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

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

The journal has been partly supported by the Korean Federation of Science and Technology Societies. KJA is indexed/tracked/covered by ESCI (Emerging Sources Citation Index), KCI (indexed by the National Research Foundation of Korea), PubMed, PubMed Central, EBSCOhost Databases, KoreaMed, KoMCI Web, KoreaMed Synapse, Science Central, SCOPUS, Embase, CAS (Chemical Abstracts Service), WPRIM (Western Pacific Regional Index Medicus), DOI, DOAJ (Directory of Open Access Journal) and Google Scholar. It has been indexed in MEDLINE by U.S. National Library of Medicine. The KCI journals have been seamlessly integrated into the Web of Science since 2014.
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Epidural analgesia versus intravenous analgesia after minimally invasive repair of pectus excavatum in pediatric patients: a systematic review and meta-analysis

Min Hee Heo, Ji Yeon Kim, Jung Hyeon Kim, Kyung Woo Kim, Sang Il Lee, Kyung-Tae Kim, Jang Su Park, Won Joo Choe, Jun Hyun Kim

Letter to the Editor

Self-learning software tools for data analysis in meta-analysis

Thrivikrama Padur Tantry, Harish Karanth, Pramal Karkala Shetty, Dinesh Kadam

Corrigendum

Sex/gender and additional equity characteristics of providers and patients in perioperative anesthesia trials: a cross-sectional analysis of the literature

Cole Etherington, Michael Wu, Sylvain Boet
Bridion (sugammadex) offered significantly fast and predictable recovery in patients with moderate to profound rocuronium-induced neuromuscular blockade (NMB).1,2

Reappearance of T1 for a re-administration of NMB: 98% of Bridion (sugammadex) patients had recovered to a TOF ratio of 0.9 compared with only 11% of neostigmine patients within 5 minutes. In comparison, it took 101 min for 98% of patients receiving neostigmine to recover to a TOF ratio of 0.9.3

Reappearance of T2-PTCs: The median [range (interquartile range)] time to recovery of the TOF ratio to 0.9 was 2.7 (1.2–16.1 [2.1–4.1]) min in the Bridion (sugammadex) group versus 49.0 (13.3–145.7 [35.7–65.6]) min in the neostigmine group.4

Indication of Bridion is reversal of neuromuscular blockade induced by rocuronium or vecuronium.5

The safety and efficacy of Bridion for pediatric and adolescent patients under the age of 18 has not been established.6

* For more information, please refer to the full prescribing information.

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1. Reappearance of T1 for reversal of a NMB: 98% of Bridion (sugammadex) patients had recovered to a TOF ratio of 0.9 compared with only 11% of neostigmine patients within 5 minutes. In comparison, it took 101 min for 98% of patients receiving neostigmine to recover to a TOF ratio of 0.9.

2. Reappearance of T2-PTCs: The median [range (interquartile range)] time to recovery of the TOF ratio to 0.9 was 2.7 (1.2–16.1 [2.1–4.1]) min in the Bridion (sugammadex) group versus 49.0 (13.3–145.7 [35.7–65.6]) min in the neostigmine group.4

3. Indication of Bridion is reversal of neuromuscular blockade induced by rocuronium or vecuronium.5

4. The safety and efficacy of Bridion for pediatric and adolescent patients under the age of 18 has not been established.6

---

**Study design**: This randomized, double-blind, parallel-group phase III study included 1016 adults. Patients received prophylactic infusion of sugammadex (16 mg/kg) to reverse rocuronium-induced moderate-to-severe neuromuscular blockade (NMB). Postoperative pain was assessed using a visual analog scale (VAS).

5. Before administering BRIDION, please refer to the full prescribing information.

---

**Drug Interactions**: Sugammadex (Bridion) is a non-opioid neuromuscular blocking agent that is a competitive inhibitor of rocuronium-induced neuromuscular blockade. BRIDION is contraindicated in patients with known hypersensitivity to sugammadex or any of its excipients.

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**Bridion Product Label. Ministry of Food and Drug Safety.**
Concepts and emerging issues of network meta-analysis
네트워크 메타분석의 개념 및 새로운 문제

EunJin Ahn, Hyun Kang
Department of Anesthesiology and Pain Medicine, Chung-Ang University College of Medicine, Seoul, Korea

 대부분의 질병은 두 가지 이상의 중재 또는 치료 방법이 있으며, 각각의 중재 또는 치료 방법의 우월성을 비교 평가하기 위한 방법으로 네트워크 메타분석(network meta-analysis, NMA) 연구가 증가하고 있다. NMA를 이해하기 위해서는 체계적인 문헌검토와 메타분석의 개념과 과정을 먼저 이해하여야 한다. 체계적인 문헌검토 및 메타분석과 마찬가지로 NMA의 구현 과정에는 주제 설정, 검색, 모든 관련 연구 선택 및 선택한 연구에서의 데이터 추출이 포함된다. NMA는 각 치료의 효과를 평가하기 위해 직접 및 간접 증거를 모두 사용하여 세 가지 이상의 중재 또는 치료 방법을 종합, 비교 및 분석한다. NMA를 수행할 때에는 여러 가지 변항이 존재할 수 있다. 따라서 NMA를 수행하기 전에 주요 가정이 충족되어야 한다. 이러한 주요 가정 중 일관성은 통계적으로 검정 가능한 방법이다. 이 논문은 NMA의 개념, 분석 및 해석 방법, 제시 방법을 소개하는 것을 목표로 NMA의 일관성과 새로운 문제를 평가하는 방법을 간략하게 소개하였다.

Keywords: Bayesian approach; Meta-analysis; Mixed treatment meta-analysis; Multiple treatment comparison meta-analysis; Network meta-analysis; Statistics; Systematic review.
Explanation of trial sequential analysis: using a post-hoc analysis of meta-analyses published in Korean Journal of Anesthesiology

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Keywords: Anesthesia; Medical education; Meta-analysis; Review; Sample size; Statistics.
Continuous peripheral nerve blocks compared to thoracic epidurals or multimodal analgesia for midline laparotomy: a systematic review and meta-analysis

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Keywords: Abdominal surgery; Catheters; Conduction anesthesia; Laparotomy; Multimodal analgesia; Nerve block; Statistics; Systematic review.

Continuous peripheral nerve blocks compared to thoracic epidurals or multimodal analgesia for midline laparotomy: a systematic review and meta-analysis

Continuous peripheral nerve blocks (CPNB) are used for abdominal surgery as an alternative to intravenous analgesics or thoracic epidurals. This study aimed to compare CPNB to multimodal analgesia and thoracic epidural analgesia for midline laparotomy. The study included 26 studies involving 1,646 patients. There were no statistically significant differences in pain control between CPNB and multimodal analgesia or thoracic epidural analgesia. CPNB was associated with lower opioid consumption compared to multimodal analgesia (MD: -31.52, 95% CI [-42.81, -20.22], lower evidence level). CPNB was also associated with shorter hospital stays compared to thoracic epidural analgesia (MD: -1.41, 95% CI [-2.45, -0.36], lower evidence level).

The use of CPNB should be considered in patients with contraindications to thoracic epidural analgesia.

Keywords: Abdominal surgery; Catheters; Conduction anesthesia; Laparotomy; Multimodal analgesia; Nerve block; Statistics; Systematic review.
Effect of single dose preoperative intravenous ibuprofen on postoperative pain and opioid consumption: a systematic review and meta-analysis

Su Yeon Kim, Sangseok Lee, Yeji Lee, Hyunho Kim, Kye-Min Kim

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배경: 이부프로펜(ibuprofen)은 수술 후 통증 조절 및 다중모드 진통요법을 위해 흔히 사용되고 있다. 하지만, 수술 전 이부프로펜 투여가 술 후 통증 및 아편유사제 사용량에 미치는 영향을 다룬 연구들에서 일치하지 않는 결과들이 보고되어 왔다. 본 연구에서는 체계적 문헌고찰 및 메타분석을 통하여 수술 전 이부프로펜 단회 정주가 수술 후 통증 및 아편유사제 사용량에 미치는 영향을 확인하고자 하였다.

방법: PubMed/MEDLINE, Embase, Cochrane Library (CENTRAL) 및 Web of Science 데이터베이스을 기반으로 2020년 5월까지 발표된 연구를 검색하였다. 수술 시작 전 이부프로펜을 단회 정주하고 수술 후 통증이나 아편유사제 사용량을 위약군과 비교한 무작위 대조군 연구를 대상으로 하였으며, 전신마취하에 시행된 수술이 아닌 경우는 대상에서 제외하였다.

결과: 총 여섯 개의 연구가 메타분석에 포함되었으며, 대상자 수는 366명이었다. 위약군과 비교할 때 수술 전 이부프로펜을 단회 정주할 경우, 0–10점으로 측정한 통증 점수는 수술 후 1시간째(MD: −1.64, 95% CI [−2.56, −0.72], P < 0.001, I² = 95%), 4–6시간째(MD: −1.17, 95% CI [−2.09, −0.26], P < 0.001, I² = 94%) 및 24시간째(MD: −0.58, 95% CI [−0.99, −0.18], P < 0.001, I² = 90%)에 유의하게 감소하였다. 또한, fentanyl 용량으로 환산한 아편유사제의 누적 사용량도 수술 후 4–6시간째(MD: −56.35 μg, 95% CI [−101.10, −11.60], P < 0.001, I² = 91%)와 24시간째(MD: −131.39 μg, 95% CI [−224.56, −38.21], P < 0.001, I² = 95%)에 유의하게 감소하였다.

결론: 전신마취하에 시행된 수술에서 수술 전 이부프로펜 단회 정주는 수술 후 24시간까지 통증 및 아편유사제 사용량을 감소시킬 수 있다. 다만, 포함된 연구 수가 적고, 연구 간 높은 이질성을 보였음을 감안할 때 이러한 결과를 일반화할 때에는 주의가 필요하다.

Keywords: Analgesics; Anesthesia and analgesia; Ibuprofen; Pain management; Postoperative pain; Preoperative period; Statistics; Systematic review.
Prophylactic measures to prevent cerebral oxygen desaturation events in elective beach-chair position shoulder surgeries: a systematic review and meta-analysis

Thrivikrama Padur Tantry\textsuperscript{1}, Baikunje Golitadka Muralishankar\textsuperscript{1}, Harish Karanth\textsuperscript{1}, Pramal Karkala Shetty\textsuperscript{1}, Sunil Purushotham Shenoy\textsuperscript{2}, Dinesh Kadam\textsuperscript{3}, Gururaj Tanthry\textsuperscript{1}, Rithesh Shetty\textsuperscript{1}

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Keywords: Arthroscopy; Oximetry; Prophylaxis; Randomized controlled trial; Shoulder; Sitting position; Statistics; Systematic review.

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배경: 어깨 수술을 위해 반좌위 자세(beach chair position, BCP)에서 마취 도중 대뇌 산소 불포화(cerebral desaturation event, CDE)에 대한 예방적 조치에 관하여는 평가된 적이 없다. 우리는 임상 환경에서 사용되는 다양한 예방 조치의 효과에 대해 체계적으로 분석하였다.

방법: 우리는 BCP에서 어깨 수술을 받은 마취 환자의 CDE 및 국소 대뇌 산소 포화도(rSO2), 경정맥 산소 포화도(SjvO2) 값을 보고한 임상시험에 대해 메타분석(PROSPERO; no. CRD 42020167285)을 수행하였다. 예방 조치의 유형(약리학적 또는 비약리학적)을 고려하여 하위군 분석을 계획하였다. 결과에는 (1) CDE에 대한 예방 조치가 있거나 없는 다른 시간 간격으로 기록된 rSO2 및 SjvO2 데이터가 포함되었으며, (2) CDE 및 저혈압을 경험한 환자의 수가 포함되었다.

결과: 12건의 연구(786명의 환자)가 분석에 포함되었다. 혈관작용제를 이용한 예방 조치의 경우 초기 및 전체 기간 동안 더 낮은 rSO2 값이 관찰되었다. 가장 낮은 rSO2 값은 혈관작용제 예방 조치시 더 높았다. CDE의 위험은 혈관작용제 예방조치시 더 높았다. 하위군 분석에서는 경도의 고탄산혈증을 목표로 하는 예방조치가 대뇌 산소 공급을 보존하는데 효과적인 것으로 확인되었다. 이와 비슷하게, 경도 고탄산혈증 목표법은 자세 변화에 따른 rSO2의 감소를 방지하였다. 메타회귀 분석결과 경도 고탄산혈증 목표법과는 대조적으로 혈관작용제 예방 조치법이 통계적으로 유의미하게 가장 높은 추정치를 보였으며, CDE가 발생하지 않음을 가능성을 경도 고탄산혈증 목표법에서 더 높았다. rSO2와는 달리 대부분의 예방적 방법은 저혈압 발생을 감소시켰다.

결론: 경도의 고탄산혈증을 목표로 하는 예방조치는 BCP 관련 CDE를 감소시킬 수 있다. 근거는 혈관작용제의 사용이 대뇌 산소 측정기 판독을 방해하는지 여부와 상관없이 대뇌 산소 불포화 방지를 위한 혈관작용제의 예방적 사용을 지지하지 않았다.

Keywords: Arthroscopy; Oximetry; Prophylaxis; Randomized controlled trial; Shoulder; Sitting position; Statistics; Systematic review.
Video laryngoscopy vs. direct laryngoscopy for nasotracheal intubation in oromaxilofacial surgery: a systematic review and meta-analysis of randomized controlled trials

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 배경: 비기관 삽관(nasotracheal intubation, NTI)은 구강악안면 수술에서 흔히 시행된다. NTI 대상 환자들의 비디오 후두경(VL) 대 직접 후두경(DL)의 비교 특성은 명확하지 않다.

방법: 우리는 NTI가 필요한 정규 구강악안면 수술을 받는 성인에서 VL과 DL을 비교한 무작위 대조 시험을 비교하기 위해 체계적인 검색을 수행하였다. 일차평가변수는 삽관까지의 시간(time to intubation, TTI)이었다. 이차평가변수에는 첫 번째 시도 성공, 전체 성공, 비강 출혈 발생률, Cormack 및 Lehan 등급 및 NTI 조작에 대한 요구 사항이 포함되었다.

결과: 체계적인 검색을 통해 확인된 456건의 연구 중 10건이 포함되었다. 메타분석 결과 증가는 유의하게 적은 것으로 나타났다(평균 차이 -9.04; (95% CI) -12.71, -5.36; P < 0.001). V2는 또한 첫 번째 시도 성공이 더 큰 것과 관련이 있었다(relative risk [RR]: 1.10, 95% CI [1.04, 1.16], P = 0.001). 삽관을 용이하게 하는 조작은 VL에서 더 적었다(RR: 0.22, 95% CI [0.10, 0.51], P < 0.001). 전반적인 삽관 성공에는 차이가 없었다(RR: 1.04, 95% CI [0.98, 1.10], P = 0.17). 출혈의 발생률은 DL과 VL 간에 차이가 없었다(RR: 0.59, 95% CI [0.32, 1.08], P = 0.09).

결론: RCT에 대한 체계적인 문헌검토 및 메타분석에서 DL의 사용은 NTI에 대한 유의하게 짧은 시간, 더 높은 첫 번째 시도 성공률 및 NTI를 용이하게 하기 위한 조작의 필요성 감소와 관련이 있다. 그러나 두 기구 사이에 전반적인 성공, 성문 관찰 또는 출혈에는 차이가 없었다.

Keywords: Intratracheal intubations; Intubation; Laryngoscopes; Meta-analysis; Oral surgical procedures; Orthognathic surgical procedures; Statistics; Systematic review.
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Epidural analgesia versus intravenous analgesia after minimally invasive repair of pectus excavatum in pediatric patients: a systematic review and meta-analysis

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배경: 오목가슴의 최소침습교정술(minimally invasive repair of pectus excavatum, MIRPE) 후 통증 조절이 필수적이며, 경막외 진통과 정맥주사(IV) 진통 사이에 더 나은 진통 방법에 대한 논란이 있다. 이번 체계적인 문헌검토 및 메타분석에서는 MIRPE 후 경막외 진통 대비 IV 진통의 효과를 비교하는 것을 목표로 하였다.

방법: PubMed, MEDLINE, Embase, Cochrane Central Register 및 ClinicalTrials.gov에서 2021년 5월 31일까지의 무작위 대조 시험(RCT)을 검색하였다. 1차 결과는 MIRPE 후 가중평균 시각통증척도(VAS)의 곡선 아래면적(AUC)이었다. 2차 결과는 수술 후 오심, 수술 시간, 총 수술실 시간, 수술 후 입원 기간이었다.

결과: 243명의 환자가 포함된 4건의 RCT가 최종적으로 이 메타분석에 포함되었다. 가중평균 VAS의 AUC는 경막외군에서 343.62, IV군에서 375.24였다. 경막외군은 수술 후 12~48시간 동안 IV군보다 더 낮은 VAS를 보였다. 수술 후 오심, 수술실 시간 및 입원 기간은 두 군 간에 차이가 없었다. 경막외군은 경막외 카테터 삽입 시간으로 인해 총 수술 시간이 유의하게 더 길었다.

결론: MIRPE 후 경막의 진통은 IV 진통보다 진통 효과가 더 좋았다. 그러나 IV 진통도 실행 가능한 옵션일 수 있으며, 의사는 MIRPE 후 진통 방식을 현명하게 선택해야 한다.

Keywords: Epidural analgesia; Funnel chest; Intravenous administration; Minimally invasive surgical procedures; Postoperative pain; Statistics; Systematic review; Thoracic surgery.
Systematic reviews (SRs) and meta-analyses (MAs), which attempt to gather all available empirical evidence, have several strengths, namely, that they focus on a narrow research question; involve a search of the evidence that is comprehensive and systematic; select and evaluate all relevant articles; synthesize data in a clear, explicit, systematic, and rigorous way; investigate and explore sources of heterogeneity; and use the results from multiple studies, thereby providing more precise effect estimates with increased statistical power [1,2]. Furthermore, if SRs and MAs are conducted appropriately, they can provide sufficient statistical power that could only be achieved by large-scale randomized clinical trials. In addition to a summary of the literature relevant to a specific question, SRs and MAs can provide clear answers to questions related to “Who”, “Why”, “How”, “What”, and “When” of the studies.

SRs and MAs are located at the top of the hierarchy of evidence since they provide balanced and transparent evidence, which increases their influence on clinical practice, healthcare, and policy development [1–4]. Currently, SRs and MAs are used to evaluate uncertain and unanswered questions in areas that require further research, making them an inevitable starting point for the research process. They have also become an integral part of clinical practice guidelines.

However, not all SRs and MAs are conducted and reported appropriately and rigorously. Many SRs and MAs are still conducted and reported in nonsystematic and untransparent ways; thus, they are often biased, conflicted, and misleading [5]. Although the pre-registration of SR and MA protocols is encouraged to improve transparency, only a small portion are registered in open registries, such as PROSPERO, before being conducted [6]. Additionally, some SRs and MAs are carried out by companies that are contracted by sponsors from the pharmaceutical and medical device industries. Therefore, if the results are not favorable for the sponsors, they may not wish to publish them, leading to publication bias.

Many of the topics that have been evaluated by SRs and MAs are overlapping and redundant, which leads to a waste of resources. Other SRs and MAs, even if well-conducted, may conclude that the evidence is weak or insufficient and thus not be informative for clinical practice, healthcare, and policy development.

To overcome these criticisms, reporting guidelines for SRs and MAs [7,8] or their protocols [9], appraisal tools [10], and tools for evaluating the quality of primary studies [11] have become standards for planning, conducting, and reporting of SRs and MAs. Furthermore, various methodologies for synthesizing data from primary studies [12,13] and automation tools for searching, screening, and extracting data [14] have been developed and introduced. Currently, the use of these methodologies and tools has even expanded to the synthesis of data from qualitative, observational, and animal studies.

These advances and changes are expected to improve the quality, accountability, and transparency of SRs and MAs. However, many clinicians, researchers, and policymakers
are still insufficiently aware of them. In addition, there are plenty of data in the field of anesthesiology that have never been comprehensively and systematically evaluated by SRs and MAs.

The current issue of the *Korean Journal of Anesthesiology* includes various studies that apply several types of SRs and MAs, including network MAs. I expect this issue to help us anesthesiologists, as researchers and readers, to broaden our understanding and knowledge of SRs and MAs, thereby increasing their use and applicability.

**Conflicts of Interest**

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

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Before we begin: systematic review and meta-analysis

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Most diseases have more than two interventions or treatment methods, and the application of network meta-analysis (NMA) studies to compare and evaluate the superiority of each intervention or treatment method is increasing. Understanding the concepts and processes of systematic reviews and meta-analyses is essential to understanding NMA. As with systematic reviews and meta-analyses, NMA involves specifying the topic, searching for and selecting all related studies, and extracting data from the selected studies. To evaluate the effects of each treatment, NMA compares and analyzes three or more interventions or treatment methods using both direct and indirect evidence. There is a possibility of several biases when performing NMA. Therefore, key assumptions like similarity, transitivity, and consistency should be satisfied when performing NMA. Among these key assumptions, consistency can be evaluated and quantified by statistical tests. This review aims to introduce the concepts of NMA, analysis methods, and interpretation and presentation of the results of NMA. It also briefly introduces the emerging issues in NMA, including methods for evaluation of consistency.

Keywords: Bayesian approach; Meta-analysis; Mixed treatment meta-analysis; Multiple treatment comparison meta-analysis; Network meta-analysis; Statistics; Systematic review.

Before the introduction of network meta-analysis (NMA), understanding the concepts and processes of systematic review and meta-analysis is necessary. A meta-analysis, including NMA, which is located higher in the hierarchy of evidence, should be preceded by and based on a systematic review [1].

In recent years, the publication of systematic reviews, meta-analyses, and network meta-analyses has increased with an increase of frequent citation [2,3]. They have become essential for making clinical decisions and developing health policies, which require balanced decisions regarding effectiveness, tasks, and resources [3]. A systematic review attempts to collate and identify the best available empirical evidence [1]. The research question of a systematic review usually focuses on pre-specified question(s). The search process for the evidence is comprehensive because a systematic review aims to find all the eligible evidence related to the research questions; it is also reproducible. The methodology for a systematic review is clear, explicit, systematic, and rigorously focused on minimizing bias, thereby providing more reliable findings [4,5]. The objective, inclusion and exclusion criteria, search strategy, selection and evaluation of articles, extraction of information, methods for data synthesis, and presentation should be determined before the commencement of the study.

However, a meta-analysis, per se, refers to a statistical analysis which quantitatively in-
integrates and summarizes the results from separate studies [6] and investigates the source of heterogeneity [7]. A meta-analysis uses the results from multiple studies, provides more precise effect estimates, and increases statistical power [8]. Therefore, generalizing the results from individual studies aside from providing pooled analysis, a meta-analysis has the advantage of qualitatively assessing risk factors, investigating rare exposures and diseases, and studying heterogeneity (i.e., identifying the reason for the difference or dispersion between studies).

However, meta-analysis has received criticism for the following reasons: 1) a single number cannot summarize the entire research field, 2) discrepancies exist between meta-analyses and large randomized controlled trials (RCTs) [9], 3) a possible file drawer problem (publication bias) [10], and 4) mixing different kinds of studies without considering their heterogeneity causes the ‘apples and oranges’ conundrum [11]. Therefore, the validation or assessment of the quality within or between the included studies is important as it can deteriorate the validity of the meta-analysis [6].

Introduction to NMA

More than two interventions or treatment methods generally exist for most diseases, and not all existing interventions or treatment methods are directly compared. Furthermore, the continually developing interventions or treatment methods are generally compared with placebo or standard interventions or treatment methods. They are not always compared with interventions or treatments currently employed in clinical practice.

Most clinicians, patients, and health policymakers want to be aware of the interventions or treatment methods that are superior based on all available evidence. However, organizing or performing a mega-RCT that compares all existing interventions or treatment methods that analyzes their effects and harms is practically impossible.

NMA, an extension of the traditional pairwise meta-analysis, synthesizes, compares, and analyzes three or more interventions and treatment methods using both direct and indirect evidence to evaluate the effects or harms of each treatment. The NMA includes multiple groups and is also called ‘multiple-treatment meta-analysis’. Moreover, NMA includes both direct and indirect comparisons and is also called ‘mixed-treatment comparison’.

Therefore, the NMA aims to collect all the RCTs performed and to compare the effects and harms of all interventions or treatment methods. The advantages of NMA are that (1) it provides useful evidence via indirect comparison even if no previous study has directly compared the effect and harm of the interventions or treatment methods; (2) because NMA uses information from both direct and indirect evidence, it increases the precision of estimate or power compared to that when using direct evidence alone; and (3) it ranks the relative effects and harm of all interventions and treatment methods.

Direct comparison refers to comparison of two or more interventions or treatment methods within a study, whereas indirect comparison refers to comparisons of interventions or treatment methods made through one or more common comparators [12].

In Fig. 1A, the solid blue and dotted red lines indicate direct and indirect comparisons, respectively. $T_A$, $T_B$, $T_C$, and $T_D$ are used as abbreviated version of treatment A, B, C and D in the following manuscript and figures. In this figure, $T_A$ serves as an anchor that indirectly compares $T_A$ and $T_C$ or $T_B$, $T_D$, and $T_P$. $T_A$ (anchor) is also called a common comparator. $T_B$ and $T_C$ or $T_C$ and $T_D$ are indirectly compared using anchor A. This type of comparison is called an ‘anchored indirect treatment comparison.’ When the shape formed by direct comparisons is incomplete, it is also called an ‘open triangle.’

A mixed-treatment comparison (Fig. 1B) exists when both direct and indirect comparisons between TB and TC and through anchor A (not shown in the figure) are noted. When the shape formed by direct comparison is complete, it is also called a ‘closed loop’. Open triangles and closed loops together, as shown in Figs. 1A and 1B, are called NMA. Mixed-treatment comparison can be explained as a generalized concept of the synthesis and summary of the effects of direct and indirect comparisons.

The sample NMA presented in Table 1 includes seven studies. Studies 1, 2, and 7 directly compared $T_A$ and $T_C$; studies 5 and 6 directly compared $T_A$ and $T_B$; and studies 3, 4, and 7 directly compared $T_A$ and $T_C$. In addition to information from the direct comparison of $T_A$, $T_B$, $T_C$, and $T_D$, information from the indirect comparison can also be used to compare the two treatments. $T_A$ and $T_B$ can be indirectly compared using $T_C$ as a common comparator in studies 3, 4, 5, and 6. As $T_C$ has also been investigated in study 7, $T_A$ and $T_B$ can also be indirectly compared via the common comparator $T_C$ in this study.

Two studies compared $T_A$ versus $T_B$ and $T_A$ versus $T_C$ (Fig. 2A). The red rectangle represents the difference between the treatment effects of $T_A$ and $T_B$ ($T_{AB} = T_B - T_A$), and the sky blue rectangle represents the difference between the treatment effects of $T_A$ and $T_C$ ($T_{AC} = T_C - T_A$). The difference between the treatment effects of $T_A$ and $T_C$ ($T_{AC}$) may be obtained by subtracting the treatment effect of B from that of C ($T_{AC} = T_C - T_B$). However, it may lead to bias when the treatment effect of $T_A$ in study AB (a study that compared $T_A$ and $T_B$ is named study AB) may be different from that in study AC. Therefore, the possibility of baseline differences between studies regarding the treatment effect of A as a common
Comparator should be considered (Fig. 2A).

Critical views exist on indirect comparisons performed in NMA. First, although indirect comparisons assume randomization, it is not randomized evidence. All interventions or treatment methods compared are not randomized across the studies. Statistically, the indirect comparison is a specific type of meta-regression, and meta-regression only provides observational evidence. Second, constant critical voices have existed on whether indirect comparisons show better evidence compared with direct comparisons and whether NMA can be performed only by indirect comparison when no direct comparison is present [13].

Steps of NMA

Attempt to include all relevant RCTs

The first step in conducting an NMA is same as that in a conventional meta-analysis. The author should define the research question based on population, intervention, comparison, and outcome (PICO), eligibility criteria, search strategies, processes for study selection, data extraction, and quality assessment of studies. Studies that include a common comparator are important when defining the eligibility criteria.

Explore network geometry

In a scenario with studies comparing $T_A$ and $T_B$ (study AB) and $T_C$ and $T_D$ (study CD) (Fig. 2B), when no connection between the treatments is noted, the relative treatment effect between $T_{AB}$ (difference in the treatment effect of $T_A$ and $T_B$) and $T_{CD}$ (difference in the treatment effect of $T_C$ and $T_D$) cannot be assumed. However, with a study comparing $T_A$ and $T_C$ (study AC), $T_{AC}$ (difference in the treatment effect of $T_A$ and $T_C$) can be assumed through the common comparator $T_A$ (Fig. 2C). Moreover, $T_{AD}$ (difference in the treatment effect of $T_A$ and $T_D$) can be assumed through the common comparator $T_C$ (Fig. 2C).

To allow comparisons of treatment effects across all interventions and treatment methods, all included studies must be connected in the network, which means that any two treatments can be compared either directly or indirectly through a common comparator. The network plots allow visual inspection of the direct and indirect evidence (Supplementary Figs. 1A and 1B).

Table 1. The Example of Studies Comparing Each Treatment

<table>
<thead>
<tr>
<th>Studies comparing treatments</th>
<th>A vs. B</th>
<th>B vs. C</th>
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Fig. 1. Direct and indirect comparisons in network meta-analysis. (A) Direct ($T_A$ versus $T_B$, $T_A$ versus $T_C$, and $T_A$ versus $T_D$) and indirect ($T_B$ versus $T_C$ and $T_C$ versus $T_D$) comparisons anchored by $T_A$. Anchored indirect treatment comparison is called an open triangle. (B) Direct comparisons are called a closed loop.
Assess key assumptions

NMA only provides observational evidence, as in a conventional meta-analysis, and the risk of confounding bias exists. To lower the risk of confounding bias, key NMA assumptions must be assessed. Moreover, the key assumptions, including similarity, transitivity, and inconsistency, are explained separately in the following section.

Performance of analyses and NMA

Free software, such as WinBUGS [14], R [15–17], Python, OpenBUGS [18], and ADDIS, or commercially available software, such as Stata [19], SAS, and Excel (NetMetaXL) [20], can be used to perform NMA statistics. Statistical approaches for NMA are divided into frequentist and Bayesian frameworks [12]. Frequentist NMA can be performed using R (nemeta package [21]) and Stata software [19], and Bayesian NMA can be performed using R (gemtc [16], pcnemeta [17], and BUGSnet package [15]) and WinBUGS software.

The frequentist framework NMA using Stata can be performed using the methods of White IR [19].

Key assumption in network meta-analysis

To perform NMA using data from several studies, the following three assumptions must be satisfied [22]: similarity or homogeneity assumption generally applies to direct comparisons, transitivity assumption applies to indirect comparisons, and consistency assumption applies to mixed comparisons (direct and indirect comparisons).

Similarity and homogeneity for direct comparisons

According to the concept of similarity or homogeneity, ‘combining studies should only be considered if they are clinically and methodologically similar.’ Similarity or homogeneity is observed when the true treatment effects of two interventions or treatment methods are similar in direct comparisons, and heterogeneity appears when the true treatment effect varies. Similarity should be shown in PICO; for example, the similarity assumption may be violated if the administration methods for a similar drug are different (for example, injection and oral pill). The similarity is evaluated qualitatively; therefore, testing for the statistical hypothesis is not done. Similarity or homogeneity of the methodology employed in the included studies should also be observed.

Transitivity for indirect comparisons

Transitivity is the validity for logical reasoning, which means that the difference $T_{AB}$ and $T_{AC}$ can be used to calculate the $T_{BC}$, an indirect comparison. If the treatment effect of A is similar between the direct comparison of $T_{AB}$ and $T_{AC}$, the common comparator A can be used from $T_{AB}$ and $T_{AC}$, which is ‘transitive’ from
treatments B through A to C.

Transitivity is a conceptual definition and an assumption that cannot be calculated. However, its validity can be evaluated in terms of the clinical, epidemiological, and methodological aspects. If intransitivity is suspected, the existence of an effect modifier should be thoroughly examined.

The distribution of patient and study characteristics, which are effect modifiers, must be sufficiently similar between studies AB and AC to generalize $T_{ab}$ to $T_{ac}$. If an imbalance in the distribution of effect modifiers exists between the studies, incorrect estimates may be obtained. Fig. 3 shows that the assumption of transitivity is violated when effect modifier D (between $T_a$ and $T_b$) is not similar to effect modifier E (between $T_a$ and $T_c$).

For example, if study AB included 30 male and 30 female patients and study AC included 20 male and 20 female patients, combining both would satisfy the transitivity assumption because the gender distribution is same in both studies. The assumption of transitivity is violated if an imbalance exists between studies AB and AC. However, if an imbalance exists between studies AB and AC, the transitivity assumption is assumed to be satisfied if the gender distribution does not affect the outcome (i.e., gender is not an effect modifier).

All treatments included in NMA should be 'jointly randomizable', which means that a trial including all treatments would be clinically reasonable. It is assumed that the investigators have included RCTs. Comparisons within an RCT are compared between the randomized groups, while those between RCTs are not randomized. However, comparisons between RCTs are not randomized. Therefore, the comparisons between RCTs should be assumed to be 'jointly randomizable' to perform an NMA. Thus, it is essential to consider this when conducting an evidence network. Transitivity may be violated if the intervention or treatment method has a different target patient group or indication between studies. For example, when $T_a$ is the primary treatment and $T_b$ and $T_c$ are both primary and secondary treatments, patients in study BC cannot be assumed to be randomly assigned to study AC.

**Consistency for mixed comparisons**

Consistency, the agreement between direct and indirect evidence for a given pair of intervention and treatment methods, is an objective assessment of transitivity during data manifestation. The consistency assumption is satisfied when the magnitude of the effect through direct and indirect comparisons is consistent. The consistency assumption is a statistical confirmation of transitivity, which can be evaluated by determining if the effect size is similar through direct and indirect comparisons. Moreover, consistency can be evaluated not in an open triangle but in a closed loop because only some comparisons are indirect in an open triangle.

Consistency is also called coherence or transitivity across loops. The four causes of inconsistencies are (1) chance, (2) genuine diversity, (3) bias in direct comparison, and (4) bias in indirect comparison [5].

Unlike similarity and transitivity, which are evaluated qualitatively, consistency is evaluated using a statistical method. Several statistical methods have been suggested to check the assumptions regarding consistency. Of these, six methods that are commonly used to assess NMA inconsistency have been described.

**Cochran’s Q statistics**

Cochran’s Q statistic is a commonly used method for assessing heterogeneity within the NMA [23]. When performing Cochran’s Q statistic, the null hypothesis is that the treatment effectiveness in all studies is equal. An alternative hypothesis is that the treatment effectiveness in these studies is different [24].

Cochran’s Q statistic can be calculated by summing the squared deviations of each study’s estimate from the overall meta-analytic estimate, weighting the contribution of each study. P values for Cochran’s Q statistic can be obtained using the $\chi^2$ distribution [24].

The overall Cochran’s Q statistic from the fixed-effect NMA can be used for both within- and between-design heterogeneities. However, it has lower power in detecting heterogeneity when the numbers of included studies or samples size are small.

The quantity of heterogeneity, $I^2$, is provided to measure the degree of inconsistency. $I^2$ can be calculated as $I^2 = 100\% \times (Q - \chi^2)$.

![Fig. 3. Transitivity-visualized diagram. Transitivity between studies $A_b$ and $A_c$ via $T_a$ as a common comparator. The assumption of transitivity is violated when the effect modifier D (between $T_a$ and $T_b$) is not similar to effect modifier E (between $T_a$ and $T_c$).](https://doi.org/10.4097/kja.21358)
df) / Q, where Q is Cochran’s heterogeneity statistic and df is the degree of freedom. A value of 0% indicates no heterogeneity, and larger values indicate increasing heterogeneity.

Loop inconsistency (Supplementary Fig. 2)

The Bucher method is a simple z-test developed to assess loop inconsistency in loops of three treatments with two-arm trials in a network [25]. The measurement of loop inconsistency is discussed below. The absolute value of the difference in the effect size between the direct and indirect comparisons between treatments is called the IF.

For example, IF for treatment BC is as follows:

\[ IF = \left| \mu_{BC} - \mu_{BC} \right| = \left| \mu_{AB} - \mu_{AB} \right| = \left| \mu_{AC} - \mu_{AC} \right|, \]

where

- \( \mu_{BC} \) is the indirect treatment effect of BC,
- \( \mu_{BC} \) is the direct treatment effect of BC,
- \( \mu_{AB} \) is the indirect treatment effect of AB,
- \( \mu_{AB} \) is the indirect treatment effect of AB and the difference in treatment effect of interventions A and B.
- \( \mu_{AC} \) is the indirect treatment effect of AC, and
- \( \mu_{BC} \) is the indirect treatment effect of AC.

The variance of IF, var(IF), was calculated by summing the variance of direct and indirect comparisons.

\[ \text{var}(IF) = \text{var}(\mu_{BC}) + \text{var}(\mu_{BC}) \]

The null hypothesis is that the effect sizes of the direct and indirect comparisons are equal, and the alternative hypothesis is that the effect sizes of the direct and indirect comparisons are different.

A test for \( H_0: IF = 0 \)
A test for \( H_1: IF \neq 0 \)

Z is calculated by dividing IF by the square root of var(IF), and the distribution of z follows a standard normal distribution.

\[ z = \frac{IF}{\sqrt{\text{var}(IF)}} \sim N(0, 1) \]

The 95% CI of IF was calculated by the summation or subtraction of the square root of var(IF). 95% CI IF \( \pm 1.96 \sqrt{\text{var}(IF)} \)

If the 95% CI does not contain 0, the consistency assumption is rejected. These steps were repeated for each independent loop in the network.

This method has the advantages of simplicity, ease of application, and intuitive for loops with large inconsistencies. However, evaluating the consistency of the entire network and discriminating a particular comparison with a problem within the loop when inconsistency appears in the loop is difficult. Furthermore, multiple testing must be considered, which may be both cumbersome and time-consuming when this approach is applied to a large network wherein each treatment loop is considered one at a time [26,27].

Inconsistency parameter approach

One of the most popular models for evaluating NMA inconsistency is the inconsistency parameter approach proposed by Lu and Ades (Bayesian hierarchical model) [28]. This model is a generalization of the Bucher method and relaxes the assumption regarding consistency by including an inconsistency parameter (\( \omega_{ABC} \)) in each loop wherein inconsistency could occur.

Consistency model
\[ \mu_{BC} = \mu_{AC} - \mu_{AB} \]

Inconsistency model
\[ \mu_{BC} = \mu_{AC} - \mu_{AB} + \omega_{ABC} \]

where

- \( \mu_{BC} \) is the treatment effect of BC,
- \( \mu_{AB} \) is the treatment effect of AB,
- \( \mu_{AC} \) is the treatment effect of AC, and
- \( \omega_{ABC} \) is the inconsistency parameter.

These additional inconsistency parameters can be fitted as fixed or random effects. Models with and without inconsistency parameters are then compared to assess whether a network is consistent and arbitrarily chosen. An inconsistency model can be obtained by omitting the consistency assumption. If it is assumed that the inconsistency parameter (\( \omega_{ABC} \)) is 0 in the inconsistency model, it can be classified as a consistency model. The distribution of the inconsistent variable is \( \omega \sim N(0, \sigma^2) \).

Node-splitting (Supplementary Fig. 3)

Node-splitting is a conceptual extension of the loop inconsistencies. This method separates the evidence into direct and indirect evidence from the entire network and assesses the discrepancy between them, which is repeated for all treatment comparisons [29]. When all treatment nodes are split simultaneously, they can be considered equivalent to the inconsistent parameter approaches of Lu and Ades.

Different methods to evaluate potential differences in the relative treatment effects estimated by direct and indirect compari-
Statistical methods in NMA

Two approaches exist to conduct the NMA: the Bayesian and frequentist frameworks [21]. The frequentist framework regards the parameters that represent the characteristics of the population as fixed constants and infers them using the likelihood of the observed data. The frequentist framework calculates the probability under the assumption that the observed data repeats infinitely. The results of the frequentist framework are given as a point estimate (effect measures such as odds ratio, risk ratio, and mean difference) with a 95% CI. Therefore, the frequentist framework is unrelated to external information, and the probability that the research hypothesis is true within the current data is already specified. The frequentist method can only help decide whether to accept or reject the hypothesis based on the significance level.

The Bayesian framework expresses the degree of uncertainty using a probability model by applying the probability concept to the parameters. Moreover, the Bayesian methods rely not only on the probability distribution of all the model parameters given the observed data, but also on the prior beliefs from external information about the values of the parameters. It calculates the posterior probability, which is presented as a point estimate with a 95% credibility interval and is performed using Markov Chain Monte Carlo (MCMC) simulations, allowing the reproduction of the model several times until convergence (Supplementary Fig. 5). Unlike the frequentist method, the Bayesian method has the advantage of a straightforward way of making predictions and the possibility of incorporating different sources of uncertainty with a more flexible statistical model. Therefore, it is free from the effects of the large-sample assumption. Moreover, it can be used in NMAs involving a small number of studies. This method could be more logical and persuasive than the frequentist method.

Similar to the traditional pairwise meta-analysis, NMA can utilize fixed- or random-effect approaches. The fixed-effect approach assumes that the effect size and difference between each estimate from the included studies is attributable only to the sampling error. A random-effects approach assumes that the observed difference in the effect size considers not only sampling error but also the variation of true effect size across studies, called heterogeneity. When this concept is extended to NMA, the effect size estimates vary across studies as well as comparisons (direct and indirect). Therefore, both models were tested for each network.

Choosing a better NMA model that fits the included data is important when using the Bayesian approach. Convergence of models derived from MCMC simulations can be assessed using trace and density plots and the Gelman–Rubin–Brooks methods with a potential scale reduction factor of up to 1 (Supplementary Figs. 6...
and 7). The deviance information criterion (DIC) for changes in heterogeneity and statistical methods can also be used for model fit. However, a low DIC is more suitable (Supplementary Fig. 8).

**Result presentation**

**Network plot**

The network plot is a concise visual presentation of the evidence. The network plot is composed of nodes and edges, wherein the nodes represent the interventions or treatment methods compared, and the edges represent the available direct comparison between interventions or treatment methods. In some packages or programs, the size of the nodes is proportional to the number of patients, and the widths of the edges are proportional to the amount of data (for example, the number of studies directly compared or 1/standard error of treatment effect²; Supplementary Figs. 1A and 1B).

The network plot is sometimes used to check the transitivity assumption using a weighted edge proportional to the effect modifier (for example, baseline risk) or applying color by a possible effect modifier (for example, risk of bias).

**Contribution plot**

The contribution plot is a diagram presenting the contribution of each direct comparison to the estimation of the network summary effect. In the contribution plot, the size of each square is proportional to the weight that is attached to each direct comparison (horizontal axis) and the estimation of each network summary effect (vertical axis). The number represents the weight percentage (Supplementary Fig. 9).

**Net heat plot**

The net heat plot, an extension of the contribution plot, is a diagram that checks both contribution and inconsistency. In the net heat plot, the size of each square has a similar meaning to that in the contribution plot. The net heat plot also presents a matrix visualization that shows inconsistency as highlight hotspots [31]. The color of the diagonal line indicates the contribution to design inconsistency, and the color outside the diagonal indicates the degree of inconsistency between the direct and indirect rationale of the design (Supplementary Fig. 4).

**Predictive interval plot**

A predictive interval plot (Supplementary Fig. 10) is a forest plot of the estimated summary effects, along with their CIs and their corresponding predictive intervals. The predictive interval shows the range of values of future results in specified settings of the predictors [32]. If a new observation is added, the 95% confidence will fall within this range.

**Credible interval plot**

The credible interval plot (Supplementary Fig. 11) is a forest plot of the estimated summary effects, along with their credible intervals. A credible interval is that in which an unobserved parameter value falls with a particular probability in Bayesian statistics.

**League table**

The league table shows the relative effectiveness of possible pairs of interventions and their 95% CI (Supplementary Fig. 12). For example, the first cell in the upper left corner shows that propofol has a postoperative nausea (PON) incidence risk ratio of 0.77 (0.02–23.96) compared with palonosetron. Further, propofol shows a PON incidence risk ratio of 0.14 (0.01–2.54) compared with dexamethasone.

**Rankogram and cumulative ranking curve**

The rankogram presents the probabilities of each intervention or treatment method to be ranked at a specific place (1, 2, 3, etc.), based on the results of the NMA (Supplementary Fig. 13). The cumulative ranking curve represents the cumulative probabilities to reach a corresponding rank (the sum of the probabilities from those ranked 1, 2, 3, and so on; Supplementary Fig. 14). Using a cumulative ranking curve, the treatments can be ranked according to the surface under the cumulative ranking curves (SUCRA) by summing all cumulative probabilities in the cumulative ranking curve for each intervention or treatment method. The SUCRA value represents the probability that a treatment is among the best options. The Y-axis of the SUCRA value indicates the certainty of effectiveness in the network. Therefore, the rank of an intervention in the network is higher if the intervention has a larger SUCRA value (Supplementary Fig. 15).
Emerging issues of network meta-analysis

Multicomponent intervention and treatment method

In standard NMA, all existing intervention and treatment methods are considered different nodes. However, an alternative model that utilizes the information that some intervention and treatment methods are combinations of common components is called component network meta-analysis (CNMA) [33]. Let us consider a network of six treatments presented in Fig. 4 that includes three two-arm studies comparing treatments A with B + C, B with A + C, and A + B with C. If no subnetwork is connected to the others, the networks are illustrated in Fig. 4A, which shows disconnected networks. CNMA models allow ‘reconnecting’ a disconnected network if the treatment and intervention methods have common components. Fig. 4B shows that all studies have common components A, B, and C, and their contributions can be estimated using the CNMA model. CNMA has two models (additive and interactive). The additive CNMA model assumes that a combination of A and B (A + B) has similar treatment effects with the sum of treatment effects A and B. The interactive CNMA model allows for the interaction between treatments A and B. These models can now be analyzed in a frequentist framework using the R package netmeta.

Multiple outcome-borrowing information

For multiple outcome settings, the standard NMA model can be extended by borrowing information across outcomes as well as across studies by modeling the within- and between-study correlation structure. For the next stage, the additional assumption that intervention effects are exchangeable between outcomes is utilized to predict effect estimates for all outcomes. Moreover, multivariate meta-analysis has more areas of meta-analysis to compare treatments with two or more endpoints [34,35]. The multivariate approach has an advantage over the univariate approach because it accounts for the interrelationship between outcome and borrowed strength across studies and across outcomes via the modeling of the correlation structure [36]. NMA is another rapid methodological development area [37], and multiple outcome settings extended by borrowing information have been proposed to enhance NMA methodology [38,39].

Conclusion

NMA is a meta-analysis that synthesizes, compares, and analyzes three or more intervention/treatment methods, including both direct and indirect evidence extracted from various studies. Moreover, NMA collects information from direct and indirect evidence, which improves estimate precision. Furthermore, NMA can compare the relative effects and rank the effects of all interventions of treatments. Although indirect comparison assumes randomization, this does not mean that randomization has been performed. Therefore, assumptions of similarity, transitivity, and consistency must be satisfied for NMA; there are various strategies to overcome this challenge, and an NMA should not be performed unless these criteria are satisfied.

Conflicts of Interest

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

Author Contributions

EunJin Ahn (Investigation; Methodology; Project administration; Validation; Visualization; Writing – original draft; Writing – review & editing)
Hyun Kang (Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing)

Supplementary Materials

Supplementary Fig. 1. Network plot. (A) The nodes indicate the type of intervention or treatment method, and edges indicate direct comparison between intervention or treatment method. The size of nodes is proportional to the number of patients included and the width of the edges is proportional to the amount of information available (1/sta...
standard error of treatment effect2). This figure is produced using STATA software. (B) The nodes indicate the type of intervention or treatment method, and edges indicate direct comparison between intervention or treatment method. The size of nodes is proportional to the number of patients included and the width of the edges is proportional to the amount of information available (number of studies directly compared). This figure is produced using R software (netmeta package).

Supplementary Fig. 2. Loop inconsistency. This plot evaluates the inconsistency of the network using a design-by-treatment interaction model in multi-arm trials. Dot and black line indicate the mean and 95% confidence interval of loop inconsistency. When 95% confidence interval includes “0”, the assumption of consistency is satisfied. However, 95% confidence interval does not include “0”, the assumption of consistency is satisfied.

Supplementary Fig. 3. Node-splitting plot. The forest plot shows a difference between the direct and indirect evidence for each pairwise comparison after node-splitting. White circle and black line indicate the mean and 95% confidence interval of loop inconsistency. This method is a conceptual extension of loop inconsistency. Node-splitting methods separate the evidence into the direct and indirect evidence from entire network and assessing the discrepancy between them, and repeated for all treatment comparisons.

Supplementary Fig. 4. Net heat plot. The gray square indicates the degree to which treatment located in the column contributes to the overall estimate of the row. The color of the diagonal line means the contribution to the inconsistency of the design, and the color outside the diagonal means the degree of inconsistency between the direct/indirect rationale of the design.

Supplementary Fig. 5. Markov chain Monte Carlo (MCMC) flow chart. Markov chain Monte Carlo (MCMC) simulation and convergence diagnosis. Flow chart of network meta-analysis using the “gemtc” R package using the Bayesian method. MCMC, Markov chain Monte Carlo; DIC, deviance information criterion. The process is follows as below: After coding the data, setup the network. After setting the network, select network model (fixed or random). To verify if the MCMC simulation converged well, you can check MCMC error, DIC (deviance information criterion), trace plot, density plot and Gelman-Rubin statistics. Then, select the MCMC convergence optimal model. Inconsistency test, forest plot, treatment ranking, league table can be performed.

Supplementary Fig. 6. Trace and density plot. A trace plot shows the values that the relevant parameter took during the runtime of the chain, and density plot is the histogram of the values in the trace-plot of the relevant parameter in the chain. The trace plot with no specific pattern and with entangled chains, the convergence can be considered to be good. The density plot with significant difference for the same number of simulation means the convergence is not good.

Supplementary Fig. 7. Gelman-Rubin-Brooks Plot. In Gelman-Rubin-Brooks methods, as potential scale reduction factor (PSRF) approaches 1, and the variations must be stabilized as the number of simulations increases. When PSRF approached to 1, and stabilized, it means good convergence.

Supplementary Fig. 8. Bayesian Statistics. DIC (deviance information criterion). DIC = Dbar+pD. The deviance information criterion (DIC) is expressed as DIC = Dbar+pD, where Dbar is the sum of residual deviances and pD is an estimated value of the parameter. Thus, the DIC considers both the fitness and complexity of the model, and the smaller the DIC is, the better the model.

Supplementary Fig. 9. Contribution plot. The size of each square is proportional to the weight which is attached to each direct comparison (horizontal axis) to the estimation each network summary effect (vertical axis). The number presents the weight as percentage.

Supplementary Fig. 10. Predictive interval plot. Forest plot of success rate of supraglottic airway devices. Prl: predictive intervals. Black line represents 95% confidence interval. Red line represents 95% predictive interval. I-gel versus FLMA shows significant result when presented by 95% confidence interval. However, considering 95% predictive interval, which shows the range of values of the future result, the result become insignificant.

Supplementary Fig. 11. Credible interval plot. Forest plot showing credible interval. Crl: credible intervals. Black outline circle represents odds ratio, and black line represents 95% credible interval. Credible interval is an interval within which an unobserved parameter value falls with a particular probability in Bayesian statistics.

Supplementary Fig. 12. League table. RR (95% CI) is calculated between both horizontal axis treatment and vertical axis treatment. Comparisons between treatments should be read from left to right, and the estimates in the cell in common between the vertical axis treatment and the horizontal axis treatment. Treatments are reported from left upper quadrant to right lower quadrant as per the cluster ranking for transition and acceptability. For transition, an RR less than 1 favors the row-defined treatment. For acceptability, an RR less than 1 favors the row-defined treatment. RR: relative ration; CI: confidence interval.

Supplementary Fig. 13. Rankogram. Profiles indicate the probabilities for treatments to assume any of the possible ranks. It is the probability that a given treatment ranks first, second, third, and so on, among all of the treatments evaluated in the NMA.

Supplementary Fig. 14. The cumulative ranking curves. The profile indicates the sum of the probabilities from those ranked first, second, third, and so on. A higher cumulative ranking curve (surface of under cumulative ranking curve [SUCRA]) value is regarded as an improved result for an individual’s intervention. When ranking treatments, the closer the SUCRA value is to 100%, the higher the treatment ranking is relative to all other treatments.
Supplementary Fig. 15. SUCRA-Mean Ranking. Each color represents a group of treatment that belong to the same cluster. Treatments represented in the right upper quadrant are more effective and acceptable compare to the left lower quadrant.

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Introduction

Traditional meta-analyses are only able to examine the pooled effect size rather than to evaluate whether the number of participants and the corresponding number of trials in a meta-analysis are sufficient to draw any conclusions. Moreover, the use of the traditional 95% CI or the 5% statistical significance threshold will lead to too many false-positive conclusions (type I errors) and too many false-negative conclusions (type II errors) [1].

Trial sequential analysis (TSA) is a recently described cumulative frequentist meta-analysis method [2] used to weigh type I and II errors and to estimate when the effect is large enough to unlikely be affected by further studies [3,4]. While TSA is based on frequentist thinking as it is founded on P value and type I and type II error methods, it in-
corporates elements of Bayesian thinking. Indeed, the calculated sample size in TSA is related to the pooled effect estimated in a meta-analysis.

TSA generates a graphical outcome divided into four areas by four lines: “benefit,” “harm,” “inner wedge,” or “non-statistically significant,” representing a statistically significant result for the first two areas (“benefit” and “harm”) and a strong evidence that further studies will hardly be able to change the no-effect results for the “inner wedge” area (Fig. 1). Lying in the “non-statistically significant” area means that further studies are needed for a conclusion on the analyzed topic. The cumulative z-statistic line is drawn on this chart by adding the included studies with a chronological criterion, with the last study representing the end of the line and the area (“benefit,” “harm,” “inner wedge,” or “non-statistically significant”) [5].

The aim of this study was to illustrate the possible scenarios and possible significance of TSA using meta-analyses published in the Korean Journal of Anesthesiology (KJA) as working material.

**Materials and Methods**

We performed a systematic search of the medical literature following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement Guidelines for the identification, screening, and inclusion of articles. The search was performed by two researchers (ADC and MT) in close collaboration with the rest of the research team.

**Search strategy**

The search was performed on May 10, 2021, using the search tool in the KJA site and using the following terms: “meta-analysis,” “metaanalysis,” “meta analysis.” In our search, we did not apply any restrictions on publication type or date, language or status.

**Study selection**

Two researchers (ADC and MT) independently screened the titles and abstracts of the identified papers to select those that were

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**Fig. 1.** Graphical representation of the trial sequential analysis (TSA) outcome. A: favors intervention (benefit), B: non-statistically significant, C: inner wedge, D: favors control (harm).
Data extraction and data retrieval

After identifying those studies meeting the inclusion criteria, two researchers (FG and AB) independently reviewed and assessed each of the included studies. The following information was collected: first author, year of the study, total number of patients per group, registration number, main outcome, and data for intervention and control relative to the main outcome.

If the main outcome was not clearly stated, it was retrieved by examining the registered protocol or by contacting the main author of the paper.

Statistical methods

TSA was performed on the main outcome for each paper using TSA software (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen). The effect measure and model (mean difference, odds ratio, relative risk, risk difference, or Peto odds ratio) were used. A fixed effects model, random effects model using the DerSimonian–Laird method, random effects model using the Sidik–Jonkman method, or random effects model using the Biggerstaff–Tweedie method was selected according to the outcome measure and model. No continuity correction was applied in the case of a zero event. We estimated the required sample size on the calculated effect size for the intervention, considering a type I error of 5% and a power of 90%; benefit, harm, and inner wedge boundaries were drawn using the O’Brien–Fleming spending function.

Moreover, a more conservative approach, performing a second TSA with a type I error of 5% and a power of 99% was performed for each main outcome. This post-hoc conservative approach allowed us to assess whether the data provided convincing evidence of the true effect.

Results

We identified 11 papers [6–16] in our initial search (Table 1). However, four of them were excluded [6–9] because they were statistical rounds; the remaining seven were clinical meta-analyses. One of the meta-analyses [10] did not have sufficient information to perform a TSA and was therefore excluded, leaving six papers for the final analysis [11–16] (Fig. 2).

The topics of the meta-analyses were as follows: curare side effects [11], regional anesthesia [12,16], postoperative efficacy of ibuprofen [14], postoperative shivering [13], and postoperative nausea and vomiting [15]. Notably, only two of them had a pre-registered protocol [12,14]. Four papers [11–14] had two main outcomes, and for this reason, a total of 10 TSAs were performed.

Choi et al. [11] evaluated the effect of pretreatment with lidocaine or opioids opioid pretreatments in the incidence of rocuronium-induced withdrawal movement. For both outcomes, the cumulative z-score line crossed the line to reach the required sample size in both the 90% and 99% analyses (Figs. 3 and 4).

Bailey et al. [12] evaluated the cumulative opioid consumption at 48 hours after midline laparotomy, comparing, on the one hand, continuous peripheral nerve blocks and multimodal analgesia and, on the other hand, continuous peripheral nerve blocks and epidural analgesia. In the TSA, the cumulative z-score line crossed the benefit boundary, but did not reach the required sample size for the outcome relative to the continuous peripheral nerve block in either the 90% or the 99% analysis (Fig. 5). For the other outcome, the cumulative z-score line did not reach any boundary and remained in the zone that is “non-statistically significant” area (Fig. 6).

Min et al. [13] evaluated meperidine and clonidine for the prevention of postoperative shivering. A TSA of the meperidine outcome revealed that the cumulative z-line crosses the 90% but not the 99% boundary for benefit (Fig. 7), while a TSA of the clonidine outcome revealed that the cumulative z-line crossed both the 90% and 99% boundaries for benefit without reaching the required sample size (Fig. 8).

The effect of a single dose of ibuprofen was evaluated by Kim et al. [14] on both postoperative opioid consumption and pain. While the cumulative z-line does not cross the 90% power boundary for effect but lies immediately below that in the opioid consumption outcome (Fig. 9), it crosses both the 90% and 99% boundary for benefit without reaching the required sample size in the analysis relative to pain scores (Fig. 10).

Kim et al. [15] evaluated the efficacy of ramosetron in preventing postoperative nausea and vomiting. A TSA revealed that the cumulative z-line crossed the boundary for benefit in both the
90% and 99% analyses, without reaching the required sample size (Fig. 11).

Another study by the same group of authors [16] investigated the pharmacological efficacy of lidocaine/tetracaine patches and peels on pain (Fig. 12). In the post-hoc analysis, the cumulative z-line crossed the boundary for benefit and the required sample size for both the 90% and 99% analyses.

**Discussion**

A TSA analyzes the cumulative evidence in a meta-analysis. Its output is represented by a cumulative z-line score that may lie in one out of four areas: benefit (labeled A in Fig. 1), harm (labeled D in Fig. 1), non-statistically significant (labeled B in Fig. 1), and inner wedge (labeled C in Fig. 1).

A pooled effect in favor of the intervention (benefit) or in favor of the control (harm), or the absence of any effect (inner wedge), may be established to assess if the cumulative sample size is large enough. On the contrary, when the cumulative z-line lies in the area that is not statistically significant, further studies with an increase in the overall sample size are deemed necessary.

**Confirmation of the meta-analysis pooled effect**

Seven out of ten TSAs confirmed the results of meta-analyses. However, only in three of them (Figs. 3, 4, and 12) the required sample size was reached. These TSAs suggest that the result is definitive and that other randomized controlled trials are unlikely to modify the effect on the outcomes.

On the contrary, in four TSAs (Figs. 5, 8, 10, and 11), the cumulative z-line, after crossing the boundary for effect, did not reach the required sample size. These TSAs suggest that, although the pooled effect is statistically significant, with regard to sample size, the result is not definitive, and future studies are necessary to be conclusive.
No confirmation of the meta-analysis pooled effect

In the two TSAs (Figs. 6 and 9), the cumulative z-line lies in the zone with no statistical significance. This implies that the sample size of the meta-analysis was too small, and it is therefore impossible to infer where the cumulative z-line will lie in future trials. If a TSA had been performed by the authors, more cautious conclusions could have been drawn.

Inner wedge

No studies have reported examples of the inner wedge zone. However, for completeness, we would like to briefly illustrate this eventuality. The inner wedge zone is delimited by the futility boundaries, creating an isosceles triangle with its base on the sample size line. If the cumulative z-score lies in the inner wedge zone, future studies on the argument must be considered futile because they will hardly be able to change the no-effect results.

Pre-registering TSA

The importance of registering the TSA protocol before conducting the analysis is depicted in Fig. 7). This TSA resulted in statistical significance using a power of 90%, but the statistical significance was lost using an analysis with a power of 99%. Despite no guidelines or clear recommendations regarding the choice of the power of the analysis, this example shows the limitation of a post-hoc analysis in which the power could be arbitrarily changed to confirm or not the recommended result.

Limitations

Our study has some limitations that we would like to discuss. A limited number of TSAs were included in the analysis, and no examples of a TSA lying in the inner wedge were available.

Other methods such as the law of iterated logarithm penalizing the z-value by the strength of the available evidence and number

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Fig. 5. Trial sequential analysis (TSA) of the effect of multimodal anesthesia compared to that of continuous peripheral nerve blocks on pain at 48 hours following midline laparotomy [12]. CPNB: continuous peripheral nerve block.

Fig. 6. Trial sequential analysis (TSA) of the effect of epidural anesthesia compared to that of continuous peripheral nerve blocks on pain at 48 hours following midline laparotomy [12]. CPNB: continuous peripheral nerve block.

of statistical tests could be used to adjust the issues of repeated significance testing. In our study, we chose the cumulative z-curve approach, but we recognize this was an arbitrary choice.

We also presented a guide to help clinicians interpret TSA; however, we recognize that we have not explained the statistical basis of this analysis and we recognize this as a limitation.
Fig. 7. Trial sequential analysis (TSA) of the effect of meperidine compared to that of placebo on postoperative shivering [13].

Fig. 8. Trial sequential analysis (TSA) of the effect of clonidine compared to that of placebo on postoperative shivering [13].
Fig. 9. Trial sequential analysis (TSA) of the effect of ibuprofen on postoperative opioid consumption [14].

Fig. 10. Trial sequential analysis (TSA) of the effect of ibuprofen on postoperative pain [14].
We showed several examples of how a TSA can be applied to meta-analyses published in the KJA. We believe that this study provides useful insights to better understand the use of this statistical tool.
Table 1. Characteristics of the Included Studies

<table>
<thead>
<tr>
<th>Author (yr)</th>
<th>Registration number</th>
<th>Main outcome</th>
<th>n</th>
<th>Intervention</th>
<th>Control</th>
<th>Overall effect (95% CI)</th>
</tr>
</thead>
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<tr>
<td>Choi et al. (2014) [11]</td>
<td>-</td>
<td>Incidence of rocuronium-induced withdrawal movement following pretreatment with lidocaine</td>
<td>905</td>
<td>223/480</td>
<td>316/425</td>
<td>Random effects using the M-H method: RR 0.60 (0.49, 0.74)</td>
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<td></td>
<td>Incidence of rocuronium-induced withdrawal movement following pretreatment with opioids</td>
<td>1016</td>
<td>146/582</td>
<td>353/434</td>
<td>Random effects using the M-H method: RR 0.28 (0.18, 0.44)</td>
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<tr>
<td>Bailey et al. (2020) [12] CRD42017051770</td>
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<td>Cumulative opioid consumption at 48 hours in patients undergoing midline laparotomy with continuous peripheral nerve blocks versus multimodal analgesia</td>
<td>1080</td>
<td>552</td>
<td>528</td>
<td>Random effects using the MD IV: –31.52 (–42.81, –20.22)</td>
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<td></td>
<td>Cumulative opioid consumption at 48 hours in patients undergoing midline laparotomy with continuous peripheral nerve blocks versus epidural analgesia</td>
<td>566</td>
<td>293</td>
<td>273</td>
<td>Random effects using the MD IV: 16.13 (–0.10, 32.36)</td>
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<tr>
<td>Min et al. (1999) [13]</td>
<td>-</td>
<td>Meperidine for prevention of postoperative shivering</td>
<td>70</td>
<td>5/35</td>
<td>17/35</td>
<td>Fixed effects using Peto OR: 0.2 (0.1, 0.5)</td>
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<tr>
<td></td>
<td></td>
<td>Clonidine for prevention of postoperative shivering</td>
<td>518</td>
<td>99/259</td>
<td>161/259</td>
<td>Fixed effects using Peto OR: 0.3 (0.2, 0.5)</td>
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<tr>
<td>Kim et al. (2021) [14] CRD42020166141</td>
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<td>Opioid consumption following treatment with ibuprofen</td>
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<td>135</td>
<td>134</td>
<td>Random effects using MD IV: –170.70 (–265.64, –75.77)</td>
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<td>Postoperative pain scores following treatment with ibuprofen</td>
<td>266</td>
<td>185</td>
<td>181</td>
<td>Random effects using MD IV: –0.58 (–0.99, –0.18)</td>
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<td>Kim et al. (2011) [15]</td>
<td>-</td>
<td>Incidence of postoperative nausea and vomiting following pretreatment with ramosetron</td>
<td>685</td>
<td>106/340</td>
<td>216/345</td>
<td>Random effects using RR IV: 0.40 (0.27, 0.58)</td>
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<tr>
<td>Kim et al. (2012) [16]</td>
<td>-</td>
<td>Efficacy and safety of lidocaine/tetracaine patch and peel to treat pain</td>
<td>574</td>
<td>211/298</td>
<td>70/276</td>
<td>Fixed effects using RR IV: 2.49 (2.01, 3.07)</td>
</tr>
</tbody>
</table>


Acknowledgements

We deeply thanks Michele Salvagno, MD for drawing Fig. 1.

Conflicts of Interest

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

Author Contributions

Alessandro De Cassai (Conceptualization; Formal analysis; Methodology; Project administration; Supervision; Writing – original draft; Writing – review & editing)
Martina Tassone (Conceptualization; Writing – original draft; Writing – review & editing)
Federico Geraldini (Writing – original draft; Writing – review &
References


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Continuous peripheral nerve blocks compared to thoracic epidurals or multimodal analgesia for midline laparotomy: a systematic review and meta-analysis

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Background: Continuous peripheral nerve blocks (CPNBs) have been investigated to control pain for abdominal surgery via midline laparotomy while avoiding the adverse events of opioid or epidural analgesia. The review compiles the evidence comparing CPNBs to multimodal and epidural analgesia.

Methods: We conducted a systematic review using broad search terms in MEDLINE, Embase, Cochrane. Primary outcomes were pain scores and cumulative opioid consumption at 48 hours. Secondary outcomes were length of stay and postoperative nausea and vomiting (PONV). We rated the quality of the evidence using Cochrane and GRADE recommendations. The results were synthesized by meta-analysis using Revman.

Results: Our final selection included 26 studies (1,646 patients). There was no statistically significant difference in pain control comparing CPNBs to either multimodal or epidural analgesia (low quality evidence). Less opioids were consumed when receiving epidural analgesia than CPNBs (mean difference [MD]: –16.13, 95% CI [–32.36, 0.10]), low quality evidence) and less when receiving CPNBs than multimodal analgesia (MD: –31.52, 95% CI [–42.81, –20.22], low quality evidence). The length of hospital stay was shorter when receiving epidural analgesia than CPNBs (MD: –0.78 days, 95% CI [–1.29, –0.27], low quality evidence) and shorter when receiving CPNBs than multimodal analgesia (MD: –1.41 days, 95% CI [–2.45, –0.36], low quality evidence). There was no statistically significant difference in PONV comparing CPNBs to multimodal (high quality evidence) or epidural analgesia (moderate quality evidence).

Conclusions: CPNBs should be considered a viable alternative to epidural analgesia when contraindications to epidural placement exist for patients undergoing midline laparotomies.

Keywords: Abdominal surgery; Catheters; Conduction anesthesia; Laparotomy; Multimodal analgesia; Nerve block; Statistics; Systematic review.
Introduction

It is estimated that 43.8% of the North American population will undergo abdominal surgery during their lifetime [1]. These procedures are associated with high rates of complications, particularly for comorbid or older patients [2]. Many physiologic insults are associated with inadequate pain control [3]. Given that pain increases postoperative morbidity, recovery time, duration of opioid use, health care costs, and quality of life impairment, optimizing pain control can help mitigate the negative consequences of surgery [3].

Open laparotomies, particularly those in the upper abdomen, are associated with respiratory complications if pain is not adequately controlled [4]. The incidence of postoperative pulmonary complications can be as high as 39% in high risk abdominal surgery, with increasing incidence each day that patients are not mobilized [5]. Currently, intravenous opioids are the most common medication for postoperative pain control following surgery [6]. Intravenous opioids attenuate the pain response and associated complications; however, in high doses some complications are exacerbated including respiratory depression, pneumonia, and ileus that in turn contribute to longer hospital stays and higher health care costs [7].

The most common regional anesthetic technique used for abdominal surgery is thoracic epidural [8]. Studies have consistently found that patients using thoracic epidural analgesia experience superior pain control and quality of life after laparotomy [9]. Guidelines for ‘Management of Postoperative Pain’ and ‘Enhanced Recovering After Surgery (ERAS) for Gastrointestinal Surgery’ both strongly recommend thoracic epidural analgesia [10,11]. There is reservation regarding the use of epidurals due to potentially devastating complications, such as epidural hematoma and abscesses [12]. In an attempt to avoid complications from systemic opioids or epidural placement, peripheral nerve blocks have been investigated. Initial reports described single shot nerve blocks that were effective at reducing pain; however, most reduction in opioid consumption occurs within the first 24 h [13,14]. Additionally, these studies do not compare the techniques to each other; thus, their relative efficacy and risk remain unclear.

Previous reviews have compared single shot transversus abdominis plane (TAP) blocks to placebo and wound infiltration [14]. Another review compared paravertebral blocks to epidural catheters, with only four of 20 using continuous catheters [15]. One systematic review examined the analgesic efficacy of wound infiltration compared to epidural analgesia [16]. The review included multiple types of incisions increasing the clinical heterogeneity. The purpose of this review is to determine the relative analgesic efficacy of continuous peripheral nerve blocks (CPNBs) compared to (i) multimodal analgesia and (ii) epidural analgesia in patients undergoing abdominal surgery via a midline laparotomy.

Materials and Methods

Search strategy

Our protocol was registered on PROSPERO (2017, https://www.crd.york.ac.uk/PROSPERO, no. CRD42017051770), at the beginning of the review process. Using broad search terms, we conducted a comprehensive search of three databases: Ovid MEDLINE, Embase, and the Cochrane Library. Our search strategy was developed in consultation with an expert medical librarian. We adapted the search terms used in Ovid MEDLINE (Supplementary Table 1) for other databases. We initially completed the search on November 30, 2016 later repeating it on July 1, 2018.

We did not apply language restrictions to this search. We conducted a search of the grey literature using OpenSIGLE (Supplementary Table 2) and conference abstracts. Once studies were selected for inclusion, a reference search and a forward citation search (using Web of Science) were conducted for each included study.

Inclusion criteria

Population

We included randomized controlled trials (RCTs) and cohort studies involving adult patients (aged > 18 years) undergoing elective abdominal surgery via a midline laparotomy. Urology, general surgery, or vascular surgery procedures performed through an open midline laparotomy were included.

Intervention

We included studies using regional anesthesia techniques to block pain transmission from the peripheral nerves of the abdominal wall. To be included, the technique must have blocked pain transmission on a continuous basis either by continuous infusion of a local anesthetic agent via a catheter for > 48 h, intermittent bolus injection of local anesthetic for > 48 h, or by administering liposomal bupivacaine. We included studies that compared these techniques to 1) continuous epidural analgesia covering the abdominal dermatomes and/or 2) multimodal analgesia with systemic opioids.

Outcomes

The primary outcomes of interest were pain control as measured...
sured by a visual analog scale (VAS) or a Numerical Rating Scale (NRS) and opioid consumption at 48 h. All VAS pain scores reported on a scale from 0 to 100 mm were converted to NRS pain scores by dividing by 10. Opioid consumption was compared by converting the reported consumption into oral morphine equivalents (OME) [17]. To be included, studies must have reported either pain scores or opioid consumption up to 48 h postoperatively. Secondary outcomes of interest were length of stay (LOS) in hospital and postoperative nausea and vomiting (PONV).

Exclusion criteria

Studies were excluded if they involved obstetrical, gynecologic, or trauma surgery. Studies involving children (< 18 years) or animals were also excluded. Case studies, case series, and reviews were excluded. If > 20% of patients were treated on an urgent or emergent basis, the study was excluded. Likewise, studies involving > 20% laparoscopic procedures were excluded. Patients undergoing procedures via other incisions were excluded.

Selection procedure

Two investigators (JB, CM) independently reviewed the title, abstract, and full text to assess inclusion and exclusion criteria. If consensus could not be reached between the two investigators, then a third investigator (RC, KK) resolved the disagreement.

Risk-of-bias assessment

We critically appraised each cohort study that met the inclusion criteria for potential biases using a modified version of the quality in prognosis studies (QUIPS) tool for cohort studies [18]. Each RCT was assessed using the Cochrane Risk of Bias Tool [19]. Two of the four investigators (JB, CM, RC, or JK) independently rated each domain in every study [19]. We categorized a study as having a high risk of bias in a domain if the bias was likely to change the results significantly [19].

Once all the studies were assessed independently, the reviewers came to a consensus on each domain. If a consensus was not reached, a third reviewer resolved the disagreement. Funnel plots were created for the primary outcomes to assess for publication bias if more than 10 studies reported a particular outcome. The overall certainty of the evidence was rated using the Cochrane handbook risk-of-bias tool and summarized using GRADEpro software (Evidence Prime, Inc., McMaster University, Canada) [19].

Data extraction

One of the four reviewers (JB, CM, RC, or JK) extracted pertinent data points from each included study using a standardized data extraction form. Each data point was then checked for accuracy by a second reviewer (JB, CM, RC, or JK). If further information or clarification was required, we contacted the corresponding author of the study.

Statistical analysis

We synthesized the data using random-effects meta-analysis with Revman 5.3.5 software (The Nordic Cochrane Centre, Denmark). We analyzed continuous data using inverse-variance mean differences and dichotomous data using Mantel–Haenszel odds ratios. Statistical heterogeneity was assessed using an I² statistic. Forest plots are displayed and interpreted using mean difference (MD) rather than standardized MD since pain scores were all converted to NRS and all opioid consumption was converted to OME in keeping with the Cochrane recommendations [19]. For any study with three comparison groups, the overall means of the shared control group with half the number of patients were used for comparison as per the Cochrane recommendations [19]. Since this review included various CPNBs, forest plots included subgroup analyses for each CPNB separately. These subgroup analyses were planned to evaluate the relative contribution of each technique toward the combined effect, and to evaluate the efficacy of each CPNB separately.

Our PROSPERO registration included two planned sensitivity analyses. First, any study found to have a high risk of bias in one or more categories would be removed. Since 19 of our 26 studies had at least one high risk of bias category, we modified our sensitivity analysis to remove studies with two or more high risk categories. A sensitivity analysis was performed to examine the effect of upper versus lower midline laparotomy (i.e., above or below the umbilicus) on the primary outcomes. In addition to the planned sensitivity analyses, we conducted additional post-hoc sensitivity analyses. We separated the results of those studies using an epidural solution that included opioids. We performed a sensitivity analysis removing cohort studies from the meta-analyses.

Results

Our search strategy yielded 19,889 results. Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20], we generated a flow chart of our selection process (Fig. 1). We contacted 31 authors for additional in-
formation. Of these authors, nine responded with the specific data we requested [21–29]. One author [30] responded by providing us with the raw anonymized study data. Two authors responded but did not have the data requested. One author declined to provide additional information unless given authorship on this review. Two authors had emails that were not current, and we were unable to reach them.

After title/abstract screening, correspondence with authors, hand-searching, and full-text assessment for eligibility, 26 studies involving 1,646 patients met the final inclusion for this review. Two studies [31,32] were cohort studies, while the rest were RCTs. Two studies [33,34] were divided into two subgroups for a total of 28 comparisons.

Risk of bias

We found that 19 studies had high potential for bias in one domain and, of those, nine had high potential for bias in at least two domains. The most common source of bias was blinding of participants and personnel. Blinding of personnel was considered to be high risk of bias if the study protocol allowed for differential treatment. Random sequence generation was considered to be high risk of bias if the described technique was known to not adequately randomize, whereas studies were rated as moderate or unclear risk of bias if the technique was not adequately described in the paper. Blinding of outcome assessment was deemed high risk of bias if the assessors were aware of the assignment to a study group.

Funnel plots did not suggest publication bias for pain scores or opioid consumption comparing between CPNB and multimodal analgesia (Supplementary Fig. 1). The funnel plots were not created for the comparisons between CPNB and epidural analgesia since there were less than 10 studies.

Multimodal analgesia

The types of multimodal analgesia were not specified a priori in our protocol. Two studies did not describe their multimodal analgesia approach [35,36]. The following agents were used as part of the multimodal analgesia strategy in included studies: Acetaminophen/Paracetamol (20 studies), non-specific NSAIDs (12 studies), COX-2 inhibitors (four studies), gabapentin (three studies), and tramadol (three studies). In two studies, both the intervention and control groups were provided with patient-controlled epidural analgesia [25,37]. These studies were considered multimodal in this review. The intervention group also received epidurals, lessening the potential effect of the CPNB.

Wound catheter

Three studies evaluated the effectiveness of wound catheters on pain management following midline laparotomies [28,34,38]. All three studies compared the use of wound catheters to systemic opioids, while Zheng et al. also compared wound catheters to epidurals. See Table 1 for baseline characteristics, local anesthetic dosing, and comparison groups. The wound catheters were all placed by surgeons.

Zheng et al. [34] found no difference in pain scores at rest or with movement among groups. Although Zheng et al. displayed these results as figures, exact numbers were not available for meta-analysis. Overall, patients with wound catheters used less opioids over 48 h (MD: –21.46 mg, 95% CI [–40.33, –2.59], P = 0.03, I^2 = 94%, three studies, n = 403) (Fig. 2).

Wang et al. [28] reported higher rates of PONV among wound catheter participants compared to controls. Zheng et al. [34] recorded lower PONV and sedation scores in the wound catheter group compared to the patient-controlled analgesia (PCA) group, particularly in the first 12 postoperative hours. There was a shorter LOS among participants in the wound catheter group than par-
<table>
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<th>Control</th>
<th>Age (Mean SD) years</th>
<th>Sex (% male)</th>
<th>BMI (Mean SD) m²/kg</th>
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<th>Control</th>
<th>CPNB type</th>
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<td>57 15 55 15 50 50</td>
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<td>59 12 56 12 36 48</td>
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<td></td>
<td></td>
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<td>62 10 61 14 25 33</td>
<td>25 4 28 3 Rectus</td>
<td>Surgeon</td>
<td>Levobupi 0.125%</td>
<td>n/a 25 mg q4h</td>
<td>Multiple</td>
<td></td>
<td></td>
<td></td>
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<tr>
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<td>50</td>
<td>50</td>
<td>60 12 59 14 64 28</td>
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<td>n/a n/a</td>
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<td>Kadam 2011</td>
<td>Australia</td>
<td>10</td>
<td>10</td>
<td>NR NR NR NR NR NR NR TAP</td>
<td>Anesthesia</td>
<td>Ropi 0.2%</td>
<td>8–10 n/a</td>
<td>Multiple</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>B. Epidural</td>
<td></td>
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<tr>
<td>Zheng 2016§</td>
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<td>25</td>
<td>12</td>
<td>62 13 62 10 64 56</td>
<td>23 2 23 3 Wound</td>
<td>Surgeon</td>
<td>Ropi 0.3%</td>
<td>5 n/a</td>
<td>Gastrectomy</td>
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<td></td>
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<td>25</td>
<td>68 12 62 18 36 44</td>
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<td>Surgeon</td>
<td>Ropi 0.2%</td>
<td>10 n/a</td>
<td>Colorectal, UGI, HPB</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ball 2016</td>
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<td>26</td>
<td>25</td>
<td>73 3 74 2 92 84</td>
<td>26 3 27 3 Preperitoneal</td>
<td>Surgeon</td>
<td>Levobupi 0.25%</td>
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<td></td>
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<td>10 n/a</td>
<td>Colorectal</td>
<td></td>
<td></td>
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<td>Ropi 0.2%</td>
<td>10 n/a</td>
<td>Colorectal</td>
<td></td>
<td></td>
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<td>7</td>
<td>6</td>
<td>56 17 60 16 43 67</td>
<td>31 10 32 8 Preperitoneal</td>
<td>Surgeon</td>
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<td>4–5 n/a</td>
<td>Colorectal</td>
<td></td>
<td></td>
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<tr>
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<td>64 10 61 13 64 70</td>
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<td>Colorectal, urology, UGI</td>
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<td>Shaker 2018</td>
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<td>29 8 28 4 TAP</td>
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<td>LB + Bupi 0.5%</td>
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<td>66 5 66 5 50 45</td>
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<td>Anesthesia</td>
<td>Bupi 0.25%</td>
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<td>Colorectal, UGI, hernia</td>
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<td>Yassin 2017</td>
<td>Egypt</td>
<td>29</td>
<td>31</td>
<td>48 9 48 12</td>
<td>23 21 28 2 28 1 Rectus</td>
<td>Anesthesia</td>
<td>Bupi 0.25%</td>
<td>n/a 20 ml q8h</td>
<td>UGI, HPB</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hutchins 2018</td>
<td>USA</td>
<td>25</td>
<td>23</td>
<td>68 12 64 9 48 61</td>
<td>NR NR NR Paravertebral</td>
<td>Anesthesia</td>
<td>Ropi 0.2%</td>
<td>14 n/a</td>
<td>Pancreatectomy</td>
<td></td>
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</tbody>
</table>

(Continued to the next page)
Participants in the PCA group. Rates of PONV and LOS were not significantly different between the wound catheter and epidural groups.

Intraperitoneal catheters

The evidence for intraperitoneal catheters comes from two double-blind placebo-controlled RCTs using the ON-Q® system [37,39]. In the first RCT, Baig et al. [39] studied 66 patients undergoing elective colectomy and found that intraperitoneal catheters decreased the 48-h opioid consumption. There was no significant difference in pain scores except for postoperative day two afternoon. The generalizability of the study is limited by the lack of multimodal analgesia.

The second RCT consists of 60 patients undergoing colectomy, with both groups also receiving thoracic epidurals [37]. This study also found that an intraperitoneal catheter infusion for three days further decreased the pain scores with movement and coughing at multiple time points within the first week postoperatively. However, the data need to be interpreted in the context of overall low pain scores (maximum 4/10) in both groups. We were not able to obtain opioid consumption data from the study authors for meta-analysis.

Preperitoneal catheters

There were 12 studies included involving preperitoneal catheters with seven compared against multimodal analgesia [25,30,31,35,40–42] and five compared against epidural catheters [21,24,43–45]. In all cases, the catheters were placed by the surgeon during wound closure. In one case, both the preperitoneal and the comparison groups received thoracic epidurals [25]. We considered this study to compare multimodal analgesia with preperitoneal catheters since both groups received epidurals, which we assumed would decrease the overall effect of preperitoneal catheters.

Of the studies comparing preperitoneal catheters to multimodal analgesia, only four of seven reported 48-h pain scores. There was no significant difference in pain at 48 h, either individually or pooled (MD: –0.01, 95% CI [–0.12, 0.10], \( P = 0.84, I^2 = 0\%\), four studies, 294 patients). The pooled results of six studies showed less cumulative opioid consumption at 48 h in patients with preperitoneal catheters than those receiving multimodal analgesia (Fig. 2). When compared to epidurals, there was no significant difference in pain scores (MD: 0.38, 95% CI [–0.10, 0.86], \( P = 0.12, I^2 = 12\%\), three studies, 114 patients). The pooled results of these two studies showed less opioid consumption among patients.
with epidurals (Fig. 3).

Compared to placebo, preperitoneal catheters reduced LOS in two of four studies reporting hospital stay duration; however, the overall effect was not statistically significant (MD: –1.77 days, 95% CI [–5.04, 1.54], P = 0.29, I² = 65%, three studies, 192 patients) (Supplementary Table 2) [25,35,40,42]. Epidurals reduced LOS compared to preperitoneal catheters in two of three studies (MD: 1.11 days, 95% CI [0.71, 1.51], P < 0.001, I² = 65%, three studies, 157 patients) (Supplementary Table 3) [43–45].

**TAP catheters**

Five studies involving TAP catheters were included, with two comparing to multimodal analgesia [23,32] and three comparing to epidural analgesia [26,36,46]. In one study, the TAP catheters were placed by the surgeon [32], whereas in the other four studies TAP catheters were placed by anaesthetists under ultrasound guidance [23,26,36,46]. The opioid groups did not have catheters placed and all patients in those studies received PCA pumps.

Kadam and Field [23] found a significant reduction in pain scores during coughing in the first two days for patients with TAP catheters compared to multimodal analgesia. Wahba and Kamal [36] found that the epidural group had significantly lower pain scores at all time points compared to the TAP group. The other three studies found no differences in pain scores. There was no significant difference overall in pain scores compared to multimodal analgesia (MD: –1.32, 95% CI [–2.70, 0.06], P = 0.06, I² = 52%, two studies, 120 patients) or epidural analgesia (MD: 0.89, 95% CI [–1.10, 2.88], P = 0.38, I² = 95%, three studies, 133 patients). Both studies comparing with opioid analgesia found a sig-
significant reduction in opioid use over 48 h when patients received TAP catheters (Fig. 2) [25,32]. The evidence for comparing TAP catheters to epidurals was conflicting. One study comparing TAP to epidural catheters found no difference in opioid consumption [46], one found a significant reduction in opioid use with epidural analgesia [36], and the other found less opioid use in the TAP group [26] (Fig. 3). It must be noted that the study finding higher opioid use in the epidural group included a converted dose of the epidural opioids in the total opioid consumption [26]. Wahba and Kamal [36], and Rao Kadam et al. [46] did not use opioids in their epidural solution [36,46].

Fig. 3. Cumulative opioid consumption (in oral morphine equivalents) at 48 h comparing between continuous peripheral nerve blocks (CPNB) and epidural analgesia for patients undergoing midline laparotomy. CPNB: continuous peripheral nerve block, IV: inverse variance, SD: standard deviation, green color: low risk of bias, yellow color: unclear/moderate risk of bias, red color: high risk of bias, bold text: indicates subgroups, subtotal and total effect sizes and weighting.

Two studies involving rectus sheath block (RSB) catheters were included with one comparing to multimodal analgesia [33] and one comparing to epidural analgesia [29]. Purdy et al. [33] included three groups: RSB with intermittent dosing, RSB with continuous infusion, and a control (opioid analgesia). The catheters were placed by the surgeon in the Purdy et al. [33] study and under ultrasound guidance by an anesthesiologist in the Yassin 2017 study.

Purdy et al. [33] found no differences in pain scores at any time point [29]. In terms of opioid consumption at 48 h, Purdy et al. [33] found a reduction among both RSB groups compared to multimodal analgesia (Fig. 2), whereas Yassin et al. [27] found opioid consumption to be sig-

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>CPNB</th>
<th>Epidural</th>
<th>Mean Difference</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
<td>25</td>
<td>22.00%</td>
<td></td>
</tr>
<tr>
<td>Mean Difference</td>
<td>1.59</td>
<td>(-1.47, 4.65)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean Difference</td>
<td>1.59</td>
<td>(-1.47, 4.65)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.02 (P = 0.31)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Total (95% CI)    |       |          |                |              |
| Weight            | 12    | 12       | 22.00%         |              |
| Mean Difference   | 1.59  | (-1.47, 4.65) |                |              |
| Mean Difference   | 1.59  | (-1.47, 4.65) |                |              |
| Heterogeneity: Not applicable |       |          |                |              |
| Test for overall effect: Z = 1.02 (P = 0.31) |       |          |                |              |
significantly lower in the epidural group compared to the RSB group (Fig. 3).

Paravertebral catheters

Two randomized trials on paravertebral catheters met the inclusion criteria [22,27]. Hutchins et al. [22] studied 48 patients undergoing open pancreatic surgery randomized to T8 paravertebral catheters or T7–8 epidurals. This trial found that while opioid consumption was decreased within the first 24 h in the epidural group, there was no difference in opioid consumption at other time points (Fig. 3). Moreover, there was no significant difference in pain scores.

In a pragmatic randomized trial of 70 patients comparing bilateral paravertebral versus epidurals, all inserted between T7 and T9, Sondekoppam et al. [27] found that paravertebral catheters provided non-inferior analgesia for the primary outcome of 24-h pain score with movement. Within the follow-up period of 72 h, there was no significant difference in pain scores or opioid consumption. The LOS in hospital was also similar (MD: –1.40 days, 95% CI [–4.31, 1.51], P = 0.34, I² = 23%, two studies, 116 patients) (Supplementary Fig. 3).

Overall comparison and sensitivity analyses

Primary outcomes

When comparing the combined effects of all CPNB studies, there was no statistically significant difference in pain scores between CPNB and either multimodal analgesia or epidural analgesia (MD: –0.35, 95% CI [–0.77, 0.07], P = 0.10, I² = 95%, 10 studies, 909 patients; MD: 0.45, 95% CI [–0.13, 1.04], P = 0.13, I² = 84%, eight studies, 375 patients, respectively) (Tables 2 and 3). Patients receiving CPNB used significantly less opioids than those receiving multimodal analgesia (MD: –31.52, 95% CI [–42.81, –20.22], P < 0.001, I² = 93%, 13 studies, 970 patients). This was observed for the subgroups receiving continuous wound and preperitoneal catheters (Fig. 2). There was no statistically significant difference in opioid use between CPNB and epidural analgesia in the overall comparison (MD: 16.13, 95% CI [–0.10, 32.36], P = 0.05, I² = 94%, eight studies, 342 patients); however, opioid consumption was reduced in patients receiving epidural analgesia in the preperitoneal, rectus sheath, and paravertebral subgroups (Fig. 3).

Secondary outcomes

Length of hospital stay was significantly shorter for the epidural group compared to the CPNB group (MD: 0.78 days, 95% CI [–2.45, 0.36], P = 0.34, I² = 23%, two studies, 116 patients) (Supplementary Fig. 3).

### Table 2. Summary of Findings for Continuous Peripheral Nerve Block (CPNB) Compared to Multimodal for Patients Undergoing Surgery via Midline Laparotomy

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain assessed with Numeric Rating Scale</td>
<td>MD 0.35 lower (0.77 lower to 0.07 higher)</td>
<td>Risk with CPNB</td>
<td>0.99</td>
<td>⨁⨁◯◯</td>
<td>The evidence suggests CPNB results in little to no difference in pain. Low certainty: We have very little confidence in the estimate of the effect; the true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td>Opioid consumption assessed with Oral morphine equivalents</td>
<td>MD 31.52 lower (42.81 lower to 20.22 lower)</td>
<td>Risk with CPNB</td>
<td>0.97</td>
<td>⨁⨁◯◯</td>
<td>The evidence suggests CPNB reduces opioid consumption. Low certainty: We have very little confidence in the estimate of the effect; the true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td>Length of hospital stay assessed with days</td>
<td>MD 1.41 (lower 0.45 to higher 2.86 lower)</td>
<td>Risk with CPNB</td>
<td>0.70</td>
<td>⨁⨁◯◯</td>
<td>The evidence suggests CPNB reduces length of hospital stay. Low certainty: We have very little confidence in the estimate of the effect; the true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td>Postoperative nausea and vomiting 127 per 1,000</td>
<td>RR 0.89 (0.72 to 1.0)</td>
<td></td>
<td>568</td>
<td>⨁⨁⨁⨁</td>
<td>CPNB results in little to no difference in PONV. High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident that the true effect is close to the estimate of the effect; we believe there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.</td>
</tr>
</tbody>
</table>
### Table 3. Summary of Findings for Continuous Peripheral Nerve Block (CPNB) Compared to Epidural Analgesia for Patients Undergoing Surgery via Midline Laparotomy

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Anticipated absolute effects* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No. of participants (studies)</th>
<th>Certainty of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
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<tr>
<td>Pain assessed with: Numeric rating scale</td>
<td>The mean pain score was 1.8</td>
<td>MD 0.45 higher (0.13 lower to 1.04 higher)</td>
<td>-</td>
<td>375 (8 RCTs)</td>
<td>★★★★★ The evidence suggests that CPNB results in little to no difference in pain.</td>
</tr>
<tr>
<td>Opioid consumption assessed with: Oral morphine equivalents</td>
<td>The mean opioid consumption was 35.4 mg</td>
<td>MD 16.13 mg higher (0.10 lower to 32.36 higher)</td>
<td>-</td>
<td>342</td>
<td>★★★★★ The evidence suggests epidural analgesia slightly decreases opioid consumption compared to CPNB.</td>
</tr>
<tr>
<td>Length of hospital stay assessed with: days</td>
<td>The mean length of hospital stay was 5.7 days</td>
<td>MD 0.78 days higher (0.27 higher to 1.29 higher)</td>
<td>-</td>
<td>399 (8 RCTs)</td>
<td>★★★★★ The evidence suggests epidural analgesia decreases length of hospital stay compared to CPNB.</td>
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<tr>
<td>Postoperative nausea and vomiting</td>
<td>103 per 1,000</td>
<td>104 per 1,000 (60 to 175)</td>
<td>OR 1.02 (0.56 to 1.86)</td>
<td>265 (5 RCTs)</td>
<td>★★★★★ CPNB likely results in little to no difference in PONV compared to epidural analgesia.</td>
</tr>
</tbody>
</table>

*The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). †The majority of included studies had at least one high risk of bias domain. ‡There was statistically significant heterogeneity. CPNB: continuous peripheral nerve block, MD: mean difference, OR: odds ratio, PONV: postoperative nausea and vomiting, RCT: randomized controlled trial, RR: relative risk. GRADE Working Group grades of evidence: High certainty: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of the effect.
[0.27, 1.29], \( P = 0.003, I^2 = 59\%\), eight studies, 399 patients, Table 3 & Supplementary Fig. 3) and again less for the CPNB group compared to multimodal analgesia (MD: –1.41 days, 95% CI [–2.45, –0.36], \( P = 0.008, I^2 = 98\%\), eight studies, 770 patients, Table 2 & Supplementary Fig. 2). PONV was not statistically significantly different between either multimodal or epidural analgesia overall (odds ratio [OR]: 0.89, 95% CI [0.72, 1.10], \( P = 0.30, I^2 = 0\%\), seven studies, 568 patients; OR: 1.02, 95% CI [0.56, 1.86], \( P = 0.96, I^2 = 36\%\), five studies, 265 patients), nor for any of the subgroups (Tables 2 and 3).

Sensitivity analyses

We examined the robustness of the main outcomes by conducting a series of sensitivity analyses (Supplementary Table 3). Nine studies had two or more domains that were deemed to have high risk of bias [21–23,26–28,32,42,46]. In the primary analyses, the difference in opioid consumption between CPNPs and epidurals only bordered on statistical significance. However, there was a significant difference in opioid consumption favoring epidurals once the high risk of bias studies were removed (MD: 16.66, 95% CI [2.48, 30.84], \( P = 0.02, I^2 = 96\%\), five studies, 205 patients). Removing the high risk of bias studies resulted in the LOS difference becoming non-significant between CPNB and multimodal analgesia (MD: –1.57 days, 95% CI [–3.61, 0.48], \( P = 0.13, I^2 = 88\%\), six studies, 570 patients). Other outcomes were minimally affected by removing the high risk of bias studies.

The only two studies that included patients with a lower midline incision were removed to examine the effect [30,42]. Removing these studies had minimal effect on the pain scores, PONV, opioid consumption, or LOS. The two cohort studies comparing CPNBs to multimodal analgesia were removed to examine the effect [31,32]. Removing cohort studies had minimal effect on pain scores, PONV, and opioid consumption. However, the difference in LOS became a statistical non-significant result (MD: –1.29 days, 95% CI [–3.16, 0.57], \( P = 0.17, I^2 = 94\%\), seven studies, 670 patients).

Eight studies [21,22,26,27,34,43–45] used opioids in the epidural solution while four studies [24,29,36,46] used only local anesthetics. Removing the studies that did not use opioids in the epidural solution did not change the effect size of pain scores but made the results statistically significant (MD: 0.48, 95% CI [0.34, 0.61], \( P < 0.001, I^2 = 0\%\), four studies, 216 patients). Only one study explicitly stated that epidural opioids were included in the calculation of cumulative opioid consumption [26]. Removing these studies reduced the effect size of opioid consumption between CPNB and epidural analgesia (MD: 4.48 mg, 95% CI [–14.95, 23.91 mg], \( P = 0.65, I^2 = 93\%\), four studies, 183 patients). Removing these studies had minimal effect on the LOS and PONV rates.

Discussion

The use of CPNBs, often in the form of fascial plane blocks, is increasingly common [47]. The popularity of these techniques has grown in response to the potential complications and drawbacks of neuraxial analgesia such as hypotension from sympathetic blockade, leg weakness, epidural hematomas, and epidural abscesses [47]. However, many of these techniques are relatively new and their efficacy has not been established relative to epidural analgesia, opioid analgesia, or to one another.

We found that pain scores were not significantly different when comparing the combined effect of all CPNBs to either multimodal or epidural analgesia for abdominal surgery via a midline laparotomy. Our meta-analysis found that opioid consumption was significantly less for CPNBs compared to conventional analgesia with opioids, particularly for wound, preperitoneal, and rectus sheath catheters. There was no significant difference in opioid consumption when comparing CPNBs as a whole to epidural analgesia. However, opioid consumption was significantly less for patients receiving epidural analgesia when compared to preperitoneal, rectus sheath, and paravertebral catheters. In a number of cases, this review states that there are no significant differences between CPNBs and either multimodal or epidural analgesia. This does not necessarily imply equivalency between the two techniques, but rather insufficient data to suggest superiority of one technique over the other. This is particularly true when a small number of studies are used in the comparison. Although meta-analysis seeks to increase statistical power by combining studies, the power may decrease when a small number of studies are included. Because the random-effects model accounts for between-study variation, five or more studies are required to reliably achieve greater power than the primary studies [48].

Overall, the main findings of this review were robust, being only minimally influenced by the sensitivity analyses. Removing studies with procedures using lower midline incisions did not significantly change the results of the meta-analyses. When studies with two or more high risk of bias domains were removed from the opioid consumption, comparison moved from bordering on statistical significance to favoring epidurals; however, the change in effect size between groups was negligible. LOS was the most sensitive to removing high risk studies. When high risk of bias and cohort studies were removed the difference in LOS became not statistically significant with the point estimate moving in the opposite direction.
One area of concern is that we were not able to determine whether most studies included opioids administered via the epidural route in the calculation of total cumulative opioid consumption. This was only explicitly stated in one study. This may have a large impact on whether one technique is favored over another in terms of opioid reduction for a few reasons. Although there is some uncertainty about equianalgesic dose conversion from IV systemic to epidural opioids, the most commonly cited conversion is 10 : 1 for both morphine and hydromorphone [49]. Thus, even low dose opioids added to epidural solutions can contribute to a large proportion of the cumulative opioid consumption. Furthermore, the patients would receive this amount of opioid regardless of whether they needed it. This creates a conflict for pain research because including epidural opioids in the cumulative opioid consumption will favor other techniques, while not including them will favor epidurals. Our recommendation is future studies comparing CPNB to epidural analgesia use only local anesthetic without opioids in the epidural solution if using opioid consumption as an outcome. The next best option is to be very explicit in the method of equianalgesic opioid conversion from the epidural solution to the cumulative opioid consumption.

The majority of studies in this review had at least one domain that was deemed to have high potential for bias. Our ability to draw firm conclusions from this review was hampered by this high risk of bias. However, removing the studies with two or more domains of high risk of bias did not influence the pain score comparison. The finding that epidurals may reduce opioids more than CPNBs was strengthened when removing these studies and the finding that CPNBs may reduce LOS compared to multimodal analgesia was lessened. Overall, if bias was influencing the results of the studies, it seems to exaggerate the benefits of CPNBs in our included studies.

In addition to the risk of bias, our ability to draw conclusions was limited by heterogeneity. There was some clinical heterogeneity between studies due to various types of surgery and practice patterns regarding the type and dose of analgesics and adjuncts. However, pooled results for pain scores and opioid consumption were deemed acceptable by our team since the bulk of postoperative pain originates from the abdominal wall [50]. All included studies involved a midline incision and each intervention was aimed at reducing afferent nociceptive signaling from the thoracoabdominal nerves. There was also statistical heterogeneity found in many of our analyses. This was expected given the practice variation in terms of pain management and uses of adjunct therapies. The heterogeneity seen in terms of pain and opioid consumption also relates strongly to the type of surgery. Despite these differences, the pooled results were deemed acceptable given that in each case the two comparison groups were undergoing the same surgical procedure and were subject to the same pain management practice patterns. Ideally, we would have compared various CPNB techniques to one another using a network meta-analysis. We contemplated this but decided that, given the degree of clinical and statistical heterogeneity described above, the assumptions of transitivity and consistency would not be met.

This review did not find evidence of superior pain scores between CPNBs and either multimodal or epidural analgesia. CPNBs may decrease postoperative opioid consumption and hospital LOS compared to multimodal analgesia. Epidural analgesia may further decrease opioid consumption and LOS when compared to CPNBs. CPNBs should be considered a viable alternative to epidural analgesia when contraindications to epidural placement exist for patients undergoing midline laparotomies. Future studies should directly compare various CPNB techniques to one another. Future systemic reviews should seek to directly or indirectly compare various CPNB techniques once enough high-quality studies allow assumptions to be met.

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**Conflicts of Interest**

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

**Author Contributions**

Jonathan G. Bailey (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Writing – original draft)

Catherine W Morgan (Data curation; Formal analysis; Funding acquisition; Project administration; Writing – review & editing)

Russell Christie (Data curation; Formal analysis; Investigation; Writing – review & editing)

Janny Xue Chen Ke (Data curation; Formal analysis; Investigation; Writing – review & editing)

M. Kwesi Kwofie (Conceptualization; Writing – review & editing)

Vishal Uppal (Conceptualization; Formal analysis; Methodology; Writing – review & editing)
Supplementary Materials

Supplementary Table 1. Search strategy for Embase, Cochrane, and MEDLINE databases
Supplementary Table 2. OpenGrey search strategy (adapted from the MEDLINE search)
Supplementary Table 3. Summarized results of sensitivity analyses
Supplementary Fig. 1. Funnel plot to assess publication bias for studies comparing pain scores and cumulative opioid consumption between continuous peripheral nerve blocks (CPNB) and multimodal analgesia. A: pain scores, B: opioid consumption, MD: mean difference, TAP: transversus abdominis plane, SE: standard error
Supplementary Fig. 2. Length of stay (LOS) in hospital comparing between continuous peripheral nerve blocks (CPNB) and multimodal analgesia for patients undergoing midline laparotomy. CPNB: continuous peripheral nerve block, IV: inverse variance, PCA: patient-controlled analgesia, SD: standard deviation, green color: low risk of bias, yellow color: unclear/moderate risk of bias, red color: high risk of bias, bold text: indicates subgroups, subtotal and total effect sizes and weighting.
Supplementary Fig. 3. Length of stay in hospital comparing between continuous peripheral nerve blocks (CPNB) and epidural analgesia for patients undergoing midline laparotomy. CPNB: continuous peripheral nerve block, IV: inverse variance, SD: standard deviation, green color: low risk of bias, yellow color: unclear/moderate risk of bias, red color: high risk of bias, bold text: indicates subgroups, subtotal and total effect sizes and weighting.

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Effect of single dose preoperative intravenous ibuprofen on postoperative pain and opioid consumption: a systematic review and meta-analysis

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Background: Ibuprofen, a well-known analgesic, is commonly used as a component of a multimodal analgesic approach for postoperative pain. This systematic review and meta-analysis aimed to investigate whether a single-dose preoperative intravenous ibuprofen can reduce postoperative pain and opioid consumption.

Methods: PubMed/MEDLINE, Embase, Cochrane Library (CENTRAL), and Web of Science databases were searched to identify relevant studies published up to May 2020. Randomized controlled trials comparing preoperative single-dose intravenous ibuprofen effect with the control group on postoperative pain and opioid consumption after surgery under general anesthesia were included.

Results: Six studies involving 366 participants were included. Single-dose administration of intravenous ibuprofen preoperatively significantly reduced postoperative pain score on a scale of 0–10 at 1 h (MD: –1.64, 95% CI [–2.56, –0.72], P < 0.001, I² = 95%), at 4–6 h (MD: –1.17, 95% CI [–2.09, –0.26], P < 0.001, I² = 94%), and 24 h (MD: –0.58, 95% CI [–0.99, –0.18], P < 0.001, I² = 90%). Cumulative opioid consumption, presented as fentanyl equivalents, was also reduced significantly in the ibuprofen group compared to placebo group until postoperative 4–6 h (MD: –56.35 μg, 95% CI [–101.10, –11.60], P < 0.001, I² = 91%) and 24 h (MD: –131.39 μg, 95% CI [–224.56, –38.21], P < 0.001, I² = 95%).

Conclusions: Preoperative single-dose intravenous ibuprofen can reduce postoperative pain and opioid consumption until 24 h postoperatively. Considering the high heterogeneity and small number of studies included, care should be taken when generalizing these findings.

Keywords: Analgesics; Anesthesia and analgesia; Ibuprofen; Pain management; Postoperative pain; Preoperative period; Statistics; Systematic review.

Introduction

Poorly controlled postoperative pain may negatively affect patients’ clinical outcomes, such as postoperative complications and rehabilitation [1,2]. Multimodal analgesia is strongly recommended for the effective management of postoperative pain rather than using opioids alone [3,4]. In addition, multimodal analgesia is one of the key components of the enhanced recovery after surgery protocol, which aims to achieve early recovery through diverse approaches. Through multimodal analgesia, patients experience fewer opioid-induced adverse effects, early recovery, and early discharge by reducing the perioperative use of opioids [5].
Nonsteroidal anti-inflammatory drugs (NSAIDs) are an important part of multimodal regimens for postoperative analgesia [6]. In combination with opioids, NSAIDs reduce opioid consumption and opioid-related side effects, such as nausea and vomiting [7].

Ibuprofen is an NSAID that inhibits cyclooxygenase enzymes, which convert arachidonic acid to prostaglandin H2, a mediator of inflammation, pain, and fever. Among the widely used NSAIDs, ibuprofen is less likely to cause gastrointestinal adverse events and cardiovascular risk [8,9]. Ibuprofen is preferred in various types of surgeries and patient populations because of its safety profile.

Although ibuprofen has a long history of use as an oral analgesic, intravenous ibuprofen has been used in clinical practice for just over 10 years, since its approval by the United States Food and Drug Administration in 2009. In adults, it is recommended to administer 400–800 mg of intravenous ibuprofen every 6 h as necessary, with a maximum limit of 3,200 mg per day [10].

The usefulness of multiple doses of IV ibuprofen in conjunction with opioids has been reported in the perioperative setting [11,12]. However, limited data are available on its usefulness when administered preoperatively through the intravenous route. Recently, a single dose of preoperative intravenous ibuprofen was suggested as an intervention to enhance the effectiveness of postoperative analgesia; however, inconsistent results were presented [13–18].

We hypothesized that the preoperative single dose administration of intravenous ibuprofen to surgical patients reduces postoperative pain and subsequent analgesic requirements. The objective of this study was to determine the effect of preoperative single dose intravenous ibuprofen on the severity of postoperative pain and opioid consumption by meta-analysis of data from previous randomized controlled studies.

Materials and Methods

Study design

This meta-analysis followed the ‘Preferred Reporting Items for Systematic Reviews and Meta-Analyses’ (PRISMA; Appendix 1). The study was registered in the ‘International Prospective Register of Systematic Reviews’ (PROSPERO; https://www.crd.york.ac.uk/PROSPERO, no. CRD42020166141).

Information sources and search strategy

Two authors (SK and KK) searched PubMed/MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science databases. The search terms included variants of terms, such as ‘ibuprofen,’ ‘intravenous,’ ‘postoperative pain,’ ‘analgesia,’ ‘opioid,’ ‘fentanyl,’ ‘morphine,’ and ‘patient controlled analgesia,’ as well as Medical Subject Heading or Embase Subject Heading terms (Appendix 2).

There was no limitation on the year of publication, but we limited the search to randomized controlled trials conducted on humans. The language of the article was limited to English and Korean. The date of the last search was May 12, 2020.

Study selection and eligibility criteria

After searching the articles from the databases listed above, two authors (SK and KK) selected the studies independently. Selection consisted of the following three steps: the two authors first selected the articles based on the title and then the abstract, and for the remaining articles, the two authors reviewed the full text of each article for the final selection. In case of disagreement, the two authors discussed the final selection of the articles until an agreement was reached.

The inclusion criteria were as follows: (1) patients under general anesthesia; (2) ibuprofen was administered intravenously; (3) ibuprofen was administered preoperatively, which is defined as before surgical incision; (4) control group using placebo was reported with results; and (5) primary outcomes of original articles were postoperative pain scores or opioid consumption.

Studies were excluded based on the following criteria: (1) articles not written in English or Korean; (2) patients not under general anesthesia; (3) ibuprofen was not administered intravenously; (4) ibuprofen was administered after skin incision or multiple times; (5) did not include appropriate postoperative outcomes; (6) non-randomized clinical trials; (7) non-human studies; and (8) did not compare with the appropriate control group. We also excluded articles that were not available in full text.

Risk of bias in individual studies

Based on the ‘risk of bias’ of the Review Manager software (RevMan, version 5.3; The Cochrane Collaboration, UK), two authors (SK and KK) independently evaluated the quality of articles. A third author (SL) was included to resolve disagreements when needed. Seven categories were included to assess the risk of bias: random sequence generation and allocation concealment for detecting selection bias, blinding of participants for performance bias, blinding of outcome assessor for detection bias, incomplete outcome data for attrition bias, selective reporting for reporting
bias, and other biases that were not covered by the above categories. We specified the adequacy of the sample size calculation as ‘other bias,’ the seventh category. The risk of bias was rated as ‘high,’ ‘low,’ or ‘unclear’ in each original article. The agreement of two independent raters regarding the risk of bias for the seven categories was evaluated using Cohen’s kappa. The authors interpreted the Cohen’s kappa values based on Cohen’s suggestions as follows: (1) below 0.00, no agreement; (2) 0.00–0.20, slight agreement; (3) 0.21–0.40, fair agreement; (4) 0.41–0.60, moderate agreement; (5) 0.61–0.80, substantial agreement; and (6) 0.81–1.00, almost perfect agreement.

Data collection process and extracted items

Two authors (SK and KK) extracted data from the articles and cross-checked the data to avoid missing any information or extracting incorrect information. The extracted information included patient age, study design, publication year, authors’ first name, type of surgery, timing and dosage of study drug, and measured outcomes. The measured outcomes were as follows: postoperative pain score, postoperative analgesic regimen, and analgesic consumption. Two authors (SK and KK) independently extracted the data from the text, tables, and graphs. Cohen’s kappa was used to assess the agreement between the two authors on the extracted data, and the values were interpreted in a manner similar to the risk of bias.

We extracted pain scores at postoperative 1, 4–6, and 24 h to reflect immediate, early, and late postoperative pain, respectively, for the analysis of pain scores. If the pain score was not measured at postoperative 6 h in the original articles, we used pain scores measured at postoperative 4 h as a replacement [13,15–17]. Cumulative opioid consumption up to postoperative 4–6 h and 24 h was included. We extracted data on cumulative opioid consumption at postoperative 6 h, and if data were not available at 6 h, we extracted data measured at postoperative 4 h as a replacement [16,17].

To analyze the intensity of postoperative pain, pain scores measured using the visual analog scale (VAS) or numerical rating scale (NRS) were extracted from each study. When the studies evaluated pain scores during movement and resting state simultaneously, we only used scores assessed in the resting state. If the studies used opioids other than fentanyl, we converted them into fentanyl equivalents [14,18].

Statistical analysis

Summary measures

Pain scores were extracted using the mean and standard deviation at specified time points. We also extracted the mean and standard deviation of cumulative opioid consumption in a similar manner.

Synthesis of results

The VAS and NRS scores were strongly correlated [19], and pain scores were measured on the same scale (0–10) in all included studies. In addition, opioid consumption was converted into fentanyl equivalents (μg). Therefore, we calculated the mean differences (MDs) for continuous outcomes (postoperative pain scores or cumulative opioid consumption). We calculated the 95% CI for all estimates. A random-effect model was used for all trial results, because of the possibility of different effect sizes across the studies. To measure heterogeneity among the trials, Higgins’ $I^2$, the heterogeneity statistic Cochrane’s Q, and the corresponding P values were calculated. We considered $I^2 > 50\%$ as significant heterogeneity.

Sensitivity analysis was performed by leave-one-out analyses using meta and dmetar packages in R software (version 3.6.3, R Foundation for Statistical Computing, Austria).

Publication bias was not assessed in this meta-analysis, because the number of included studies was less than 10. We used Review Manager (RevMan, version 5.3, The Cochrane Collaboration) and R software (version 3.6.3, R Foundation for Statistical Computing, Austria) for all analyses.

Results

Study selection and characteristics

The authors obtained 1,534 articles after an initial database search of PubMed (n = 154), Embase (n = 880), the Cochrane Library (n = 348), and Web of Science (n = 152). We excluded 350 duplicate articles. Two authors reviewed the articles independently, and subsequently excluded 109 reports based on the title and 1011 articles based on the abstract. Final full-text reviews were performed on the remaining 64 articles. Of the 64 articles, 58 were excluded based on exclusion criteria. Details of the reason for the exclusion are described in Fig. 1.

The characteristics of the six studies are presented in Table 1. All articles were randomized clinical trials. The types of surgeries were diverse, including laparoscopic cholecystectomy [16,17], septrhinoplasty [13,18], pancreaticoduodenectomy [14], and thyroidectomy [15]. Ibuprofen was administered intravenously in all the studies; however, the doses were different: one study administered 400 mg of ibuprofen [17], while other studies injected 800 mg of ibuprofen. Furthermore, opioids used in these studies...
Articles searched from databases with keywords
• PubMed (n = 154)
• Embase (n = 880)
• Cochrane (n = 348)
• Web of Science (n = 152)

Duplicated articles were removed
(n = 350)

Articles excluded
(n = 109)

Articles excluded
(n = 1011)

Full-text articles removed, with following reasons (n = 58)
• Not under general anesthesia (n = 7)
• Multiple administration (n = 5)
• Drug not administered intravenously (n = 15)
• Drug administered after skin incision (n = 7)
• Unable to obtain appropriate postoperative outcomes (n = 8)
• Non-randomized controlled trials (n = 11)
• No control group (n = 4)
• Inability to obtain full text (n = 1)

Screened by the title
(n = 1,184)

Screened by the abstract
(n = 1,075)

Articles evaluated for eligibility in full text
(n = 64)

Studies included in quantitative synthesis
(meta-analysis)
(n = 6)

Fig. 1. Flow diagram of study selection.

Table 1. Characteristics of the Included Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Surgery</th>
<th>Interventions (No. of patients)</th>
<th>Postoperative outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahiskalioglu et al. 2017 [17]</td>
<td>Laparoscopic cholecystectomy</td>
<td>IV Placebo (30) IV ibuprofen 400 mg (30)</td>
<td>VAS (0–10) at PACU, 30 min, 1, 2, 4, 8, 12, 24 h Fentanyl consumption between 0–4, 4–8, 8–24 h, and accumulative fentanyl consumption at 24 h</td>
</tr>
<tr>
<td>Çelik et al. 2018 [18]</td>
<td>Open septorhinoplasty</td>
<td>IV Placebo (50) IV ibuprofen 800 mg (50)</td>
<td>VAS (0–10) at 1, 6, 12, 24 h Tramadol consumption between 0–6, 6–12, 12–24 h, and accumulative tramadol consumption at 24 h</td>
</tr>
<tr>
<td>Gozeler et al. 2018 [13]</td>
<td>Septorhinoplasty</td>
<td>IV Placebo (25) IV ibuprofen 800 mg (26)</td>
<td>VAS (0–10) at 10, 20, 30 min, 1, 2, 4, 8, 12, 24 h Accumulative fentanyl consumption at 24 h</td>
</tr>
<tr>
<td>Karaca et al. 2019 [16]</td>
<td>Laparoscopic cholecystectomy</td>
<td>PO Pregabalin 150 mg and IV Placebo (29) PO Pregabalin 150 mg and IV ibuprofen 800 mg (29)</td>
<td>VAS (0–10) at PACU, 1, 2, 4, 8, 12, 24 h Fentanyl consumption between 0–4, 4–8, 8–24 h, and accumulative fentanyl consumption at 24 h</td>
</tr>
<tr>
<td>Koo et al. 2016 [14]</td>
<td>Pancreaticoduodenectomy</td>
<td>IV Placebo (27) IV ibuprofen 800 mg (30)</td>
<td>NRS (0–10) at 1, 3, 6, 12, 24, 48 h Accumulative morphine consumption at 1, 3, 6, 12, 24, 48 h</td>
</tr>
<tr>
<td>Mutlu and Ince 2019 [15]</td>
<td>Thyroidectomy</td>
<td>IV Placebo (20) IV ibuprofen 800 mg (20)</td>
<td>VAS (0–10) at 30 min, 1, 2, 4, 8, 12, 24, 48 h Accumulative fentanyl consumption at 48 h</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial, IV: intravenous, VAS: visual analogue scale, PACU: post-anesthesia care unit, PO: per os; by mouth, NRS: numerical rating scale.

were diverse and included fentanyl [13,15–17], morphine [14], and tramadol [18]. The timing of pain score measurement and opioid consumption varied among the studies.

**Quality assessment of included studies (risk of bias within studies)**

The risk of bias assessment indicated that all included studies
had low bias (Figs. 2 and 3). All trials were evaluated as having a low risk of random sequence generation. Of all included studies, 66.6% in allocation concealment, 16.6% in blinding of participants and personnel, 16.6% in blinding of outcome assessment, 66.6% in selective reporting, and 16.6% in other bias categories were assessed as ‘unclear’. Only two trials [14,18] were clear about allocation concealment, while other trials (66.6%) did not describe the allocation concealment method in detail. With respect to blinding of patients, one study [18] did not mention the term ‘double-blinded’ or describe its method of blinding. Furthermore, it did not specify blinding of the outcome assessor method, so we assessed it as ‘unclear’. Only two studies [14,16] provided information regarding protocols written in advance. All studies were rated as ‘low’ in other bias, except for two trials: one study [15] without calculation of required sample size and power analysis rated as ‘unclear’, and the other [18] with inappropriate power analysis rated as ‘high’.

Agreement between the two raters for assessing the risk of bias was moderate (Cohen’s kappa = 0.52).

Meta-analysis

One study [14] reported the effects of intraoperative remifentanil infusion along with preoperative ibuprofen on postoperative pain and opioid consumption. Patients in this study received intraoperative remifentanil infusion targeting 4 ng/ml or 1 ng/ml as effect-site concentration, with or without preoperative ibuprofen administration. In this study, we extracted the data from subgroups with low remifentanil infusion only, because most of the other articles included in our meta-analysis did not use opioid infusion or used a low infusion rate of opioids during surgery.

Pain scores at postoperative 4 h were extracted from four reports [13,15–17], since data at 6 h were not available. Opioid con-

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Fig. 2. Risk of bias graph: review authors’ judgements about each risk of bias item presented as percentages across all included studies.

Fig. 3. Risk of bias summary: review authors’ judgements about each risk of bias item for each included study. +: low risk, ?: unclear risk, –: high risk.

https://doi.org/10.4097/kja.21050
Pain intensity at postoperative 1 h

A meta-analysis of six studies [13–18] (n = 366; 185 in the ibuprofen group and 181 in the control group) showed that pain scores measured at 1 h postoperatively were significantly reduced in the preoperative ibuprofen group (MD: −1.64, 95% CI [−2.56, −0.72], P < 0.001, I² = 95%) (Fig. 4A).

In the sensitivity test, the pain score measured at 1 h postoperatively was lower (MD: −1.94, 95% CI [−2.30, −1.57], P < 0.001, I² = 29%) than the estimated pooled effect with consistent direction and significance after excluding the outlier study [14]. It can be concluded that the results were robust. In addition, there was an effect of a reduction in heterogeneity to an acceptable level.

Pain intensity at postoperative 4–6 h

A meta-analysis of six studies [13–18] (n = 366; 185 in ibuprofen group and 181 in control group) showed that the preoperative ibuprofen group reported lower pain intensity with a statistical

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ibuprofen Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference (IV, Random, 95% CI)</th>
<th>Mean Difference (IV, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahiskalioglu 2017 [17]</td>
<td>2.63</td>
<td>0.89</td>
<td>30</td>
<td>2.97</td>
<td>2.06</td>
<td>30</td>
<td>16.7%</td>
<td>-1.34 [-2.14, -0.54]</td>
</tr>
<tr>
<td>Celik 2018 [18]</td>
<td>2.42</td>
<td>1.08</td>
<td>50</td>
<td>4.64</td>
<td>0.69</td>
<td>50</td>
<td>18.5%</td>
<td>-2.22 [-2.58, -1.86]</td>
</tr>
<tr>
<td>Gozeler 2018 [13]</td>
<td>3</td>
<td>0.5</td>
<td>26</td>
<td>4.8</td>
<td>1.5</td>
<td>25</td>
<td>17.6%</td>
<td>-1.80 [-2.42, -1.18]</td>
</tr>
<tr>
<td>Karaca 2019 [16]</td>
<td>2.75</td>
<td>1.38</td>
<td>29</td>
<td>4.48</td>
<td>1.86</td>
<td>29</td>
<td>16.4%</td>
<td>-1.73 [-2.57, -0.89]</td>
</tr>
<tr>
<td>Koo 2016 [14]</td>
<td>8.72</td>
<td>0.33</td>
<td>30</td>
<td>9.13</td>
<td>0.29</td>
<td>27</td>
<td>19.0%</td>
<td>-0.41 [-0.57, -0.25]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>185</td>
<td>181</td>
<td>100.0%</td>
<td>-1.64 [-2.56, -0.72]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 1.16; Chi² = 105.58, df = 5 (P < 0.00001); I² = 95%

Test for overall effect: Z = 3.49 (P = 0.0005)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ibuprofen Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference (IV, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahiskalioglu 2017 [17]</td>
<td>2.33</td>
<td>0.99</td>
<td>30</td>
<td>3.2</td>
<td>1.83</td>
<td>30</td>
<td>16.8%</td>
</tr>
<tr>
<td>Celik 2018 [18]</td>
<td>2</td>
<td>0.69</td>
<td>50</td>
<td>4.38</td>
<td>0.63</td>
<td>50</td>
<td>18.6%</td>
</tr>
<tr>
<td>Gozeler 2018 [13]</td>
<td>2</td>
<td>0.5</td>
<td>26</td>
<td>3.3</td>
<td>1.4</td>
<td>25</td>
<td>17.5%</td>
</tr>
<tr>
<td>Karaca 2019 [16]</td>
<td>1.66</td>
<td>1.29</td>
<td>29</td>
<td>2</td>
<td>1.2</td>
<td>29</td>
<td>17.3%</td>
</tr>
<tr>
<td>Koo 2016 [14]</td>
<td>7.05</td>
<td>0.46</td>
<td>30</td>
<td>7.4</td>
<td>1.09</td>
<td>27</td>
<td>18.1%</td>
</tr>
<tr>
<td>Mutlu 2019 [15]</td>
<td>4.3</td>
<td>2.86</td>
<td>20</td>
<td>6.3</td>
<td>2.38</td>
<td>20</td>
<td>11.8%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>185</td>
<td>181</td>
<td>100.0%</td>
<td>-1.17 [-2.09, -0.26]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 1.17; Chi² = 85.22, df = 5 (P < 0.00001); I² = 94%

Test for overall effect: Z = 2.50 (P = 0.001)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Ibuprofen Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Mean Difference (IV, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahiskalioglu 2017 [17]</td>
<td>0.7</td>
<td>0.53</td>
<td>30</td>
<td>1.43</td>
<td>1.17</td>
<td>30</td>
<td>16.8%</td>
</tr>
<tr>
<td>Celik 2018 [18]</td>
<td>1.64</td>
<td>0.66</td>
<td>50</td>
<td>2.72</td>
<td>0.6</td>
<td>50</td>
<td>19.9%</td>
</tr>
<tr>
<td>Gozeler 2018 [13]</td>
<td>0.5</td>
<td>0.5</td>
<td>26</td>
<td>1.1</td>
<td>0.8</td>
<td>25</td>
<td>18.3%</td>
</tr>
<tr>
<td>Karaca 2019 [16]</td>
<td>0.1</td>
<td>0.31</td>
<td>29</td>
<td>0.41</td>
<td>0.21</td>
<td>29</td>
<td>21.0%</td>
</tr>
<tr>
<td>Koo 2016 [14]</td>
<td>6.07</td>
<td>0.35</td>
<td>30</td>
<td>5.96</td>
<td>0.64</td>
<td>27</td>
<td>19.6%</td>
</tr>
<tr>
<td>Mutlu 2019 [15]</td>
<td>3</td>
<td>2.75</td>
<td>20</td>
<td>5.1</td>
<td>2.8</td>
<td>20</td>
<td>4.4%</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>185</td>
<td>181</td>
<td>100.0%</td>
<td>-0.58 [-0.99, -0.18]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.20; Chi² = 50.75, df = 5 (P < 0.00001); I² = 90%

Test for overall effect: Z = 2.83 (P = 0.005)
significance (MD: –1.17, 95% CI [–2.09, –0.26], P < 0.001, $I^2$ = 94%) (Fig. 4B).

In the sensitivity analysis, the effects of pain intensity at 4–6 h were significantly reduced (MD: –0.79, 95% CI [–1.29, –0.30], P = 0.0016, $I^2$ = 61%) compared to the pooled effect after excluding one trial [18], which was an outlier in this analysis. However, the results were reliable, because the direction and significance were maintained. Although the heterogeneity decreased, it was still of moderate intensity; hence, the results should be interpreted carefully.

**Pain intensity at postoperative 24 h**

A meta-analysis of data from six studies [13–18] (n = 366; 185 in the ibuprofen group and 181 in the control group) demonstrated that pain scores of the ibuprofen group were lower than those of the control group (MD: –0.58, 95% CI [–0.99, –0.18], P < 0.001, $I^2$ = 90%) (Fig. 4C).

In the sensitivity analysis, the pain score of the ibuprofen group measured at 24 h postoperatively was still significantly more effective (MD: –0.75, 95% CI [–1.17, –0.32], P < 0.001, $I^2$ = 88%) than the estimated effect after excluding one trial [14], an outlier. As the direction and significance of the results were maintained, the results were regarded as robust.

**Accumulative opioid consumption at postoperative 4–6 h**

A total of four studies [14,16–18] (n = 275; 139 in the ibuprofen group and 136 in the control group) showed data on the accumulative opioid consumption at postoperative 4–6 h. Preoperative ibuprofen administration significantly reduced opioid consumption, which was presented as fentanyl equivalents (MD: –56.35 μg, 95% CI [–101.10, –11.60], P < 0.001, $I^2$ = 91%) (Fig. 5A). Sensitivity analysis did not show any outliers.

**Accumulative opioid consumption at postoperative 24 h**

Meta-analysis of five studies [13,14,16–18] (n = 326; 165 in the ibuprofen group and 161 in the control group) showed that cumulative opioid consumption at 24 h postoperatively was lower in the ibuprofen group (MD: –131.39 μg, 95% CI [–224.56, –38.21], P < 0.001, $I^2$ = 95%) (Fig. 5B).

In the sensitivity analysis, the effect size of cumulative opioid consumption at 24 h increased (MD: –170.70 μg, 95% CI [–265.63, –75.76], P < 0.001, $I^2$ = 95%) after excluding one trial [14], which was indicated to be an outlier.

**Discussion**

Recently, the multimodal analgesic approach has been in the spotlight as a way to reduce pain. Supplemental analgesics for postoperative pain can be administered before, during, or after surgery. Although some studies have shown the effect of preoperative drug administration on postoperative pain and opioid consumption [20,21], limited data are available regarding the preoperative administration of ibuprofen through the intravenous

![Fig. 5. Forest plot: Effect of ibuprofen on opioid consumption. (A) Postoperative 4–6 h. (B) Postoperative 24 h. SD: standard deviation, IV: inverse variance.](https://doi.org/10.4097/kja.21050)
route. In this meta-analysis, the data showed statistically significant reductions in postoperative pain scores and opioid consumption when ibuprofen was administered intravenously before surgery.

In our study, postoperative pain scores were reduced at all analyzed time points (postoperative 1, 4–6, and 24 h) after a single dose of ibuprofen. The MDs in postoperative pain scores on a scale of 0–10 reduced over time: −1.64, −1.17, and −0.58, for postoperative 1, 4–6, and 24 h, respectively. Therefore, it can be inferred that the effect of preoperative single dose administration of ibuprofen decreases with time; however, it is still effective until postoperative 24 h. Accounting for the duration of surgery, postoperative 24 h is the time point at which more than 24 h have elapsed after ibuprofen administration. Considering that the half-life of intravenous ibuprofen is approximately 2 h [22] and the mean duration of ibuprofen is approximately 6–8 h, this result is interesting and suggests that the effect of ibuprofen persists even when the plasma concentration of ibuprofen is close to zero. In this regard, it is speculated that preoperative administration of ibuprofen may also have a preemptive effect. Preemptive analgesia limits pain response by suppressing initial pain sensitization [23].

We demonstrated that preoperative ibuprofen reduced postoperative opioid consumption and postoperative pain. This seems reasonable, as the severity of postoperative pain is one of the main factors determining analgesic requirements [24]. However, despite the reduction in the severity of pain, flurbiprofen, a similar NSAID, did not reduce opioid consumption in other meta-analyses [21].

Although we could not conduct subgroup analysis according to the dose of ibuprofen in this meta-analysis, it would be useful to compare whether the effect of ibuprofen varies depending on the dose (400 or 800 mg). In addition, a comparison between ibuprofen and other analgesics in various settings, including patient characteristics, type of surgery, and anesthetic techniques, may contribute to the determination of optimal multimodal analgesia.

Opioid-related side effects, such as postoperative nausea and vomiting, can be expected to be reduced, as opioid consumption was reduced when ibuprofen was administered preoperatively, as reported by another study using flurbiprofen [25]. In our meta-analysis, we could not analyze the effect of preoperative ibuprofen on postoperative nausea and vomiting, since the included articles reported outcomes differently. One article [13] reported the number of patients who experienced nausea and vomiting, while others [14–18] reported events of nausea and vomiting. In addition, some articles [13,14,16,17] counted nausea and vomiting as one criterion, while others [15,18] counted them as two different criteria. Therefore, we concluded that the outcomes of postoperative nausea and vomiting could not be synthesized appropriately for the meta-analysis.

In this meta-analysis, the heterogeneity in all study outcomes was quite high. Such high heterogeneity could be the result of various study designs, types of surgeries, anesthetic techniques, doses of anesthetic drugs, or drugs that were administered simultaneously, such as remifentanil or gabapentin [14,16]. The doses and type of rescue drugs and timing of rescue drug administration were also different between trials.

In this meta-analysis, heterogeneity was reduced after the exclusion of one study [18] from all analyses (results not shown). Unlike other studies, this study used remifentanil to control postoperative pain. Tramadol targets opioid receptors and inhibits the reuptake of noradrenaline and serotonin [26]. The unique mechanisms of action of tramadol may have contributed to its high heterogeneity.

This study has some limitations. First, only a few studies were included. Although we did not limit the publication year when we selected the articles, only a few studies were included. This could be because there were few published articles on this topic, or the inclusion criteria of our meta-analysis were very strict and limited. Second, heterogeneity between studies was high in all the analyses of postoperative outcomes, possibly caused by several factors, such as different surgery types and different doses of study drugs or combination drugs. We attempted to conduct subgroup analysis to determine the cause of high heterogeneity; however, owing to the small number of included studies, we could not classify them into homogenous subgroups. Third, data and analysis of opioid consumption could have been more accurate if rescue analgesia was included in opioid consumption; however, this was not performed because of a lack of information. All studies recorded the number of patients who required rescue analgesia, and not the number of rescue analgesia administrations. Therefore, we were unable to calculate the exact amount of rescue analgesics injected.

In conclusion, preoperative single dose intravenous ibuprofen can reduce pain and opioid consumption until 24 h postoperatively. We expect that these findings can contribute to multimodal analgesia by increasing the efficiency of postoperative pain management. However, the analysis reported high heterogeneity within trials, probably owing to variations in study designs and small sample sizes. In addition, the type of surgery was limited in our study. Therefore, care should be taken when generalizing these findings. Further studies with similar designs are needed to increase the reliability of evidence and to determine the effect of preoperative administration of ibuprofen on postoperative pain intensity and opioid consumption.
Conflicts of Interest

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

Author Contributions

Su Yeon Kim (Conceptualization; Data curation; Formal analysis; Methodology; Writing – original draft)
Sangseok Lee (Formal analysis; Validation; Writing – review & editing)
Yeji Lee (Writing – review & editing)
Hyunho Kim (Writing – review & editing)
Kye-Min Kim (Conceptualization; Data curation; Formal analysis; Methodology; Supervision; Validation; Writing – review & editing)

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Kye-Min Kim, https://orcid.org/0000-0003-1298-7642

References


### Appendix

#### Appendix 1. PRISMA Checklist

<table>
<thead>
<tr>
<th>Section/topic</th>
<th>#</th>
<th>Checklist item</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title</strong></td>
<td></td>
<td>1 Identify the report as a systematic review, meta-analysis, or both.</td>
</tr>
<tr>
<td><strong>Abstract</strong></td>
<td></td>
<td>2 Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.</td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
<td></td>
<td>3 Describe the rationale for the review in the context of what is already known.</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td></td>
<td>4 Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).</td>
</tr>
<tr>
<td>Protocol and registration</td>
<td>5</td>
<td>Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.</td>
</tr>
<tr>
<td>Eligibility criteria</td>
<td>6</td>
<td>Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.</td>
</tr>
<tr>
<td>Information sources</td>
<td>7</td>
<td>Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.</td>
</tr>
<tr>
<td>Search</td>
<td>8</td>
<td>Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.</td>
</tr>
<tr>
<td>Study selection</td>
<td>9</td>
<td>State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).</td>
</tr>
<tr>
<td>Data collection process</td>
<td>10</td>
<td>Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.</td>
</tr>
<tr>
<td>Data items</td>
<td>11</td>
<td>List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.</td>
</tr>
<tr>
<td>Risk of bias in individual studies</td>
<td>12</td>
<td>Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.</td>
</tr>
<tr>
<td>Summary measures</td>
<td>13</td>
<td>State the principal summary measures (e.g., risk ratio, difference in means).</td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>14</td>
<td>Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.</td>
</tr>
<tr>
<td>Risk of bias across studies</td>
<td>15</td>
<td>Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).</td>
</tr>
<tr>
<td>Additional analyses</td>
<td>16</td>
<td>Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td></td>
<td>17 Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.</td>
</tr>
<tr>
<td>Study characteristics</td>
<td>18</td>
<td>For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.</td>
</tr>
<tr>
<td>Risk of bias within studies</td>
<td>19</td>
<td>Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).</td>
</tr>
<tr>
<td>Results of individual studies</td>
<td>20</td>
<td>For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.</td>
</tr>
<tr>
<td>Synthesis of results</td>
<td>21</td>
<td>Present results of each meta-analysis done, including confidence intervals and measures of consistency.</td>
</tr>
<tr>
<td>Risk of bias across studies</td>
<td>22</td>
<td>Present results of any assessment of risk of bias across studies (see Item 15).</td>
</tr>
</tbody>
</table>

(Continued to the next page)
Appendix 1. Continued

<table>
<thead>
<tr>
<th>Section/topic</th>
<th>#</th>
<th>Checklist item</th>
<th>Reported on page #</th>
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<tbody>
<tr>
<td>Additional analysis</td>
<td>23</td>
<td>Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).</td>
<td>13-15</td>
</tr>
<tr>
<td>Discussion</td>
<td></td>
<td>Summary of evidence</td>
<td>24</td>
</tr>
<tr>
<td>Limitations</td>
<td></td>
<td>25</td>
<td>Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).</td>
</tr>
<tr>
<td>Conclusions</td>
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<td>26</td>
<td>Provide a general interpretation of the results in the context of other evidence, and implications for future research.</td>
</tr>
<tr>
<td>Funding</td>
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<td></td>
<td>27</td>
</tr>
</tbody>
</table>

Appendix 2. Search strategy for each database.

**PubMed/MEDLINE**

#1. ibuprofen
#2. intravenous* OR iv OR parenteral*
#3. pain, postoperative [MeSH Terms]
#4. postop* OR postsurg* OR postprocedur* OR “post op*” OR “post procedure*” OR “after surg*” OR “after op*” OR “after procedure*”
#5. pain OR analges* OR opioid* OR morphine OR fentanyl OR ‘patient controlled analgesia’ OR pca
#6. #4 AND #5
#7. #3 OR #6
#8. randomized controlled trial [pt]
#9. controlled clinical trial [pt]
#10. randomized [tiab] OR randomized [tiab]
#11. placebo [tiab]
#12. drug therapy [sh]
#13. randomly [tiab]
#14. trial [tiab]
#15. groups [tiab]
#16. #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
#17. animals [mh] NOT humans [mh]
#18. #16 NOT #17
#19. #1 AND #2 AND #7 AND #18

**Embase**

#1. ‘ibuprofen’/exp OR ibuprofen
#2. ‘intravenous drug administration’/exp OR ‘intravenous drug administration’ OR intravenous* OR iv OR parenteral*
#3. postoperative pain/exp OR ‘postoperative pain’
#4. Postop* OR postsurg* OR postprocedur* OR ‘post op*’ OR ‘post procedure*’ OR ‘after surg*’ OR ‘after op*’ OR ‘after procedure*’
#5. pain/exp OR pain OR analges* OR opioid* OR ‘morphine’/exp OR morphine OR ‘fentanyl’/exp OR fentanyl OR ‘patient controlled analgesia’/exp OR ‘patient controlled analgesia’ OR ‘pca’/exp OR pca
#6. #4 AND #5
#7. #3 OR #6
#8. Random*:ab,ti OR ((clinical NEXT/1 trial*):de,ab,ti) OR placebo*:de,ab,ti OR ((double NEXT/1 blind*):ab,ti) OR group*
#9. #1 AND #2 AND #7 AND #8

**The Cochrane Library**

#1. (ibuprofen):ti,ab,kw (Word variations have been searched)
#2. (intravenous* OR iv OR parenteral*):ti,ab,kw (Word variations have been searched)
#3. MeSH descriptor: [Pain, Postoperative] explode all trees
#4. (postop* OR postsurg* OR postprocedure* OR "post op*" OR "post surg*" OR "post procedure*" OR "after surg*" OR "after op*" OR "after procedure*":ti,ab,kw (Word variations have been searched)
#5. (pain OR analges* OR opioid* OR morphine OR fentanyl OR "patient controlled analgesia" OR pca):ti,ab,kw (Word variations have been searched)
#6. #4 AND #5
#7. #3 OR #6
#8. #1 AND #2 AND #7 in Trials

**Web of Science**

#1. TS = (ibuprofen)
#2. TS = (iv OR intravenous* OR parenteral*)
#3. TS = (postop* OR postsurg* OR postprocedure* OR "post op*" OR "post surg*" OR "post procedure*" OR "after surg*" OR "after op*" OR "after procedure*")
#4. TS = (pain OR analges* OR opioid* OR morphine OR fentanyl OR "patient controlled analgesia" OR pca)
#5. #3 AND #4
#6. TS = (random* OR "clinical NEXT/1 trial*" OR placebo* OR "double NEXT/1 blind*" OR group*)
#7. #1 AND #2 AND #5 AND #6
Prophylactic measures to prevent cerebral oxygen desaturation events in elective beach-chair position shoulder surgeries: a systematic review and meta-analysis

Thrivikrama Padur Tantry¹, Baikunje Golitadka Muralishankar¹, Harish Karanth¹, Pramal Karkala Shetty¹, Sunil Purushotham Shenoy², Dinesh Kadam³, Gururaj Tanthry¹, Rithesh Shetty¹
Departments of ¹Anesthesiology, ²Urology and Renal Transplant, ³Plastic and Reconstructive Surgery, A J Institute of Medical Sciences & Research Center, Kuntikana, Mangalore, India

Background: Prophylaxis for cerebral desaturation events (CDEs) during anesthesia in the beach chair position (BCP) for shoulder surgeries has not been evaluated. We systematically analyzed the effectiveness of various prophylactic measures used in this clinical setting.

Methods: We performed a meta-analysis (PROSPERO; no. CRD42020167285) of trials reporting CDEs and regional cerebral oxygen saturation (rSO₂) and jugular venous oxygen saturation (SjvO₂) values in anesthetized patients undergoing shoulder surgery in BCP. Considering the type of prophylactic measures used (pharmacological or non-pharmacological), a subgroup analysis was planned. Outcomes included (1) rSO₂ and SjvO₂ data with and without prophylactic measures for CDEs, recorded for different time intervals, and (2) the number of patients experiencing CDEs and hypotension.

Results: Twelve studies (786 patients) were included in the analysis. We observed lower absolute rSO₂ values for early and all-time periods for vasoactive agent prophylaxis. The lowest achieved rSO₂ values were also lower for vasoactive agent prophylaxis. Risk of CDEs was higher with vasoactive agent prophylaxis. Subgroup analysis identified targeted mild hypercarbia as effective in preserving cerebral oxygenation. Similarly, targeted mild hypercarbia prevented the fall in rSO₂ with position change. Meta-regressions revealed statistically significant highest estimates for vasoactive agent prophylaxis in contrast to targeted mild hypercarbia. Likelihood of not developing CDEs was higher for targeted mild hypercarbia. In contrast to rSO₂, most prophylactic methods reduced hypotensive episodes.

Conclusions: Targeted mild hypercarbia can reduce BCP-related CDEs. Evidence does not favor prophylactic use of vasoactive agents for the prevention of cerebral desaturations irrespective of whether their use interferes with cerebral oximetry readings.

Keywords: Arthroscopy; Oximetry; Prophylaxis; Randomized controlled trial; Shoulder; Sitting position; Statistics; Systematic review.

Introduction

Beach chair position (BCP) surgeries are associated with significant cerebral desaturation events (CDEs) in as many as 80% of patients [1,2]. Cerebral oxygenation is depen-
dent on a combination of multiple factors such as cerebral blood flow (CBF), mean arterial blood pressure (MAP), partial pressure of oxygen, cardiac output, and hemoglobin levels. A reduction in MAP during anesthesia in BCP may decrease the CBF [3–5]. A strong association of the hypotensive response with decrease in regional cerebral oxygen saturation (rSO₂) and jugular venous oxygen saturation (SjvO₂) has been observed [6–8]. In such situations, pharmacological agents such as ephedrine and phenylephrine, which rapidly increase MAP, are frequently used to obtain indirect benefits on cerebral oxygenation. Alternatively, prophylactic measures have been successfully used to prevent CDEs, including non-pharmacological techniques such as preloading with crystalloids/colloids or the use of sequential compression devices (SCDs) [9–11]. Vasoactive agents administered prophylactically can theoretically achieve a rapid increase of MAP and consequently the increase of CBF, however, the decline observed in rSO₂ suggests otherwise [12]. The association between the use of prophylactic compression stockings and reduced occurrence of CDEs is unclear, as similar incidences were also reported in patients with their use [13]. We could not find any analysis of pooled data in the available literature to support or refute this association.

Our study attempted to determine whether any particular pharmacological or non-pharmacological technique is useful for reducing CDEs during BCP surgeries. Confirming an association between the two would improve predictability, provide insight into the possible underlying pathophysiological mechanisms, and guide the anesthesiologist on the most efficacious method of preventing these undesirable events. Therefore, we performed a systematic review and meta-analysis to summarize the existing evidence on the ability of prophylactic measures to prevent CDEs in this clinical setting.

Materials and Methods

Registration and protocol

This meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses [14] and was registered with PROSPERO (https://www.crd.york.ac.uk/PROSPERO, no. CRD42020167285).

Eligibility criteria

We included prospective randomized clinical studies or randomized controlled trials (RCTs) with adult patients (> 18 years) who underwent elective shoulder surgeries in BCP. Reporting of monitored cerebral oxygen saturation-related data and at least one prophylactic method used to prevent CDEs were mandatory for inclusion. Publications in all languages were considered. The patients received one of the following anesthetic modalities: (1) planned general anesthesia (GA) or (2) regional anesthesia (RA), viz interscalene brachial plexus block or similar block in combination with GA. We excluded studies wherein patients underwent surgeries under RA alone, at < 45° BCP, or with American Society of Anesthesiologists physical status > 3.

Information sources

An electronic literature search, specifically restricted to randomized studies or RCTs of BCP, was conducted in MEDLINE, CINAHL (EBSCO host), Google Scholar, and the Cochrane Central Register of Controlled Trials. The bibliography of the retrieved manuscripts was searched for additional studies pertaining to data encompassing our primary outcome of interest. These included studies reporting incidence of CDEs, maximum and minimum average cerebral oxygen saturations, serial average cerebral saturation values overtime periods, critical CDEs, and the percentage change of cerebral saturations, with a caveat that both supine, pre-BCP and BCP data are available. Similar to cerebral saturation, SjvO₂ was documented whenever data were available. Twenty-first-century literature, that is, literature published only after January 1, 2000, was scanned because anesthesia protocols have remained uniform during this period. Cohorts with matched controls, retrospective studies, reviews with inadequate information on primary outcomes of interest, abstracts, and letters to the editor were not included. The detailed search strategy is shown in Supplementary Material 1, which depicts the keyword-based search inclusion terms.

Study selection and data collection

A collection of studies was conducted by TPT and HK. The manuscripts meeting the inclusion criteria were assessed, and data were extracted following a standardized format by the same authors. The extracted items comprised study characteristics, risk of bias domains [15], participant disposition, and study outcomes. The PICO inclusion criteria comprised the following elements, focusing on patients, interventions, comparisons, and outcomes, and were used to identify components of clinical evidence. Patients who underwent shoulder surgery under anesthesia in BCP with cerebral oxygen saturation monitoring using any type of cerebral oximetry device were considered. They were categorized according to the type of surgery or anesthesia, number of patients, the position adopted for surgery, and monitoring for CDEs.
ventions referred to prophylactic measures used to prevent CDEs. These patients must have had at least one type of prophylactic method to prevent cerebral desaturation in the sitting position. With regard to the type of intervention, study authors could consider any type of pharmacological or non-pharmacological method deployed before the CDE. The comparison of variables was between ‘with and without’ prophylactic measures. This is an alternative to intervention—placebo, different drugs, measures, or therapy. Outcomes were classified as primary or secondary. The former included cerebral oxygen (de)saturation data with and without the use of prophylactic measures at various time intervals using rSO2 and SjvO2 cerebral oximetry values. The latter included the incidence of CDEs and hypotension episodes, associations with MAP, and the use of vasoactive agents with CDEs.

Data synthesis and analysis of outcomes

Data relevant to the outcomes of interest were extracted from each study in this meta-analysis. The rSO2 or SjvO2 data included continuous data documented as pooled averages or sequential data at various intervals for a study. Data were collected as a single or combined value in the form of mean and standard deviation (SD) or median and interquartile range (IQR), respectively. If multiple datasets were available, they were converted into pooled statistical averages. The other dichotomous data included the number of patients experiencing CDEs.

The data were tabulated before induction (baseline) and post-induction (relating to pre-BCP and BCP categories after stabilization of vital signs). The BCP rSO2 or SjvO2 data were pooled for the time periods mentioned in the respective publications. If the recorded data timings were non-specific, they were approximated to the nearest values for pooled data estimation. If the exact time point was not specified in the manuscript, then the approximated time point was considered by the authors’ judgment.

Individual definitions for CDEs and hypotension were accepted as described by each study. Dichotomous data such as the occurrence of CDEs and hypotension were converted into incidence (n/N) for early and overall time periods. All analyses were performed assuming no incidences of CDEs in the supine position under anesthesia. CDE occurrence was counted whenever the event was reported at least once, based on the original study authors’ definitions. Complications were analyzed on an ‘intention to treat’ basis since in some subgroups, patients were repositioned back to supine following BCP-induced hemodynamic disturbances or CDEs [17].

With regard to MAP, data evaluation and synthesis were similar to those applied for CDEs or rSO2/SjvO2 values. The incidence of hypotension was counted whenever the events were reported at least once either individually or sequentially for each patient.

Pre-defined sources of heterogeneity

To explore the potential causes of heterogeneity that could influence the primary outcomes, we pre-identified certain aspects of individual study groups. These included (1) anesthetic technique (GA vs. combined GA and RA); (2) induction agent (propofol vs. thiopentone); (3) maintenance anesthetic agent (propofol vs. inhalational agents); (4) prophylactic measures (vasoactive agents vs. preloading vs. SCD vs. targeted mild hypercarbia techniques vs. compression stockings vs. others), and (5) maintenance vasopressors (phenylephrine vs. ephedrine vs. others).
Meta-analysis was conducted using Review Manager (RevMan 5.4.1, Cochrane Collaboration, Denmark, 2014). A random-effects model was used for all analyses. Heterogeneity was measured and expressed as $I^2$. For continuous variables ($rSO_2$/SjvO$_2$), mean differences (MDs) were compared using the inverse-variance (I-V) method. For dichotomous variables (incidence of CDEs and hypotension), odds ratio (OR) or risk ratio (RR) was computed using the Mantel-Haenszel (M-H) or I-V method. Natural log transformation was adopted [18], as the outcomes for incidences were expected to be non-normally distributed.

**Meta-regression analysis**

Because of overlapping of use (i.e., more than one) of different prophylactic measures, a meta-regression analysis was planned to estimate the effectiveness of the individual prophylactic measures. Pre-BCP (supine, after anesthesia induction) and BCP (all-time overall, absolute [%], and pooled) cerebral saturation values were considered for meta-regression. Meta-regression data inputs were different from the data of conventional meta-analysis, where the former included the MDs from baseline to all-time overall fall of rSO$_2$ values. Meta-regression was performed using JASP software (Version 0.9.2, BibTeX, University of Amsterdam, the Netherlands). The effect size (estimate) and standard error (SE) were used for meta-regression. A priori defined prophylactic measures were used across the study groups. We included all prophylactic measures that were identified among study groups, such as compression stockings, SCDs, targeted mild hypercarbia, crystalloid loading, hydroxyethyl starch (HES), regional ischemic preconditioning technique (RIPC), and vasoactive agents for meta-regressions. Meta-regressions were also performed for 'the number of patients experiencing CDEs', in which baseline supine, pre-BCP CDEs were assumed as 'zero' for the analysis. All meta-regressions were performed using the restricted maximum likelihood method and random effects. An omnibus test of the model coefficients and tests for heterogeneity were used for the model. Simultaneous to Egger’s regression tests for funnel plot asymmetry evaluations, a visual inspection of the funnel plot was carried out to rule out publication bias. The influence of such studies on the model was also assessed. The parameter covariance was assessed for the combined effects of prophylactic measures. Statistical significance was set at $P < 0.05$ (2-tailed).

**Grading of Recommendations Assessment, Development and Evaluation**

The certainty of the evidence was summarized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [19] approach for individual outcomes. The strength of recommendations reduces the potential to facilitate critical appraisal and improves the communication of judgments. GRADEpro GDT (GRADEpro Guideline Development Tool [Software], McMaster University, 2020 [developed by Evidence Prime, Inc.]) was used to facilitate the development of evidence summaries and recommendations.

**Results**

**Literature identification and study characteristics**

From 2,297 studies that were initially screened, 56 potentially relevant manuscripts were selected based on abstracts (Supplementary Material 2). Of these, 12 trials provided the data for analysis (Supplementary Material 3) [7,13,20–29] including Jadad scores. Data from 786 patients were included in the analysis.

Cerebral oxygenation monitoring was performed using INVOS™ 5100 B/C (Medtronic, Ireland) cerebral oximetry monitoring devices [7,13,20–27,29] (near-infrared reflectance spectroscopy) in all included studies in this review, except in a single study [28] in which the FORE-SIGHT™ device (Edwards Lifesciences, USA) was used. All the studies reported baseline data with respect to rSO$_2$ including pre- and post-induction values, except for a single study [24] in which only the mean (SD) maximum fall of cerebral saturation values was reported. The physiologic principles to prevent CDEs followed in each included study, however, were dissimilar. Because rSO$_2$ values can be affected by a variety of factors, the mechanisms used by the authors in the prevention of falls in rSO$_2$ varied. Vascular tone, cardiac output, and cerebrovascular-mediated mechanisms were considered by the authors to preserve cerebral oxygenation. To simplify, we classified the included heterogeneous studies based on whether the study authors used pharmacological (PPMs) or non-pharmacological prophylactic measures (NPPMs). For the prevention of MAP-dependent cerebral desaturations, PPMs were used in four RCTs (vasoactive agents; vasopressin [20,21,25], n = 3 and phenylephrine [7], n = 1) and NPPMs in eight (preloading with colloid [HES 130/0.4 [22], n = 1]; SCD use on legs [26], n = 1; compression stockings [13,24], n = 2; targeted mild hypercarbia [27,28], n = 2; or reduced BCP angle for surgery [23] [low BCP angle, ≤ 60°, n = 1] or RIPC [29], n = 1). However, overlapping prophylactic measures were observed among the study groups. Eight study groups [13,20,21,24] used compression stockings and five used SCDs [23,24,26] as a prophylactic measure. Crystalloid loading [7,21,22,29] and HES preloading [22,26,27] were used in 10 and 5
study groups, respectively. Vasoactive agent prophylaxis [7,20,21,25] was used in seven, whereas targeted mild hypercarbia [27,28] was used in two study groups. Similarly, low BCP angle [13,23,24] during surgery was used in five study groups. However, the RIPC technique was used in only a single study [29] group.

CDE was uniformly defined as > 20% decrease from baseline values and critical desaturation as < 55% (absolute value, Supplementary Material 3). Four studies [20,21,25,27] mentioned a duration of cerebral desaturation of > 15 s, whereas others had no duration stated. One study [29] additionally defined CDE as a fall in absolute values < 40% from baseline if it occurred for at least 1 min. Deliberate hypotension was accepted in one study [23]. All studies considered pharmacological agents for treating BCP-induced hypotension or treating CDEs via blood pressure elevation. The rest of the data related to treatment and prophylactic measures are depicted in Supplementary Material 3.

**Primary outcomes**

**Absolute values of rSO2 for an early period**

Pooled absolute rSO2 (comparisons with controls, Figs. 1A and 1B) values (in %) were obtained for the first 15 min of BCP. These were recorded from 10 studies; three used vasopressin as a PPM [20,21,25] and seven used NPPM techniques [13,22,23,26–29] to prevent CDEs. PPMs were associated with lower absolute rSO2 values than those without (controls). PPMs thus produced unfavorable results (vs. controls; MD: −13.58%, 95% CI [−16.03, −11.4], I² = 0%, P = 0.97) in contrast to NPPMs (vs. controls; MD: 2.76%, 95% CI [0.62, 4.89], I² = 56%, P = 0.03). Among NPPMs, the SCD and RIPC measures had statistically significantly higher rSO2 values than in those without their use.

**Absolute values of rSO2 for all-time period**

Pooled absolute rSO2 (comparisons with controls, Figs. 2A and 2B) values (in %) were obtained for all-time periods of BCP. These were recorded from 10 studies, four of which used PPMs (vasopressin [20,21,25] or phenylephrine [7] infusions) to regulate MAP. Preloading with HES [22], reduction of BCP angle [23], SCDs [26], and RIPC [29] were used in one study each, and targeted mild hypercarbia [27,28] was used in two RCTs. PPMs were associated with lower absolute all-time overall rSO2 values (vs. controls; MD: −12.23%; 95% CI [−14.59, −9.87], I² = 0%, P = 0.82) in contrast to NPPMs (vs. controls; MD: 2.92%; 95% CI [0.34, 5.49], I² = 76%, P = 0.0009). Among NPPMs, the use of SCDs, targeted mild hypercarbia, and RIPC measures had statistically significantly higher rSO2 values than those without their use.

**Lowest achieved absolute rSO2 values**

The lowest achieved rSO2 (comparisons with controls, Figs. 3A and 3B) was recorded (in %) from nine studies. Three of these used PPMs (vasopressin [20,21,25] infusions), and NPPMs were used in others (preloading with HES [22], reduction of BCP angle [23], SCDs [26], and RIPC [29] techniques in one study each; targeted mild hypercarbia [27,28] in two). PPMs had lower rSO2 for ‘lowest achieved’ absolute values during BCP compared to their controls (MD: −12.72%, 95% CI [−15.28, −10.15], I² = 0%, P = 0.99). However, the use of NPPMs was associated with higher values than in the control group patients for the same studied parameter (vs. controls; MD: 4.87%, 95% CI [2.69, 7.05], I² = 30%, P = 0.21). More specifically, use of targeted mild hypercarbia, SCDs, and RIPC techniques had favorable effects on rSO2 compared to those without their use.

**Prophylactic measures and SjvO2**

The SjvO2 values (comparisons with controls, Figs. 1C, 2C, and 3C) were recorded for only the PPM subgroup in three studies [20,21,25] (150 patients). Arginine vasopressin (AVP) was used in all studies, and both rSO2 and SjvO2 were monitored. The early, all-time overall and lowest achieved SjvO2 values were considered for analysis. With the use of prophylactic AVP infusions, the study group had comparable values to those of the control group patients, indicating the absence of beneficial effects of AVP in BCP. Furthermore, in contrast to rSO2, the negative effects of AVP were not observed for the BCP SjvO2 values.

**Meta-regression results for ‘baseline to all-time overall rSO2 differences’**

Meta-regression analysis included 11 studies [7,13,20–23,25–29]. One study [24] did not report baseline values; therefore, the study was not considered for meta-regression analysis. Meta-regressions revealed a statistically significant highest estimate (estimate: 7.8, SE: 1.534, 95% CI [4.8, 10.8], P < 0.001) for vasoactive agent prophylaxis use (PPMs, higher positive coefficients represent a greater fall of rSO2 in BCP compared to supine) compared to NPPMs (Table 1A). The use of SCDs, crystalloid loading, targeted mild hypercarbia, HES, and RIPC had beneficial effects (visual analysis of coefficients, Table 1A). The use of compression stockings and maintenance of a low BCP angle during surgery failed to demonstrate these benefits.

In contrast, targeted mild hypercarbia, HES, and RIPC techniques had statistically significant coefficients (Omnibus P < 0.001, test for heterogeneity P = 0.646, Egger’s P = 0.514, Table 2;
Fig. 1. Forest plots depicting (A) absolute values of rSO2 for early period (first 15 min of BCP) for vasoactive agents and targeted mild hypercarbia techniques, (B) absolute values of rSO2 for early period (first 15 min of BCP) based on whether prophylactic measures are pharmacological or non-pharmacological, and (C) absolute values of SjvO2 for an early time period for PPMs. The mean differences between individual trials and 95% CIs are shown for prophylactic measures. Absolute values are expressed in %. The overall effects for each prophylactic measure and the differences between the subgroups are shown. The 95% CIs are shown as lines for individual studies and as diamonds for pooled estimates. IV: inverse variance, NPPM: non-pharmacological prophylactic methods, PPM: pharmacological prophylactic methods, rSO2: regional cerebral oxygen saturation, SjvO2: jugular venous oxygen saturation.
Fig. 2. Forest plots depicting (A) absolute values of rSO₂ for an all-time period for vasoactive agents and targeted mild hypercarbia techniques, (B) absolute values of rSO₂ for an all-time period based on whether prophylactic measures are pharmacological or non-pharmacological, and (C) absolute values of SjvO₂ for all-time period for PPMs. The mean differences between individual trials and 95% CIs are shown for prophylactic measures. Absolute values are expressed in %. The overall effects for each prophylactic measure and the differences between the subgroups are shown. The 95% CIs are shown as lines for individual studies and as diamonds for pooled estimates. IV: inverse variance, NPPM: Non-Pharmacological Prophylactic Methods, PPM: Pharmacological Prophylactic Methods, rSO₂: regional cerebral oxygen saturation, SjvO₂: jugular venous oxygen saturation.
### Fig. 3. Forest plots depicting (A) absolute values for lowest achieved rSO₂ for vasoactive agent, compression stockings, and targeted mild hypercarbia techniques, (B) subgroup analysis for lowest achieved rSO₂, based on whether prophylactic measures are pharmacological or non-pharmacological, and (C) SjvO₂ changes for lowest achieved values for PPMs. The mean differences between individual trials and 95% CIs are shown for prophylactic measures. Absolute values are expressed in %. The overall effects for each prophylactic measure and the differences between the subgroups are shown. The 95% CIs are shown as lines for individual studies and as diamonds for pooled estimates. IV: inverse variance, NPPM: non-pharmacological prophylactic methods, PPM: pharmacological prophylactic methods, rSO₂: regional cerebral oxygen saturation, SjvO₂: jugular venous oxygen saturation.
for publication bias [30], Supplementary Material 4A). Among all NPPMs, the targeted mild hypercarbia technique had the lowest estimates (estimate: –5.5, SE: 1.408, 95% CI [–8.2, –2.7], P < 0.001), indicating its superior beneficial effects over others (Wald test, P < 0.001).

Secondary outcomes

Number of patients developing CDEs

Ten studies reporting patients with CDEs [7,13,20–24,27–29] were included, and two [7,29] of these declared only patients with critical CDEs. Meta-analysis (Fig. 4A) revealed that use of PPMs showed a significantly higher risk of developing CDEs than that of the control groups (vs. controls; RR: 4.01, 95% CI [1.82, 8.81], I² = 0%, P = 0.75). In contrast, there was no difference observed between NPPMs and their respective controls (vs. controls; RR: 0.44, 95% CI [0.18, 1.10], I² = 75%, P = 0.001).

Incidence of hypotension

Ten studies [7,13,20–22,25–29] reported episodes of hypotension. Both methods (PPMs and NPPMs) effectively reduced the incidence of hypotension (for PPMs vs. controls; OR: 0.13, 95% CI [0.06, 0.28], I² = 0%, P = 0.42, and for NPPMs vs. controls; OR: 0.27, 95% CI [0.10, 0.74], I² = 54%, P = 0.07) (Fig. 4B).

Vasopressor consumption

Phenylephrine was used in five studies [20,21,23,24,29], and ephedrine in nine [13,20,21,24–29] (combined use in five studies [21,23,24,27,29]), as vasopressors for the treatment of BCP-induced hypotension. The diversity in pattern and dose of individual vasopressor use precluded any analysis of their effect on altering the CDEs.

A few studies compared cerebral desaturations with respect to time-person observations, such as time from induction or time from upright positioning to the onset of CDE, and average cumulative CDE durations. However, the data were inadequate for additional analyses. Serious adverse neurological outcomes (as reported by all studies) and postoperative cognitive dysfunction (as reported by three studies [20,21,25]) were not observed. One study [28] reported nausea and vomiting with low incidence in

Table 1. Meta-regression Analysis

<table>
<thead>
<tr>
<th>Prophylactic measure</th>
<th>Estimate (SE, 95% CI)</th>
<th>P value</th>
<th>Model fit</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. All-time overall rSO2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interception</td>
<td>7.8 (0.892, 6.1 to 9.6)</td>
<td>&lt; 0.001</td>
<td>Omnibus P &lt; 0.001</td>
</tr>
<tr>
<td>Compression stocking (Y)</td>
<td>0.2 (1.491, –2.8 to 3.1)</td>
<td>0.921</td>
<td>Heterogeneity P = 0.646</td>
</tr>
<tr>
<td>Sequential compression device (Y)</td>
<td>–1.6 (1.184, –3.95 to 0.7)</td>
<td>0.167</td>
<td>Egger’s P = 0.514</td>
</tr>
<tr>
<td>Low BCP angle (Y)</td>
<td>1.2 (1.525, –1.8 to 4.2)</td>
<td>0.438</td>
<td>Log-likelihood, –37.9</td>
</tr>
<tr>
<td>Regional ischemic preconditioning (Y)</td>
<td>–2.5 (1.018, –4.5 to –0.5)</td>
<td>0.014</td>
<td>Deviance, 75.8</td>
</tr>
<tr>
<td>Crystallloid loading (Y)</td>
<td>–0.9 (0.99, –2.8 to 1.1)</td>
<td>0.387</td>
<td>AIC, 104.1</td>
</tr>
<tr>
<td>Hydroxyethyl starch (Y)</td>
<td>–3.5 (1.043, –5.5 to –1.5)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Targeted mild hypercarbia (Y)</td>
<td>–5.5 (1.408, –8.2 to –2.7)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Vasoactive agents (Y)</td>
<td>7.8 (1.534, 4.8 to 10.8)</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>B. Number of patients developing CDEs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interception</td>
<td>20.3 (6.487, 7.6 to 32.99)</td>
<td>0.002</td>
<td>Omnibus P = 0.459</td>
</tr>
<tr>
<td>Compression stocking (Y)</td>
<td>0.5 (6.335, –11.9 to 12.9)</td>
<td>0.937</td>
<td>Heterogeneity P &lt; 0.01</td>
</tr>
<tr>
<td>Sequential compression device (Y)</td>
<td>–10.2 (8.375, –26.6 to 6.3)</td>
<td>0.225</td>
<td>Egger’s P = 0.299</td>
</tr>
<tr>
<td>Low BCP angle (Y)</td>
<td>3.025 (8.235, –13.1 to 19.2)</td>
<td>0.713</td>
<td>Log-likelihood, –50.2</td>
</tr>
<tr>
<td>Regional ischemic preconditioning (Y)</td>
<td>–2.527 (12.641, –27.3 to 22.3)</td>
<td>0.842</td>
<td>Deviance, 100.3</td>
</tr>
<tr>
<td>Crystallloid loading (Y)</td>
<td>–10.752 (6.848, –24.2 to 2.7)</td>
<td>0.116</td>
<td>AIC, 120.3</td>
</tr>
<tr>
<td>Hydroxyethyl starch (Y)</td>
<td>–8.924 (8.193, –24.98 to 7.1)</td>
<td>0.276</td>
<td></td>
</tr>
<tr>
<td>Targeted mild hypercarbia (Y)</td>
<td>–12.31 (10.14, –32.2 to 7.6)</td>
<td>0.225</td>
<td></td>
</tr>
<tr>
<td>Vasoactive agents (Y)</td>
<td>5.734 (7.632, –9.2 to 20.7)</td>
<td>0.452</td>
<td></td>
</tr>
</tbody>
</table>

Meta-regression analysis of prophylactic measures used across the study groups. (A) Pre-BCP (supine, after anesthesia induction) and BCP (all-time overall, absolute, and pooled) cerebral saturation values were considered for meta-regression depending on the use of prophylactic measures (yes vs. no). (B) Meta-regressions of ‘number of patients experiencing CDEs’, where baseline supine, pre-BCP CDEs were assumed as ‘zero’ for the analysis. All meta-regressions were performed using the restricted maximum likelihood method and random effects. AIC: Akaike information criterion, BCP: beach chair position, CDE: cerebral desaturation event, rSO2: regional cerebral oxygen saturation, SE: standard error, Y: yes.
the study group (nausea/vomiting, 3/0 vs. 12/1, P < 0.05).

Meta-regression results for 'number of patients experiencing CDEs'

Meta-regression analysis of the number of patients experiencing CDEs (Table 1B) included 10 studies [7,13,20–24,27–29]. Two studies [25,26] did not report the incidence with respect to the number of patients; therefore, they were not considered in the meta-regression analysis. Meta-regressions revealed statistically significant highest estimate (estimate: 5.73, SE: 7.63, 95% CI [-9.2, 20.7], P = 0.452) for vasoactive agent prophylaxis use (PPMs, positive coefficient represents a higher number of patients experiencing CDEs) compared to that for NPPMs. Among all NPPMs, the targeted mild hypercarbia techniques had the lowest estimates observed, indicating its maximal effects over others (estimate: -12.31, SE: 10.14, 95% CI [-32.2, 7.6], P = 0.225). However, to statistically confirm the observations, poor model fit and high heterogeneity were limitations. We observed no statistically significant P values for any of the prophylactic measures used (Omnibus test for model coefficient P = 0.459; fit measure log-likelihood = -50.15, AIC = 120.3; Table 1B; for publication bias [30], see Supplementary Material 4B).

Table 2. Summary of Results with GRADE of Evidence

<table>
<thead>
<tr>
<th>No.</th>
<th>Outcomes</th>
<th>Studies</th>
<th>Number of participants</th>
<th>Relative effect; MDs (%) or RR/OR (95% CI)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Absolute values for rSO2 for early period - PPMs</td>
<td>3</td>
<td>150</td>
<td>-13.58 (–16.03, –11.4)</td>
<td>⬤⬤⬤◯, moderate</td>
</tr>
<tr>
<td>2</td>
<td>Absolute values for SjvO2 for early period - PPMs</td>
<td>3</td>
<td>150</td>
<td>-0.88 (–5.47, 3.7)</td>
<td>⬤⬤⬤◯, moderate</td>
</tr>
<tr>
<td>3</td>
<td>Absolute values for rSO2 for all-time period - PPMs</td>
<td>4</td>
<td>184</td>
<td>-12.23 (–14.6, –9.87)</td>
<td>⬤⬤⬤◯, moderate</td>
</tr>
<tr>
<td>4</td>
<td>Absolute values for SjvO2 for all-time period - PPMs</td>
<td>3</td>
<td>150</td>
<td>-0.23 (–4.67, 4.21)</td>
<td>⬤⬤⬤◯, moderate</td>
</tr>
<tr>
<td>5</td>
<td>Absolute values for lowest rSO2 achieved - PPMs</td>
<td>3</td>
<td>150</td>
<td>-12.72 (–15.28, –10.15)</td>
<td>⬤⬤⬤◯, moderate</td>
</tr>
<tr>
<td>6</td>
<td>Absolute values for lowest SjvO2 achieved - PPMs</td>
<td>3</td>
<td>150</td>
<td>1.45 (–2.85, 5.76)</td>
<td>⬤⬤⬤◯, moderate</td>
</tr>
<tr>
<td>7</td>
<td>Number of patients developing CDEs - PPMs (event)</td>
<td>3</td>
<td>124</td>
<td>RR 4.01 (1.82, 8.81)</td>
<td>⬤⬤⬤⬤, low</td>
</tr>
<tr>
<td>8</td>
<td>Number of patients developing hypotension episodes - PPMs</td>
<td>4</td>
<td>184</td>
<td>OR 0.13 (0.06, 0.28)</td>
<td>⬤⬤⬤⬤, low</td>
</tr>
<tr>
<td>9</td>
<td>Number of patients developing hypotension episodes - NPPMs</td>
<td>6</td>
<td>316</td>
<td>OR 0.27 (0.10, 0.74)</td>
<td>⬤⬤⬤⬤, low</td>
</tr>
<tr>
<td>10</td>
<td>Effect of targeted mild hypercarbia techniques (all-time overall for absolute rSO2 values)</td>
<td>2</td>
<td>110</td>
<td>4.93 (2.45, 7.41)</td>
<td>⬤⬤⬤◯, moderate</td>
</tr>
<tr>
<td>11</td>
<td>Effect of targeted mild hypercarbia techniques (lowest achieved absolute rSO2 values)</td>
<td>2</td>
<td>110</td>
<td>6.0 (3.35, 8.65)</td>
<td>⬤⬤⬤◯, moderate</td>
</tr>
<tr>
<td>12</td>
<td>Effect of targeted mild hypercarbia techniques (Pre-BCP to BCP fall in absolute rSO2 values)</td>
<td>2</td>
<td>108</td>
<td>1.56 (–0.71, 3.83)</td>
<td>⬤⬤⬤◯, moderate</td>
</tr>
<tr>
<td>13</td>
<td>Effect of targeted mild hypercarbia techniques (number of patients developing fall in rSO2, event)</td>
<td>2</td>
<td>110</td>
<td>RR 0.15 (0.05, 0.42)</td>
<td>⬤⬤⬤◯, moderate</td>
</tr>
<tr>
<td>14</td>
<td>Effect of targeted mild hypercarbia techniques (number of patients developing fall in rSO2, event)</td>
<td>2</td>
<td>110</td>
<td>RR 0.15 (0.05, 0.42)</td>
<td>⬤⬤⬤◯, moderate</td>
</tr>
<tr>
<td>15</td>
<td>Effect of targeted mild hypercarbia techniques (number of patients developing fall in rSO2, event)</td>
<td>2</td>
<td>110</td>
<td>RR 0.15 (0.05, 0.42)</td>
<td>⬤⬤⬤◯, moderate</td>
</tr>
</tbody>
</table>


Subgroup analysis of PPMs, targeted mild hypercarbia, and compression stockings

Two studies [27,28] included 110 patients for the targeted mild hypercarbia techniques. End-tidal CO2 values of 40–42 and 30–35 mmHg were used during BCP in the study and control patients, respectively. Subgroup analysis revealed targeted mild hypercarbia as an effective measure in preserving cerebral oxygenation (vs. controls; MD: 4.93%, 95% CI [2.45, 7.41], I² = 0%, P = 0.83, Fig. 2A) and (vs. controls; MD: 6.00%, 95% CI [3.35, 8.65], I² = 0%, P = 0.32, Fig. 3A), for all-time overall and lowest achieved absolute rSO2, respectively. Similar to the above results, targeted mild hypercarbia successfully prevented the fall of rSO2 values from supine-baseline values to BCP (supine vs. BCP; MD: 1.56%, 95% CI [–0.71, 3.83], I² = 6%, P = 0.30, n = 108). This is in contrast to control patients without targeted mild hypercarbia use, in whom a significant fall of rSO2 values from supine-baseline to BCP was observed (supine, pre-BCP vs. BCP; MD: 6.14%, 95% CI [3.08, 9.2], I² = 36%, P = 0.21, n = 112). Furthermore, the number of patients not developing CDE was 13 times higher than for those not using targeted mild hypercarbia techniques at BCP (OR, non-event: 13.18, 95% CI [3.84, 45.24], I² = 0%, P = 0.94, n = 110). Use of compression stockings [13,24] (n = 104) failed to demon-

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the lowest achieved rSO2 was not different from that of control desaturation event, M-H: Mantel-Haenszel, NPPMs: non-pharmacological prophylactic methods, OR: odds ratio, PPMs: pharmacological transformation was adopted, as the outcomes for incidences were expected to be non-normally distributed for CDE incidences. CDE: cerebral desaturation event, M-H: Mantel-Haenszel, NPPMs: non-pharmacological prophylactic methods, OR: odds ratio, PPMs: pharmacological transformation was adopted, as the outcomes for incidences were expected to be non-normally distributed for CDE incidences. CDE: cerebral desaturation event, M-H: Mantel-Haenszel, NPPMs: non-pharmacological prophylactic methods, OR: odds ratio, PPMs: pharmacological transformation was adopted, as the outcomes for incidences were expected to be non-normally distributed for CDE incidences. CDE: cerebral desaturation event, M-H: Mantel-Haenszel, NPPMs: non-pharmacological prophylactic methods, OR: odds ratio, PPMs: pharmacological transformation was adopted, as the outcomes for incidences were expected to be non-normally distributed for CDE incidences. CDE: cerebral desaturation event, M-H: Mantel-Haenszel, NPPMs: non-pharmacological prophylactic methods, OR: odds ratio, PPMs: pharmacological transformation was adopted, as the outcomes for incidences were expected to be non-normally distributed for CDE incidences. CDE: cerebral desaturation event, M-H: Mantel-Haenszel, NPPMs: non-pharmacological prophylactic methods, OR: odds ratio, PPMs: pharmacological transformation was adopted, as the outcomes for incidences were expected to be non-normally distributed for CDE incidences. CDE: cerebral desaturation event, M-H: Mantel-Haenszel, NPPMs: non-pharmacological prophylactic methods, OR: odds ratio, PPMs: pharmacological transformation was adopted, as the outcomes for incidences were expected to be non-normally distributed for CDE incidences. CDE: cerebral desaturation event, M-H: Mantel-Haenszel, NPPMs: non-pharmacological prophylactic methods, OR: odds ratio, PPMs: pharmacological transformation was adopted, as the outcomes for incidences were expected to be non-normally distributed for CDE incidences. CDE: cerebral desaturation event, M-H: Mantel-Haenszel, NPPMs: non-pharmacological prophylactic methods, OR: odds ratio, PPMs: pharmacological transformation was adopted, as the outcomes for incidences were expected to be non-normally distributed for CDE incidences. CDE: cerebral desaturation event, M-H: Mantel-Haenszel, NPPMs: non-pharmacological prophylactic methods, OR: odds ratio, PPMs: pharmacological transformation was adopted, as the outcomes for incidences were expected to be non-normally distributed for CDE incidences.

Fig. 4. Forest plots depicting numbers of patients who developed (A) CDEs and (B) hypotension. The individual trials’ RRs or ORs, SEs, and the pooled estimates are shown. The 95% CIs are shown as lines for individual studies and as diamonds for pooled estimates. Natural log transformation was adopted, as the outcomes for incidences were expected to be non-normally distributed for CDE incidences. CDE: cerebral desaturation event, M-H: Mantel-Haenszel, NPPMs: non-pharmacological prophylactic methods, OR: odds ratio, PPMs: pharmacological prophylactic methods, RR: risk ratio, rSO2: regional cerebral oxygen saturation, SE: standard error, StVO2: jugular venous oxygen saturation.

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strate benefits, as the odds ratio remained less than 1 (OR, non-event: 0.77, 95% CI [0.33, 1.77], I² = 0%, P = 0.45). Furthermore, the lowest achieved rSO2 was not different from that of control patients when compression stockings were used as a prophylactic measure (vs. controls; MD: -0.38%, 95% CI [-5.85, 5.09], I² = 0%, P = 0.43, n = 56).
Risk of bias and heterogeneity

The risk of bias summary and graph are presented in Figs. 5A and 5B, respectively. Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence was noted in one study [23], and selection bias due to inadequate concealment of allocations prior to the assignment occurred in a few studies [20,21,23]. Blinding is difficult [13,23,28] in BCP surgeries, although most studies were double-blinded. Therefore, performance bias and detection bias due to knowledge of the allocated interventions by participants and personnel during the study were observed in a few studies [13,28]. Further, we observed selective reporting (reporting bias) in a few [7,24], with incomplete outcome data such as reporting only ‘critical’ desaturations and mentioning ‘maximum fall’ of rSO2 from baseline values. The observed low heterogeneity for PPMs precluded further analysis, as opposed to that of NPPMs. As described earlier, the latter group included the use of different prophylactic techniques. Therefore, the results of subgroup analyses of NPPMs are uncertain because of the uneven covariate distribution among groups. Furthermore, an insufficient number of studies per group was observed. Therefore, all these factors necessitated additional meta-regression analysis. To explore the potential causes of heterogeneity that could influence primary outcome results, anesthetic factors such as the type of anesthesia and induction or maintenance agents were not considered separately, primarily due to inadequate data.

GRADE evidence

The relevant summary results are presented in Table 2 with GRADE evidence. The certainty of the evidence is summarized as ‘moderate’ for the outcome of ‘early, all-time overall, and lowest achieved rSO2/SjvO2 values’ since the risk of bias was ‘serious’ in nature. The certainty of the evidence is similar for the targeted mild hypercarbia technique. For the rest of the studied outcomes, the certainty of the evidence is described as ‘low’ since ‘inconsistency’ and ‘imprecision’ were ‘serious’.

Discussion

In our meta-analysis, we evaluated the efficacy of different prophylactic measures employed to prevent cerebral desaturation during shoulder surgeries performed in BCP. We observed that not all prophylactic measures were successful, and the methods did differ in efficacy. Our current study provides concrete evidence that PPMs cannot effectively prevent cerebral desaturation. The benefits of a few NPPM techniques, such as targeted mild hypercarbia, for maintaining cerebral oxygenation during BCP are also evident. However, a few trials have confirmed the protective effects of HES preloading, and studies of SCDs or RIPC are scarce. Our meta-analysis unequivocally confirmed the negative effect of vasoactive agents on rSO2 values (but not on SjvO2), highlighting...
their failure in protecting patients from CDEs despite their ability to prevent hypotension.

A pervasive issue in the pharmacologic prophylaxis portion of this meta-analysis is the extracranial contribution (contamination) [31] to cerebral oximetry, which must be acknowledged. This can be explained to a large extent as a ‘paradoxical effect’ of vasopressors on oximetry values when given to support blood pressure. Our analysis demonstrated that prophylactic vasoactive agents can decrease rsO$_2$ values. However, to confirm whether this decrease truly reflects cerebral desaturation, additional analysis was needed. SjvO$_2$-metry is a more accurate assessment of the balance between oxygen supply and demand in the brain, albeit globally. Therefore, we simultaneously analyzed the effects of PPM on both rsO$_2$ and SjvO$_2$. The discrepancy between rsO$_2$ and SjvO$_2$ necessarily describes the effects of PPMs on regional oximetry values. The other finding of this study is the inefficacy of vasoactive agent prophylaxis in preventing fall of cerebral oxygen saturation. Despite the higher SjvO$_2$ recorded over rsO$_2$, AVP failed to demonstrate any beneficial effect, in that its use did not prevent the fall in SjvO$_2$ during BCP. In contrast to rsO$_2$, the SjvO$_2$ values of the PPM subgroup were similar to those of the control groups, in both the supine, pre-BCP and BCP periods. A single phenylephrine study was included in the PPM subgroup. However, in the absence of SjvO$_2$ monitoring in the same study, we were unable to describe the extracranial effects of phenylephrine on rsO$_2$ monitoring. The association of AVP, CDEs, and postoperative cognitive dysfunction have also been reported in the past [32]. While some NPPMs were superior to vasoactive agent prophylaxis with respect to CDE incidence, their role in preventing cognitive dysfunction was not evaluated in our study. Reports on the effect of AVP on cerebral oxygenation in animal models have been conflicting [12,33]. Beyond auto-regulation values of MAP, AVP improves CBF via nitric oxide-mediated cerebral vasodilation [34], and this was the rationale for its use in some of our included studies.

In this review, the effectiveness of individual prophylactic measures (especially NPPMs) was analyzed through a separate analysis. Drawing conclusions on NPPMs was not possible, as we have lumped together with a disparate and diverse group. Importantly, since no study authors used a single measure to prevent cerebral desaturation, analyzing a single method (such as NPPMs) could be misleading. Therefore, the more appropriate method of meta-regression analysis was performed. Our analysis confirmed the beneficial effects of a few NPPMs, such as targeted mild hypercarbia, HES, and RIPC. Targeted mild hypercarbia during these procedures must be performed with caution and must not be performed to the exclusion of blood pressure support. Hypercarbia impairs cerebral autoregulation and puts the patient at a higher risk for cerebral hypoperfusion, should hypotension occur at the same time. Additional subgroup analysis established stronger evidence for targeted mild hypercarbia use. Few prospective studies [35] investigating the effects of targeted mild hypercarbia on rsO$_2$ during major surgery have confirmed similar effects.

One of the interpretations of this meta-analysis is that NPPMs in combination can be effectively deployed during BCP surgery to enhance rsO$_2$; this conclusion could be relevant to clinicians in maintaining cerebral oxygenation. For example, targeted mild hypercarbia of 40–42 mmHg during controlled ventilation, appropriate preloading (HES), and concomitant use of SCDs can significantly reduce CDEs. The routine use of RIPC as a prophylactic measure has not yet been recommended. While a previous prospective cohort study [9] demonstrated the efficacy of compression stockings in reducing the incidence of CDEs, our meta-regression results failed to confirm this. Confounding factors such as MAP, hemoglobin level, cardiac output, angle of BCP maintained, and partial pressures of oxygen and carbon dioxide, which can influence rsO$_2$ values, were kept constant in the RCTs included. We believe that the study authors excluded patients with cardiopulmonary disease or anemia because of possible negative effects on rsO$_2$ values.

While PPMs were inferior to a few NPPMs in the prevention of CDEs (coefficient evaluation), both exhibited similar effects with respect to lowering the incidence of hypotension (vs. controls). Thus, PPMs were unable to achieve the ultimate therapeutic benefit, despite maintaining MAP. The association of episodic decrease in MAP with the incidence of cerebral desaturation and its direct correlation with cerebral oximetry values remain unconfirmed [36,37]. Several studies have demonstrated no direct correlation between blood pressure and cerebral (de)saturation values (Supplementary Material 5) [13,38–43]. However, cardiac output has been claimed as a factor that correlates well with rsO$_2$ values in BCP-neurosurgical patients [40]. Targeting MAP alone may not be the ideal approach to prevent CDEs in BCP surgeries.

Over 80% of the patients in this meta-analysis were treated with ephedrine for BCP-related hypotension. Phenylephrine and ephedrine are commonly used for this indication. While treating hypotension in a non-BCP setting, the former was shown to decrease cerebral oxygen saturation even with correction of arterial blood pressure [44]. According to cardiac output rather than arterial blood pressure, it has been concluded that treating hypotension using vasoconstrictors to avoid cerebral hypoxia actually accomplished the opposite result [44,45]. In contemporary practice, approximately 70% of BCP-related hypotension episodes are still treated with phenylephrine. It would be prudent to choose a dif-
different vasopressor and to use the more physiological NPPMs. Additionally, while targeting cardiac output to maintain cerebral oxygenation, the use of NPPMs with ephedrine (as a vasopressor of choice to treat hypotension) could possibly be a desirable combination. Currently, the use of cerebral oximetry in patients with BCP is limited in availability. Under these circumstances, especially in susceptible patients, this combination is gaining significance.

Our study had some limitations. Higher heterogeneity values represent different NPPM methods applied over cohorts. The type of anesthesia, maintenance anesthetics, Fraction of inspired oxygen concentration, and other co-variables could have partially influenced the outcomes. The definition of 'event' could vary according to the authors' perception, and this could have a bearing on the incidence reporting. The range of rSO2 values may be significantly larger when measured with INVOS™ devices compared to FORE-SIGHT™, but the exact underlying reasons for these differences remain unknown [46]. The use of phenylephrine to treat hypotension episodes in subgroups of NPPMs could have possibly influenced the CDEs in a few studies, which is an inherent contradiction in the analysis. The difference in the timing of the application of NPPMs poses significant analytical challenges. Moreover, none of the included NPPMs reported SjvO2 data. The use of pooled data and presuming the baseline data of rSO2 values to be uniform for all patients may be another limitation. Non-availability of raw patient data and non-reporting of time-person observations for groups or lowest achieved cerebral desaturation data for many trials precluded conducting individual patient meta-analysis or correlations.

In conclusion, the evidence favors the prophylactic use of targeted mild hypercarbia techniques to effectively reduce BCP-CDEs and best preserve cerebral oxygenation. Evidence does not favor the use of prophylactic vasoactive agents for the prevention of cerebral desaturations, irrespective of whether their use interferes with cerebral oximetry readings. One may use a combination of a few NPPMs as prophylactic measures; however, an RCT investigating the effect of combined use of all NPPMs could conclusively demonstrate the benefits. At the same time, comparisons of prophylactic as well as therapeutic effects of different vasoactive agents (such as phenylephrine vs. ephedrine) for BCP-CDEs could set the direction for future research in this field.

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Conflicts of Interest

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

Author Contributions

Thrivikrama Padur Tantry (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Resources; Software; Validation; Writing – original draft; Writing – review & editing)
Baikunje Goltadka Muralishankar (Formal analysis; Investigation; Methodology; Project administration; Resources; Validation)
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Dinesh Kadam (Project administration; Validation; Writing – review & editing)
Gururaj Tanthry (Data curation; Formal analysis; Resources)
Rithesh Shetty (Data curation; Formal analysis; Resources)

Supplementary Materials

Supplementary Material 1. The search strategy. The search terms were used to search MEDLINE, CCRCT (Cochrane Central Register of Controlled Trials), CINHAL (Cumulative Index to Nursing and Allied Health Literature, EBSCO host), and Google Scholar (modified to suit each specific database with abstract, keywords, and text with the removal of duplicates).

Supplementary Material 2. The flow chart for literature identification and study selection. BCP: beach chair position, CDE: cerebral desaturation event, CCRCT: Cochrane Central Register of Controlled Trials, CINHAL: Cumulative Index to Nursing and Allied Health Literature, n: number of studies, rSO2: regional cerebral oxygen saturation.

Supplementary Material 3. The study characteristics. ASA PS: American Society of Anesthesiologists physical status, AVP: arginine vasopressin, BCP: beach chair position, BL: baseline, BP: blood pressure, CBF: cerebral blood flow, CDE: cerebral desatura-

Supplementary Material 4. Publication bias. The funnel plots for (A) pre-BCP (supine, after anesthesia induction) and BCP (all-time overall, absolute, and pooled) cerebral saturation values, (B) the number of patients experiencing the CDEs during meta-regressions of prophylactic factors to prevent cerebral desaturation. The regression test for funnel plot asymmetry (Egger’s test) P values were > 0.05; however, poor model fit – fit measures were recorded for funnel plot B.

Supplementary Material 5. Studies depicting associations between MAP and rSO2. Correlation analysis was used in most of the studies to establish the associations. BCP: beach chair position, BL: baseline, CDE: cerebral desaturation event, CO: cardiac output, DBP: diastolic blood pressure, ETCO2: end-tidal carbon dioxide, eTMAP: estimated temporal mean arterial pressure, L: left-sided measurement, MAP: mean arterial pressure, MBP: mean blood pressure, NIBP: noninvasive blood pressure, NIRS: near-infrared reflectance spectrometry, R: right-sided measurement, r: correlation coefficient, rSO2: regional cerebral oxygen saturation, SBP: systolic blood pressure, “INVOS™” (Somanetics, Troy, MI, USA) and “FORE-SIGHT™” (Cas Medical Systems Inc., Branford, CT, USA), the names of cerebral oximeter equipments that measured the regional cerebral oxygen saturation.

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References


Video laryngoscopy vs. direct laryngoscopy for nasotracheal intubation in oromaxillofacial surgery: a systematic review and meta-analysis of randomized controlled trials

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Background: Nasotracheal intubation (NTI) is commonly performed in oromaxillofacial surgeries. We did this meta-analysis to ascertain whether use of video laryngoscopy (VL) provided better NTI characteristics as compared to direct laryngoscopy (DL) in patients undergoing oromaxillofacial surgeries.

Methods: We performed a systematic search to identify randomized controlled trials comparing VL with DL for NTI in adults undergoing elective oromaxillofacial surgery. The primary outcome was time to intubation. Secondary outcomes included the first attempt success, overall success, incidence of nasal bleeding, Cormack and Lehane grade, and maneuvers required.

Results: Of the 456 studies identified following a systematic search, 10 were included. Meta-analysis showed a significantly lower time to tracheal intubation favoring VL (mean difference: –9.04, 95% CI [–12.71, –5.36], P < 0.001; I² = 59%). VL was also associated with a greater first attempt success (relative risk [RR]: 1.10, 95% CI [1.04, 1.16], P = 0.001). Maneuvers to facilitate intubation were less with VL (RR: 0.22, 95% CI [0.10, 0.51], P < 0.001). There was no difference in overall intubation success (RR: 1.04, 95% CI [0.98, 1.10], P = 0.17). The incidence of bleeding did not differ between the DL and VL groups (RR: 0.59, 95% CI [0.32, 1.08], P = 0.09).

Conclusions: Evidence as per this meta-analysis suggests VL leads to a shorter time to NTI, a greater first attempt success rate, and reduced need for maneuvers when compared to DL. The present study supports use of VL as a first line device for NTI in oral-maxillofacial surgeries in experienced hands.

Keywords: Intratracheal intubations; Intubation; Laryngoscopes; Meta-analysis; Oral surgical procedures; Orthognathic surgical procedures; Statistics; Systematic review.

Introduction

Oral and maxillofacial surgeries require nasal intubation to secure the airway [1]. According to the 4th National Audit Project, difficult airway situations account for approximately 39% of all events during anesthesia [2]. Direct laryngoscopy (DL) is usually used by positioning the head in a snifffing position to align the oropharyngeal and laryngeal...
axes and create a ‘line of sight’ for glottis visualization and tracheal intubation [3]. Video laryngoscopy (VL) function by transmitting the image from its tip to a monitor or screen attached to its handle or a distant monitor. Thus, tracheal intubation can be performed without the ‘line of sight’ approach. One may require additional maneuvers, such as optimal external laryngeal pressure, neck rotation, Magill forceps, or the cuff inflation technique to direct the endotracheal tube towards the glottis using a DL. In contrast, VL provides a better laryngeal view without significant distortion of the airway alignment and reduces the need for maneuvers. VL has been shown to improve the success rates of both orotracheal and nasotracheal intubation (NTI) [4–7].

A systematic review concluded that VL resulted in greater success and reduced time for NTI compared to DL [8]. Another systematic review found that VL shortened intubation time and improved the first attempt success rate but did not increase the overall success rate [9]. These systematic reviews included studies with varied surgical populations and did not focus explicitly on the comparative characteristics of VL and DL for NTI in patients undergoing oromaxillofacial surgery.

Therefore, we conducted this systematic review and meta-analysis of randomized controlled trials (RCTs) to study if VL reduces the intubation time, improves the overall and first-attempt success, and reduces the need for maneuvers and occurrence of complications when compared to DL for NTI in adults undergoing oromaxillofacial surgery.

Materials and Methods

We followed the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines to prepare this systematic review and meta-analysis [10]. The study was registered with PROSPERO (https://www.crd.york.ac.uk/PROSPERO, no. CRD42020222444).

Search strategy and initial review

We performed a systematic search of the PubMed and Embase databases for human subject studies published until September 9, 2020. The following free-text terms were used for the search: (nasal intubation OR nasotracheal intubation OR intubation) AND (video laryngoscope OR video laryngoscopy OR Storz DCI OR TruView PCD OR Pentax AWS OR Airway Scope OR Airtraq OR C-MAC OR Glidescope OR McGrath OR King Vision OR laryngoscope OR direct laryngoscope OR Macintosh laryngoscope) AND (buccal surgery OR mouth surgery OR oral surgery OR oral surgical procedures OR maxillofacial OR maxillofacial surgery OR maxillectomy). Review articles and editorials were also screened. References of the selected items were also searched to identify more articles. We included all RCTs that compared VL and DL for NTI in oromaxillofacial surgeries.

Data extraction

Two authors (N.G. and R.S.) assessed the titles and abstracts of all citations to identify all relevant studies. RCTs that compared VL with DL for NTI in adult patients (> 18 years of age) undergoing elective oromaxillofacial surgery were included. Studies in languages other than English, without full text, or conference abstracts were excluded. Studies on manikins, cadavers, and simulation studies, were also excluded along with those on patients with a base of skull fracture, coagulation abnormality, reduced mouth opening (< 3 cm), and midface instability. Any disagreement between the authors was resolved after mutual discussion with the other authors (A.G. and K.M.). The selection process is presented with a PRISMA flow diagram (Fig. 1) [11].

Outcomes

The primary outcome was time to intubation. The secondary outcomes were the first attempt and overall success, need for maneuvers to facilitate NTI, rate of nasal bleeding, and proportion of Cormack and Lehane (CL) classification 1 and 2. The characteristics of various studies included have been summarized in Table 1.

Statistical analysis

The baseline clinical characteristics and outcome measures of the study population were extracted by two authors (N.G. and R.S.). We extracted the sample size, mean, and standard deviation (SD) for continuous data. Data reported as median and interquartile range were transformed into mean and standard deviation with the help of the formula in the Cochrane handbook [12]. We calculated the sample size and the number of events for dichotomous variables and used the relative risk (RR) and 95% CI. Statistical significance was set at P < 0.05. We used Review Manager (RevMan)[computer program], version 5.4. The Cochrane Collaboration, 2020 for all analyses. For studies with more than two VL comparisons, the better of the two results was included in our calculation. Any discrepancy in data analysis was resolved by discussion with the other two authors (A.G. and K.M.) until an agreement was reached.
Identification
Screening
Eligibility
Included

Records identified through database searching (n = 729)
Additional records identified through other sources (n = 0)

Records after excluding duplicates (n = 273)

Records screened (n = 456)

Articles assessed for eligibility (n = 42)

Full-text articles assessed for eligibility (n = 19)

Studies included in quantitative synthesis (meta-analysis) (n = 10)

Records excluded (n = 414)

Full-text articles excluded with reasons (n = 9)
• Type of study (n = 2)
• Non-randomized controlled train (n = 2)
• Inadequate data (n = 1)
• Only video laryngoscopy (n = 4)

Assessment of risk of bias

The Risk-of-bias VISualization (Robvis) tool (McGuinness LA, USA) as used to assess the risk of bias for all selected studies by two authors (A.G. and R.S.) [13]. We evaluated the process of randomization, variation from intended intervention, outcome data that were missing, outcome measurement, and selection of reported results. We relied only on the information provided in the articles to assess the risk of bias [13].

Grading of recommendation, assessment, development, and evaluations (GRADE) system criteria were used to evaluate the quality of evidence (high, moderate, low, or very low quality) related to the outcomes based on limitations, inconsistency, imprecision, indirectness, and publication bias, and an evidence table was generated using the GRADE software (Evidence Prime, Inc., McMaster University, Canada) (www.guidelinedevelopment.org) [14] (Table 2).

Heterogeneity among trials was quantified using the Higgins and Thompson $I^2$ method. Regardless of the $I^2$ value, we considered a random-effect model. Publication bias was assessed using a funnel plot [15].

Study characteristics

We included studies with head and neck cancer surgeries [25] and dental or oral maxillofacial surgeries [26–34]. All of them were single-centered, except one, which was performed at three centers [26]. The operator criteria were defined in all studies except in one [32]. The types of video laryngoscopes used included Glidescope (three studies) [26,33,34], C-MAC D-blade (one study) [25], McGrath (four studies) [27–29,31], True View EVO2 (one study) [30], and Pentax Airway scope (two studies) [32,33].

Results

In total, 729 articles were identified. We removed 273 duplicates and screened 456 articles for eligibility. Of them, 414 were removed due to a lack of relevance. We discarded case reports, articles on the pediatric population, manikin studies, and non-English language studies from the remaining 42 articles. Of the 19 articles selected for qualitative data synthesis, nine studies were excluded because of the type of study participants [16,17], non-RCT studies [18,19], use of only VL [20–23], and inadequate data [24]. For the systematic review and meta-analysis, a total of 10 studies (n = 597) were included (Fig. 1).
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Type of Surgery</th>
<th>Devices</th>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
<th>Operator experience</th>
<th>Definition of time to intubation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazarika 2018 [25]</td>
<td>100</td>
<td>Head and neck cancer</td>
<td>C-MAC &amp; DL</td>
<td>ASA 1–3; 20–70 yr; EGR1 1–7</td>
<td>ASA 4; MO &lt; 2.5; difficult BMV; hyperkalemia; h/o malignant hyperthermia</td>
<td>20 successful nasal or oral intubations C-MAC D-blade</td>
<td>Introduction of scope to mouth till three consecutive ETCO₂ readings</td>
</tr>
<tr>
<td>Jones 2008 [26]</td>
<td>69</td>
<td>Dental or maxillofacial</td>
<td>GVL &amp; DL</td>
<td>More than equal to 18 yr</td>
<td></td>
<td>&gt; 10 successful GVL intubation</td>
<td>End of mask ventilation to detection of ETCO₂ of at least 30 mmHg</td>
</tr>
<tr>
<td>Sato 2017 [31]</td>
<td>60</td>
<td>Oromaxillofacial</td>
<td>McGrath &amp; DL</td>
<td>ASA 1–2; 20–70 yr; EGR1 1–7</td>
<td>Expected difficulty in intubation; patients with rhino stenosis</td>
<td>Experience &gt; 6 yr by JDSA</td>
<td>Passage of ETT through nasal cavity until chest rise seen</td>
</tr>
<tr>
<td>Kwak 2016 [29]</td>
<td>70</td>
<td>Oromaxillofacial with</td>
<td>McGrath &amp; DL</td>
<td>ASA 1–2; 20–60 yr; EGR1 1–7</td>
<td>Suspected difficult airway; CSE bleeding tendency; RSI required</td>
<td>Experienced anesthesiologists</td>
<td>Insertion through the nostril to detection of ETCO₂</td>
</tr>
<tr>
<td>Zhu 2019 [27]</td>
<td>66</td>
<td>Oromaxillofacial</td>
<td>MacGrath &amp; DL</td>
<td>ASA 1–2; 18–60 yr; EGR1 1–7</td>
<td>EGRI &gt; 7; Reflux; OSA; BMI &gt; 40</td>
<td>&gt; 100 NTI with both laryngoscopes</td>
<td>Mouth opening till three consecutive ETCO₂ readings</td>
</tr>
<tr>
<td>Roh 2019 [28]</td>
<td>80</td>
<td>Dental or maxillofacial</td>
<td>MacGrath &amp; DL</td>
<td>ASA 1–2; 19–60 yr; MMP4; requiring RSI; CSE bleeding tendency</td>
<td></td>
<td>&gt; 50 intubations with the study laryngoscopes</td>
<td>Intranasal placement to detection of ETCO₂</td>
</tr>
<tr>
<td>Puchner 2011 [34]</td>
<td>40</td>
<td>Dental or oromaxillofacial</td>
<td>GVL &amp; DL</td>
<td>ASA 1–2; 18–80 yr; Difficult airway or h/o bleeding</td>
<td></td>
<td>&gt; 10 intubations per laryngoscope</td>
<td>Not specified</td>
</tr>
<tr>
<td>Shrestha 2015 [30]</td>
<td>40</td>
<td>Maxillofacial</td>
<td>Truview &amp; DL</td>
<td>ASA 1–2; 18–60 yr; C/I for NTI</td>
<td>ASA 3;4; morbid obesity; upper airway structural anomalies</td>
<td>&gt; 50 intubations with Truview EVO, in normal and difficult airways</td>
<td>Insertion between teeth until first capnographic trace</td>
</tr>
<tr>
<td>Suzuki 2012 [32]</td>
<td>90</td>
<td>Elective orthodontic</td>
<td>Pentax AWS &amp; DL</td>
<td>ASA 1–2; &gt; 18 yr; h/o CSE; difficult airway; GERD; BMI &gt; 35</td>
<td></td>
<td>Experienced but not defined</td>
<td>Time from the tube passing the incisors until the ETT was traversed</td>
</tr>
<tr>
<td>Tseng 2017 [33]</td>
<td>72</td>
<td>Oromaxillofacial</td>
<td>GVL and DL</td>
<td>ASA 1–2; 20–65 yr; MO &lt; 3 cm; CS instability; h/o difficult intubation, chronic supplicative sinusitis; C/I for NTI</td>
<td></td>
<td>Experienced but not defined</td>
<td>Placement of the nasotracheal tube from selected nostril till the removal of the scope</td>
</tr>
</tbody>
</table>

Meta-analysis

Time to intubation

The definition of time to intubation varied from the mouth opening until the detection of ETCO₂ [25,27,30], end of mask ventilation until detection of ETCO₂ [26], intranasal placement until detection of ETCO₂ [28], insertion through nostril until detection of ETCO₂ [29], passing through the nasal cavity until chest rise [31], placement of the endotracheal tube [32,33], or as not clear [34]. Pooled analysis showed a significantly shorter time to intubation favoring VL (MD: −9.04, 95% CI [−12.71, −5.36], n = 597, P < 0.001, I² = 59%) (Fig. 3). The quality assessment of the GRADE was high.

First attempt success and overall success

First attempt success was reported in all studies except for three [29,32,34]. Pooled analysis demonstrated a significantly high first-attempt success with VL. The first attempt success rate was greater for all video laryngoscopes ([221 out of 233; 94.8%] vs. [197 out of 234; 84.2%]) (RR: 1.10, 95% CI [1.04, 1.16], n = 418, P < 0.001, I² = 0%; high-quality evidence) (Fig. 4). A pooled analysis of overall intubation success rates with the two types of laryngoscopes in all studies except two [28,29] showed no significant difference (RR: 1.04, 95% CI [0.98, 1.04], n = 411, P = 0.17, I² = 60%; high-quality evidence) (Supplementary Fig. 1).

Glottic view

All studies, except two, reported CL classification of the glottic view obtained [32,33]. In one study, CL grade was categorized as CL grade 1 and CL grade 2 or higher and was therefore excluded from our analysis [26]. Pooled analysis showed that the VL group showed a higher rate of CL grade 1 or 2 than DL (RR: 1.19, 95% CI [0.98, 1.45], n = 388, P = 0.07, I² = 95%; high-quality evidence) (Supplementary Fig. 2) without any statistical significance in the overall effect estimate. The high level of statistical heterogeneity could be explained by the subjective variability associated with its description.

Maneuvers used

Eight studies described maneuvers (cuff inflation technique, rotation of endotracheal tube, Magill forceps use, and external laryngeal pressure) used to guide the endotracheal tube into the glottis. Maneuvers required were significantly higher with DL than with VL (RR: 0.22, 95% CI [0.10, 0.51], n = 212; P < 0.001, I² = 83%; high-quality evidence) (Fig. 5). Because of the high level of statistical heterogeneity, no effect estimate was presented for this outcome.

Nasal bleeding

Eight studies mentioned nasal bleeding or epistaxis resulting from nasotracheal intubation. Pooled analysis showed that bleeding was more common with DL than with VL (RR: 0.59, 95% CI [0.32, 1.08], n = 100, P = 0.09; I² = 50%; high-quality evidence) (Supplementary Fig. 3), although the difference was not significant.

A funnel plot showed a low risk of publication bias (Fig. 6). The overall risk of bias based on Revman was low (Supplementary Fig. 4).

Discussion

The main conclusion from this meta-analysis of ten studies is that VL is associated with a significantly shorter time to intubate, greater first attempt success, and reduced need of maneuvers to facilitate NTI in patients undergoing oromaxillofacial surgery.
<table>
<thead>
<tr>
<th>Table 2. Quality of Evidence from GRADE System</th>
</tr>
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<tbody>
<tr>
<td><strong>Participants (studies)</strong></td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td>Follow up</td>
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<tr>
<td>Total success</td>
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<tr>
<td>Maneuvers</td>
</tr>
<tr>
<td>CL 1 &amp; 2</td>
</tr>
<tr>
<td>Bleeding</td>
</tr>
<tr>
<td>First attempt success rate</td>
</tr>
<tr>
<td>Time to intubation (Scale from: 10 to 200)</td>
</tr>
</tbody>
</table>

The overall success rate, glottis view in terms of CL grade, and nasal morbidity in terms of bleeding were similar between the two groups.

The finding of a shorter intubation time with VL is opposite to that of findings in previous studies [35,36] but was similar to the findings of Jiang et al. [9]. VL improves laryngeal vision and causes less distortion of the airway structures. Therefore, less tube manipulation is required to navigate the nasally inserted tube into the glottis. This may be responsible for the reduced total time to intubation. In the DL group, the need for maneuvers required to negotiate the tube was also greater, which must have resulted in an increased intubation time. The time to intubation through the

---

**Fig. 3.** Forest plot for comparison of time to intubation between video laryngoscopy (VL) and direct laryngoscopy (DL). IV: inverse variance.

**Fig. 4.** Forest plot for comparison of first-attempt success rate between video laryngoscopy (VL) and direct laryngoscopy (DL). M-H: Mantel-Haenszel.

**Fig. 5.** Forest plot for comparison of maneuvers used between video laryngoscopy (VL) and direct laryngoscopy (DL). M-H: Mantel-Haenszel.
McGrath VL was significantly shorter than that of DL [27–29,31]. However, in the study where Pentax AWS was used, this result was not significant, probably because of a thicker blade that could have led to difficulty in manipulating the endotracheal tube in the oropharynx [32]. A previous meta-analysis comparing Pentax AWS with DL for oral intubation also showed that Pentax AWS resulted in a similar intubation time and intubation success rate despite providing better glottis views [37]. The heterogeneity above 50% can be explained by the different time points used and experience of operators in the various studies calculating the intubation time.

We found that VL increased the first attempt success. This is in agreement with previous studies in which VL improved the first attempt success for both nasotracheal and oral intubation in patients with difficult airways [4,9,36], whereas Donald et al. [35] did not find any significant difference for the same. VL has always been considered when intubation through DL is difficult or fails altogether [24]. Any patient undergoing oromaxillofacial surgery can be considered a potentially difficult airway. Hence, we do not feel that considerations of outcome in other difficult airway cases would be different if the mouth opening is sufficient to allow insertion of a laryngoscope. However, in difficult airway scenarios with restricted mouth opening (less than 2 cm), fiberoptic bronchoscopy remains the method of choice [38].

The overall success rate of NTI was not significantly better with VL despite the better first-attempt success rate. This could be due to the use of alternative techniques and maneuvers in successive attempts with DL. In our study, VL resulted in more CL grade 1 or 2 views than DL. A meta-analysis found that intubation with acutely angled VL blades provided a better view of the glottis as they follow the anatomy of the oral cavity, and the tip of the camera lies in approximation with the glottis opening [36]. A better laryngeal view with minimal force on the anterior airway structures is one of the main reasons for the lesser number of maneuvers required to negotiate the ETT [26]. In addition, a shorter intubation time resulted in lesser device contact with the mucosa. This, in turn, may be responsible for the reduced bleeding with VL.

Our study has a few limitations. The inability to blind anesthesiologists to the devices could lead to an altered performance (Hawthorne effect). The definitions of time to intubation varied in different studies, which may have led to measurement bias. However, such a difference would affect the intubation times with both devices equally. In all the included studies, the experience of operators was specified, except in three [29,32,33] where operators were mentioned to be experienced. A meta-analysis by Donald et al. [35] found that VL by inexperienced operators improved the first attempt success rate and time to intubation, but the same was not seen with experienced operators.

The evidence from this meta-analysis suggests supports the use of a VL over DL for NTI in oral-maxillofacial surgeries. Further robust studies can be planned to ascertain the precise role of VL in NTI with a universal definition of the intubation time and inexperienced users.

**Conflicts of Interest**

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

**Author Contributions**

Nishkarsh Gupta (Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Supervision; Validation; Visualization; Writing – review & editing)

Anju Gupta (Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Writing – review & editing)

Riniki Sarma (Data curation; Formal analysis; Methodology; Validation; Writing – original draft; Writing – review & editing)

Atul Batra (Data curation; Formal analysis; Methodology; Supervision; Validation; Writing – review & editing)

Karan Madan (Conceptualization; Formal analysis; Methodology; Supervision; Validation; Visualization; Writing – review & editing)

**Supplementary Materials**

Supplementary Fig. 1. Forest plot for comparison of overall suc-
Supplementary Fig. 2. Forest plot for comparison of glottic view between video laryngoscopy and direct laryngoscopy. M-H, Mantel-Haenszel.
Supplementary Fig. 3. Forest plot for comparison of nasal bleeding between video laryngoscopy and direct laryngoscopy. M-H, Mantel-Haenszel.
Supplementary Fig. 4. Risk of bias.

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References


Epidural analgesia versus intravenous analgesia after minimally invasive repair of pectus excavatum in pediatric patients: a systematic review and meta-analysis

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Department of Anesthesiology and Pain Medicine, Inje University Ilsan Paik Hospital, Goyang, Korea

Background: Postoperative pain control after the minimally invasive repair of pectus excavatum (MIRPE) is essential, but there is a controversy about a better analgesic method between epidural and intravenous (IV) analgesia. This systematic review and meta-analysis aimed to compare the effect of epidural versus IV analgesia following MIRPE.

Methods: We searched PubMed, MEDLINE, Embase, Cochrane Central Register, and ClinicalTrials.gov for randomized controlled trials (RCTs) dated up to 31st May 2021. The primary outcome was the area under the curve (AUC) of the weighted mean visual analog scale (VAS) after MIRPE. The secondary outcomes were postoperative nausea, operation time, total operating room time, and postoperative length of hospital stay.

Results: Four RCTs involving 243 patients were finally included in this meta-analysis. The AUC of the weighted mean VAS was 343.62 in the epidural group and 375.24 in the IV group. The epidural group showed lower VAS than the IV group at 12 to 48 h after the surgery. Postoperative nausea, operation time and length of hospital stay was not different between two groups. The epidural group had a significantly longer total operating room time due to epidural catheter insertion time.

Conclusions: Epidural analgesia after the MIRPE had a better analgesic effect than IV analgesia. However, IV analgesia may also be a viable option, and physicians should wisely choose analgesic modalities after MIRPE.

Keywords: Epidural analgesia; Funnel chest; Intravenous administration; Minimally invasive surgical procedures; Postoperative pain; Statistics; Systematic review; Thoracic surgery.

Introduction

Pectus excavatum is a relatively common deformity that occurs in nearly 1 in 1,000 children [1]. In 1998, Donald Nuss introduced a minimally invasive repair of pectus excavatum (MIRPE) called the Nuss procedure or pectus bar procedure [2]. In this procedure, a substernal bar is positioned in the chest through small axillary incisions. It is a standard treatment and is less invasive than the open Ravitch procedure that it replaced. Operation time is short and blood loss is minor, but postoperative pain is not minimal [3,4]. Postoperative pain control after MIRPE has a significant effect on the length of hospital stay [5].

*Min Hee Heo and Ji Yeon Kim contributed equally and shared the first authorship to this study.
The pathophysiology of pain after the procedure has not been fully evaluated, but the primary source of pain is the chest wall's stretching caused by the substernal bar, not the incisions [6]. Previous studies have suggested that thoracic epidural analgesia is the most effective method for controlling pain during the early postoperative period [6–8]. However, thoracic epidural analgesia requires an experienced anesthesiologist. Complications, such as infection, nerve damage, and epidural hematoma, may occur; and the procedure can prolong the operation time [9]. According to the results of a recent randomized controlled trial (RCT), intravenous (IV) patient-controlled analgesia (PCA) had the same effect as epidural analgesia up to postoperative day 3 [10]. Also, Gasior et al. [11] compared the effect of epidural analgesia and IV analgesia on MIRPE patients’ long-term perceptions of their pain control experiences after an average of 3.2 years. The results did not show any significant difference in perceptions between the two methods.

The aim of our systematic review and meta-analysis was to compare the effect of epidural analgesia and IV analgesia in MIRPE patients.

Materials and Methods

Study design

This systematic review and meta-analysis were performed according to the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and Cochrane Collaboration [12,13]. The protocol was preregistered in PROSPERO (https://www.crd.york.ac.uk/PROSPERO, no. CRD42020169362).

Search strategy

Two trained reviewers, K.J.H. and L.S.I., independently searched PubMed, MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov for studies that had been completed but not published before May 31, 2021 without language restriction. The following keywords were searched: ‘Nuss,’ ‘Pectus excavatum,’ ‘Epidural,’ and ‘Patient-controlled analgesia.’ The search strategy is presented in the Supplementary Materials.

Study selection and eligibility criteria

The reviewers independently screened studies first by title and abstract and then by the full text. They assessed full-text articles separately, and any disagreements were resolved through discussion with the third author (K.J.Y.). Studies to be included in the analysis had to have met the following Population, Intervention, Comparison, Outcomes and Study (PICOS) criteria. Population: patients who received MIRPE; Interventions: Epidural PCA or block or infusion (epidural group); Comparison intervention: IV analgesics including PCA (IV group); Outcome: Primary outcome could be measured using a visual analog scale (VAS) or numeric rating scale (NRS), and the secondary outcomes could be postoperative nausea, operation time, total operating room time, postoperative length of stay in the hospital, number of calls made to anesthesiologists, and number of hours until the patient could consume a regular diet; Study design: RCTs. Observational studies, non-randomized studies, and quasi-randomized studies were excluded.

Risk of bias in individual studies

The methodological quality of the studies was assessed using the Revised Cochrane Risk-of-bias tool [12]. Two reviewers (K.J.H., L.S.I.) evaluated the methodological quality of the included studies. For the evaluation of the risk of bias, we used the Cochrane methodology. According to Cochrane’s five items, we assessed each study separately as low, high, or some concerns risk of bias [12].

Data extraction

The two trained authors (K.J.H., L.S.I.) independently extracted data from the articles and cross-checked them to avoid extracting incorrect information. The extracted information included the authors’ names, publication year, patients’ ages, patient gender ratio, number of patients in the studies, treatments they received, clinical setting information, follow-up duration, and outcome data. We contacted the corresponding authors of the studies via e-mail for which NRS or VAS data was missing or more information was needed. When pain scores were not presented in numbers, we extracted pain scores using graphs or figures.

Statistical analysis

The studies’ pain score results were measured and compared using the area under the curve (AUC) of the VAS from postoperative hour 0 to hour 108. The AUC of the mean VAS was calculated for included studies that had individual participants’ pain scores and the AUC of the weighted mean VAS was calculated otherwise [14]. These calculations were performed using MedCalc v.19.6.1 (MedCalc Software, Belgium) for Windows.
Forest plots of summarized pain scores at postoperative hours 0, 12, 24, 48, 72, and 96 are presented. The Hartung, Knapp, Sidik, and Jonkman (HKSI) method was used to reduce type I errors because the number of included studies was small [15].

If standard deviations were not reported, we used an average of the standard deviations from the other studies that reported those [16]. For articles that only reported the median and interquartile range, the Median-IQR method was used to impute the mean as the median and the SD as the third quartile to the first quartile [17]. Publication bias was checked by examining funnel plots, but Egger’s test could not be used because fewer than five studies were included. Analysis was performed with RevMan v.5.3 (Review Manager, The Nordic Cochrane Centre, The Cochrane Collaboration, Denmark) and the metafor package v.2.4.0 for R (R Foundation for Statistical Computing, Austria). This analysis was performed using a fixed-effects model to conduct a meta-analysis in the absence of significant heterogeneity (defined as P > 0.10 and I² < 40%) and a random-effects model otherwise.

**Results**

Our search strategy identified 893 records (Fig. 1). The list of the excluded articles and the reasons for their exclusion are presented in Supplementary Table 1. Four studies were eligible for the final analyses. The characteristics of the included studies are presented in Table 1 and Supplementary Table 2 [7,10,18,19]. Standard deviations were not reported in two articles, so the average of the standard deviations from the other articles that did was used instead [18,19]. Visual inspection of the funnel plots did not reveal significant publication bias (Supplementary Fig. 1). The overall risk of bias was some concerns for three articles [7,18,19], low for one article [10] (Fig. 2).

The AUC of the weighted mean VAS was 343.62 in the epidural group and 375.24 in the IV group, indicating that the epidural group had a lower cumulative pain score than the IV group (Fig. 3) [7,10,18,19].

There was no difference in VAS between the epidural and IV groups at postoperative hour 0 (4 RCTs, epidural group n = 121; IV group n = 122, mean difference [MD]: −0.81 [95% CI: −1.61, −0.01], P = 0.046, I² = 46%) (Fig. 4A). The epidural analgesia group had a lower VAS than the IV analgesia group at postoperative hour 12 (4 RCTs, epidural group n = 121, IV group n = 122, MD: −0.99 [95% CI: −1.52, −0.47], P = 0.001, I² = 0%) (Fig. 4B), and 24 (4 RCTs, epidural group n = 121, IV group n = 122, MD: −0.65, 95% CI [−1.15, −0.16], P = 0.009, I² = 0%) (Fig. 4C), and 48 (4 RCTs, epidural group n = 121, IV group n = 122, MD: −0.81, 95% CI [−1.61, −0.01], P = 0.046, I² = 46%) (Fig. 4C), and 72 and 96, there were no differences in the VAS in the epidural and IV groups (Figs. 4E and 4F) [7,10,18].

At postoperative hours 72 and 96, there were no differences in the VAS in the epidural and IV groups (Figs. 4E and 4F) [7,10,18]. Operation time did not differ between the epidural and IV groups (Fig. 6) [7,10,18,19]. The epidural group had a significantly longer total operating room time than the IV group, including epidural catheter insertion time (Fig. 7) [10,18]. The groups did not have different postoperative hospital stay lengths (Fig. 8) [7,10,18]. Significantly fewer calls to anesthesiologists were made for the IV group than the epidural group (Supplementary Fig. 2) [10,18]. There was no difference between the groups in the number of hours until patients could eat a regular diet (Supplementary Fig. 3) [10,18].

About the epidural catheter insertion failure, Weber’s study reported that there was no technical difficulty [7]. Six patients (11%)...
Table 1. The Characteristics of Included Studies [7,10,18,19].

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Total Patients (n) (Epi/IV)</th>
<th>Mean Age ± SD</th>
<th>Gender, male (%)</th>
<th>Reported Outcomes</th>
<th>Follow-up Period</th>
<th>Epidural Catheter Removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butkovic 2007 [19]</td>
<td>28 (14/14)</td>
<td>14.5 ± 75</td>
<td>75</td>
<td>Pain score (VAS)<em>, operation time</em>, the level of sedation, heart rate, systolic/diastolic arterial blood pressure, ventilator frequency, PaO₂, PaCO₂, oxygen saturation, side effects (nausea*, pruritus)</td>
<td>During the first 48 h after surgery</td>
<td>N/A</td>
</tr>
<tr>
<td>Weber 2007 [7]</td>
<td>40 (20/20)</td>
<td>15.9 ± 4.7</td>
<td>80</td>
<td>Pain score (VAS)<em>, operation time</em>, postoperative length of stay*, subjective well-being, intraoperative fentanyl, side effects (sedation, nausea*, pruritus)</td>
<td>At the end of anesthesia (0 h), every 12 h until 96 h postoperative time</td>
<td>POD 4 (96 h)</td>
</tr>
<tr>
<td>St Peter 2012 [18]</td>
<td>110 (55/55)</td>
<td>15.5 ± 2.9</td>
<td>N/A</td>
<td>Pain score* (VAS, the average of sitting and supine pain scores), operation time*, total operating room time*, postoperative length of stay*, hospital course (calls to anesthesia*, hours to regular diet*, hours to Foley catheter removal, hours to oral medications, procedure charges, anesthesia charges, nausea*, total hospital charges)</td>
<td>POD 0–5, twice daily (AM, PM)</td>
<td>POD 2.8 ± 0.5</td>
</tr>
<tr>
<td>Sujka 2020 [10]</td>
<td>65 (32/33)</td>
<td>14.75 ± 1.35</td>
<td>92</td>
<td>Pain score* (NRS, rest, and dynamic pain), operation time*, total operating room time*, calls to anesthesia*, hours to regular diet*, postoperative length of stay*</td>
<td>POD 0–4, twice daily (AM, PM)</td>
<td>POD 3</td>
</tr>
</tbody>
</table>

Epi: epidural group, IV: intravenous group, SD: standard deviation, VAS: visual analogue scale, POD: postoperative day, NRS: numeric rating scale, PaO₂: partial pressure of oxygen, PaCO₂: partial pressure of carbon dioxide, N/A: not available. *The outcomes were analyzed in this study.

Butkovic 2007 D1 D1 D1 D1 D1 Overall
Weber 2007 1 1 1 1 1
St Peter 2012 1 1 1 1 1
Sujka 2020 1 1 1 1 1

D1: Randomisation process
D2: Deviations from the intended interventions
D3: Missing outcome data
D4: Measurement of the outcome
D5: Selection of the reported result

Low risk
Some concerns
High risk

Fig. 2. Assessment of methodological quality of included studies based on the revised Cochrane risk-of-bias tool (RoB 2) for RCTs [7,10,18,19]. RCT: randomized controlled trials.

Discussion

This study compared epidural analgesia and IV analgesia at managing pain after MIRPE in terms of the AUC of weighted mean VAS. The epidural group’s VAS AUC was 343.62, which was lower than the IV group’s 375.24. The epidural group’s VAS was lower than that of the IV group from postoperative hour 12 to 48, but there was no difference in analgesic effect between the groups from postoperative hour 0 to 12 or after 72.

Thoracic epidural analgesia has been recommended as a gold standard for postoperative analgesia after MIRPE [20,21]. Muhly et al. [6] reported that 91% of surveyed institutions reported that they used epidural analgesia to manage pain after MIRPE and epidural catheters removed within 24 h after surgery and nine patients (28%) in Sujka’s study required IV PCA due to inadequate analgesia [10,18]. Two studies reported the incidence of unintended sedation, and there were no significant differences between the groups [7,19]. Pruritis was only reported in Butkovic’s study. Three patients (21.4%) in the epidural group experienced it while none in the IV group did [19].
27% use epidural and IV analgesia in combination. However, recently, a study found that 16% of the institutions do not use epidural analgesia at surgeons’ request due to concerns about neurological complications [6,9]. Thoracic epidural catheter insertion fails in 2% of pediatric patients and catheter-related complications, such as dislodgement and kinking, occur in 8% [22]. Of the studies included this article, epidural catheter insertion failure rates were 0%, 9%, and 11%, respectively [7,10,18]. When including patients who required IV analgesia because of inadequate epidural analgesia, the failure rate increased to 35% [18]. Even in adult patients, epidurals fail for various reasons, such as insufficient analgesia or catheter dislodgement, in 32% of patients [23].

There are concerns about epidural-related complications, as well as concerns about failure. Even when a well-trained anesthesiologist performs thoracic epidural catheter placement, unexpected complications can occur. In children, epidural-related complications, most of which are due to infections and medication errors, occur in 6 out of every 1,000 cases. Permanent neurological damage had also been reported to occur in 1 in every 10,000 cases [24,25]. Neurological complications included hematoma, trauma to the spinal cord or dura, and prolonged motor blockages [4,9,25]. These complications occur at a higher rate among pediatric patients than adult patients because pediatric patients are less willing to cooperate during epidural catheter insertion without sedation, so detection of neurological complications after the procedure may be delayed because the patients have to be sedated [26].

In addition to these concerns, there are several other limitations to using epidural analgesia. Epidural catheter insertion takes time, as shown in this meta-analysis. Despite the time required for and difficulties of inserting epidural catheters, they are usually removed within three days due to concerns about infection. This meta-analysis showed that epidural catheters were removed at the latest by postoperative days 3–4 [7,10,14]. There are concerns about postoperative nausea when using IV analgesia, but in this study, its incidence was similar in both groups. Also, in the retrospective review of St Peter et al. [5], the epidural group had a longer postoperative hospital stay than the IV group by 15 h (P = 0.037), but in this study, both groups had similar stays. The difference found in their study might have been caused by the need to administer oral analgesic medication to the epidural group after removing their catheters [5].

Despite the limitations of epidural analgesia, the epidural group in this study had a low weighted mean VAS AUC, suggesting that
Fig. 4. Forest plot of primary outcome data (VAS) for (A) 0 h, (B) 12 h, (C) 24 h, (D) 48 h, (E) 72 h, and (F) 96 h after surgery [7,10,18,19]. VASSD: standard deviation, VAS: visual analog scale.
epidural analgesia has a strong analgesic effect after MIRPE. Even when the weighted mean VAS AUC was analyzed without restricting the types of studies, it was shown to be also lower in the epidural group than the IV group (Supplementary Fig. 4) [7,8,10,18,19,27]. The epidural group had a lower pain score than the IV group from postoperative hours 12 to 48 (Fig. 4). This result may have been a product of the fact that epidural catheters were removed on postoperative days 3–4. Before removal, the postoperative analgesic effect was higher in the epidural group than the IV group. Interestingly, the pain score did not significantly differ immediately after surgery (Fig. 4A). This result was similar to that of the previous meta-analysis [28], and our analysis which includes RCTs and retrospective studies altogether (Supplementary Fig. 4). This result may have been a product of the fact that the patient population was children in our study and previous meta-analysis [28], and our analysis which includes RCTs and retrospective studies altogether (Supplementary Fig. 4). This result may have been a product of the fact that the patient population was children in our study and previous meta-analysis [28], and our analysis.
Pain can cause adverse physiological and psychological outcomes, such as decreased immune response, disturbed sleep, decreased physical functioning, anxiety, chronic and persistent post-surgical pain, and psychiatric problems [29]. Epidural analgesia after MIRPE can prevent respiratory depression sparing systemic narcotics and can last for the duration of three days that the epidural catheter is in place. Adequate postoperative analgesia enables early ambulation, coughing, and deep breathing, thus preventing atelectasis [5]. Therefore, physicians should be familiar with the characteristics of epidural and IV analgesia and choose between them appropriately.

The limitations of this study were as follows. First, only four RCTs met the inclusion criteria. Second, this meta-analysis can be seen as an update of a prior meta-analysis because it added Sujka et al.’s study [10,28]. Third, although the AUC of the weighted mean VAS was calculated, its statistical significance could not be calculated because the relevant raw data could not be retrieved.

Notwithstanding these limitations, this study had several significant strengths and unique qualities. First, the AUC of weighted mean VAS was calculated to analyze pain relief over time instead of just using the VAS for a specific time. Unfortunately, individual patient data meta-analysis could not be performed as was originally intended because the articles identified in this study did not include raw data. However, by comparing the groups’ weighted mean VAS’s AUCs, it was possible to compare pain management during the postoperative period. Second, the previous meta-analysis showed that the epidural had a lower pain score than the IV group at postoperative hour 0, but this study showed that there was no significant difference between the groups. In this study, the Hartung, Knapp, Sidik, and Jonkman method was used instead of the DerSimonian and Laird method that was used in the previous meta-analysis because it produces fewer type I errors than the DerSimonian and Laird method for small numbers of studies [15]. Third, only RCTs were analyzed to increase the results’ reliability. Even though only four articles were included, Cochrane does not recommend that a mix of observational studies and RCTs be used for meta-analyses [12]. Fourth, the search for articles in this study was conducted without language limitations to maximize search results. Fifth, forest plots for secondary outcomes, such as postoperative nausea, operation time, total operating room time, postoperative length of hospital stay, the number of calls to anesthesiologists, and the number of hours until patients could eat a regular diet, were analyzed. Thus, this study produced a more comprehensive understanding of how to choose between epidural and IV analgesia after MIRPE.

In conclusion, the epidural group had better pain control as reflected by a lower cumulative AUC value of the weighted mean VAS than the IV group until postoperative hour 108 and a lower VAS for postoperative hours 12 to 48. However, IV analgesia may still be a viable option because epidural analgesia has higher rates of failure and complications and a high conversion rate to IV analgesia. Therefore, physicians should carefully choose between these pain control methods after MIRPE by considering their patients’ conditions, their hospital’s usual practice, and their skill.

Conflicts of Interest

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

Author Contributions

Min Hee Heo (Formal analysis; Writing – original draft; Writing – review & editing)
Ji Yeon Kim (Conceptualization; Methodology; Supervision; Writing – original draft; Writing – review & editing)
Jung Hyeon Kim (Data curation; Validation)
Kyung Woo Kim (Data curation; Investigation; Resources)
Sang Il Lee (Conceptualization; Methodology; Resources)
Kyung-Tae Kim (Resources)
Jang Su Park (Methodology)
Won Joo Choe (Supervision)
Jun Hyun Kim (Conceptualization; Formal analysis; Methodology; Supervision; Writing – review & editing)

Supplementary Materials

Search strategy
Supplementary Table 1. Table of the excluded studies.
Supplementary Table 2. The characteristics of included studies in detail.
Supplementary Fig. 1. Funnel plots of the primary outcome of pain scores.
Supplementary Fig. 2. Forest plot of calls to anesthesiologists.
Supplementary Fig. 3. Forest plots of hour to a regular diet.
Supplementary Fig. 4. AUC graph of weighted mean VAS of epidural group and IV group including two retrospective studies which met our inclusion criteria except study type, and data could be retrieved [1,2].

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References

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Understanding how to conduct a meta-analysis helps clinicians in making clinical decisions [1]. Hence, researchers need additional knowledge regarding software programs used to perform meta-analysis. In the published literature of high-impact-factor anesthesia journals, we observed that RevMan 5 (Review Manager [RevMan], [Computer program], Version 5.4, The Cochrane Collaboration, 2020) is the most frequently used primary meta-analytical software package. However, detailed information on additional auxiliary software use is inadequate. The challenge arises when multiple analyses are required, and the researcher needs to choose the correct software program. Apart from primary statistical software programs, such as SAS (Copyright © SAS Institute Inc., SAS Campus Drive, USA), R (R Core Team [2017], R: A language and environment for statistical computing, R Foundation for Statistical Computing, Austria. Available from https://www.R-project.org/), STATA (StataCorp., 2015. Stata Statistical Software: Release 14. StataCorp LP), SPSS (IBM Corp. IBM SPSS Statistics for Windows [Internet], IBM Corp., 2017. Available from https://hadoop.apache.org) and Cochrane RevMan calculators (https://training.cochrane.org/resource/revman-calculator), one should be aware of user-friendly auxiliary software to progress in meta-analysis. This is because primary software programs are deficient in performing additional analyses, such as meta-regressions and network plotting. Generally, it is believed that clinical researchers often make mistakes when they undertake their own data analysis by not enlisting a statistician before and after undertaking a study. Contrariwise, it is also true that self-learning of additional software by a researcher critically reduces the need for collaborating with a statistician, which in turn might improve the quality of research. In subsequent paragraphs, we report the types and representative examples of software used for data management in meta-analysis.

For data extraction from images, authors can use Engauge digitizer (https://markum-mitchell.github.io/engauge-digitizer/) effectively and reliably to import images from an article directly or via Microsoft Paint. Using axis point and curve point tools, one can define the graph axis and data set points of an imported image, respectively. The numerical data obtained are exported and saved as .CSV files. Other software packages that have similar functions include WebPlotDigitizer (https://automeris.io/WebPlotDigitizer/) or Plot Digitizer (https://sourceforge.net/projects/plottdigitizer/files/). OriginPro (https://www.originlab.com/) is beneficial to obtain the data from complex formats, such as 2D-image or embedded matrix sheets. Although RevMan 5 can be used for sensitivity analysis, meta-regression requires a different software. The funnel plot asymmetry evaluation and derivation of Egger or Omnibus P values can be easily derived using JASP (https://jasp-stats.org/ 2017/11/15/meta-analysis-jasp/). The .CSV data file specifically containing study name, estimate, and standard error (SE) are exported from RevMan. Nevertheless, meta-regression factors/covariates should be entered for each study.
cients, which depict the magnitude of effect of each factor/covariate on the studied outcome, Omnibus and Egger P values are important outputs of JASP. In addition to the images of forest and funnel plots, the File-Drawer Analysis, radial, and normal Q-Q plots are additional advantages of JASP. Meta-regressions are also possible in Open-meta[analyst] (http://www.cebm.brown.edu/openmeta/) with similar outcomes. Furthermore, meta-correlations can be performed using MedCalc (https://www.medcalc.org/download.php) software by entering study, sample size, and coefficient values. A forest plot with random and mixed effect estimates can be obtained.

Recently, trial sequential analysis (TSA, https://ctu.dk/tsa/) software gained popularity for checking the power and sample sizes of each predefined meta-analytical outcome [2]. A common question for a researcher is, 'How many studies do I need to conduct a meta-analysis?' Because there is no minimum limit on trials that should be included in a meta-analysis, the total sample population for meta-analysis gains importance, and the TSA software helps to calculate the required sample size information. However, TSA software should be operated on a trial-and-error basis owing to the non-availability of help files (video/text forms). The exported .CSV files from RevMan should be converted to .TSA files prior to data entry in TSA. After performing sequential analysis and calculations, the necessary graph with the required sample size is displayed in the right upper corner. Researchers need to check whether the cumulative Z-curve surpasses the traditional or trial sequential (TS) monitoring boundaries to obtain sample size information for statistical significance. A short tutorial is produced (Supplemental Video 1A–1D) to help researchers in understanding few of the previously mentioned auxiliary software (Engauge Digitizer, JASP, MedCalc and TSA). Occasionally, when multiple treatments are compared simultaneously in a single analysis, a network meta-analysis is performed. MetaInsight is a useful software program (https://crsu.shinyapps.io/MetaInsight/) for undertaking network meta-analysis. Furthermore, Cochrane 'Comparing Multiple Intervention Methods Group' compiled a suite of online materials and software tools for conducting network meta-analysis (Available from https://training.cochrane.org/resource/network-meta-analysis-nma-toolkit as a network meta-analysis tool kit).

Online tools are often required to help with the measurement of collected data. In addition to Cochrane calculators, data synthesis, and conversion of dispersion measures, alternative tools may be needed for assorted analysis. Therefore, for pooled data conversion, statsdo.com (https://www.statsdo.com/) is user-friendly. In the A to Z 'Index (subject) link' of home menu bar, necessary program tabs can be identified. E.g., for conversion of data into a pooled data, the 'C' index (C for Combine mean and SDs) should be searched. Bookdown.org (https://bookdown.org/MathiasHarrer/Doing_Meta_Analysis_in_R/power-calculator-tool.html) is a good power calculator available for meta-analysis. With the effect size mentioned as the standardized mean difference, a power plot is displayed when the number of studies and participants are entered into the calculator. Practical meta-analysis effect-size calculator (https://campbellcollaboration.org/escalc/html/EffectSize-Calculator-OR-main.php) is a comprehensible tool. GRADepro (GRADEpro Guideline Development Tool [Software], McMaster University, 2020 [developed by Evidence Prime, Inc], https://gradepro.org/) is used to provide grading of recommendations assessment, development and evaluation (GRADE) evidence [3]. Similarly, Microsoft Publisher is of considerable help in combining images or adjusting large tables (such as a table of study characteristics) and conversion of files to a different format (.pdf). Moreover, Adobe Illustrator CC can be used (https://www.adobe.com/in/products/illustrator.html) to convert and obtain high-resolution publication quality images.

The Korean Journal of Anesthesiology is currently publishing a special issue devoted to the topic of “systematic review and meta-analysis”. This special issue will feature applications of systematic reviews and meta-analyses that will provide evidence-based knowledge that will contribute significantly to the field of anesthesiology. We believe that such contextual thinking by the editorial team will help readers to achieve their research visions. Additionally, the meta-analyses published in previous issues of high-impact-factor anesthesia journals can be used as examples by prospective researchers to answer their study goals. User help-guides in Cochrane articles and RevMan teach meta-analysis methodologies from scratch. However, knowledge of auxiliary software is essential to complete the task. Self-learning of the aforementioned software tools is not only easy and interesting, but also vital for academic anesthesia teaching faculty.

Conflicts of Interest

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

Author Contributions

Thrivikrama Padur Tantry (Conceptualization; Data curation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing)
Harish Karanth (Formal analysis; Methodology; Supervision; Vi-

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Supplementary Materials

Supplemental Video 1A. Software tutorial for data extraction using Engauge Digitizer.
Supplemental Video 1B. Software tutorial for meta-regression analysis using JASP.
Supplemental Video 1C. Software tutorial for meta-correlation analysis using MedCalc.
Supplemental Video 1D. Software tutorial for performing trial sequential analysis using TSA. The exported .CSV files from RevMan must be converted to .TSA files prior to data entry in TSA. This can be achieved by using the Review Manager of RM5 converter in the menu bar of TSA. These .TSA files can be imported directly to begin the analysis. After the effect measure and model are entered, the Trial tab is used to edit the risk of bias of the included studies. The TSA tab should be used to add and edit the information of conventional and alpha-spending boundaries. When the conventional test boundary is selected, the dialog box opens for the boundary name to be entered (author’s choice) along with the chosen alpha-error. The more important alpha-spending boundaries are selected for sample size information, and additional steps are necessary. In the Information axis section, click on sample size, and in the Required Information Size section, the buttons for estimate, empirical, and Model variance based options are essential selections. The model is ready to estimate the sample size when the Add button displayed at the bottom of window is clicked. At all levels, the alpha and beta spending functions of O’Brien-Fleming are opted. In the final step, clicking the ‘Perform calculation’ button is essential to obtain the TSA graph; subsequent selection of Graph tab will display the necessary graph with the required sample size displayed at the right upper corner.

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References

Sex/gender and additional equity characteristics of providers and patients in perioperative anesthesia trials: a cross-sectional analysis of the literature

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The first author's name Cole Etherington is the correct spell rather than Nicole Etherington.
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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], Mg2+ [X], Mg2+ [X]

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

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

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

- References

- References should be obviously related to documents and should not be exceed 50. For exceeding the number of references, it should be negotiated with the Editorial Board. References should be numbered consecutively in the order in which they are first mentioned in the text. Provide footnotes in the body text section. All of the references should be stated in English, including author, title, name of journal, etc.

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


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

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

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

- Description format
A. Regular journal
Author name. Title of journal Name of journal published
year; volume: start page-final page.
Ex) 2006; 7(Suppl 1): 64-96 ’2007; 76: H232-8’
B. Monographs
· If reference page is only 1 page, mark ‘p’.
· Mark if it is beyond the 2nd edition.
C. Chapter
D. Electronic documents
E. Online journal article
F. Papers that have been submitted and accepted for publication should be included in the list, with the phrase ‘in press’ replacing volume and page number. Authors should be prepared to give the volume and page number at the time of proof correction.
Table
· Type or print each table on a separate sheet of paper.
· Number tables consecutively in the order of their first citation in the text.
· Supply a brief title
Tables should be more than 4 rows and should not be over 1 page.
· Except for titles and first letters, all of the text in the tables should be written in small alphabetic letters.
· In demographic data, sex would be provided as M/F, and age in yr. Data of year, weight, height, and any other units would be provided with 1 decimal place.
· “±” sign in the upper column of table should be lined up with the lower column.
· Footnotes should be provided consecutively in order of the cited tables or statistics.
· Marks for footnote should be given in order of *, †, ‡, §, ‡‡... When marks are used to explain items of the table, indicate them with superscripts.
· Define all abbreviations except those approved by the International System of Units. Define all abbreviations every time they are repeated.
Legends for figures and photographs
· All of the figures and photographs should be described in the text separately.
· The description order is the same as in the footnotes in tables and should be in recognizable sentences.
· Define all abbreviations every time they are repeated.
Figures and illustrations
· The KJA publishes in full color, and encourages authors to use color to increase the clarity of figures. Please note that color figures are used without charge for online reading. However, since it will be charged upon the publication, authors may choose to use colors only for online reading.
· Standard colors should be used (black, red, green, blue, cyan, magenta, orange, and gray). Avoid colors that are difficult to see on the printed page (e.g., yellow) or are visually distracting (e.g., pink). Figure backgrounds and plot areas should be white, not gray. Axis lines and ticks should be black and thick enough to clearly frame the image. Axis labels should be large enough to be easily readable, and printed in black.
· Figures should be uploaded as separate tif, jpg, pdf, gif, ppt files. Width of figure should be 84 mm (one column). Contrast of photos or graphs should be at least 600 dpi. Contrast
of line drawings should be at least 1,200 dpi. Number figures as “Fig. (Arabic numeral)” in the order of their citation. (ex. Fig. 1).

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

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

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

⑦ Figures (line drawings) should be clearly printed in black and white.

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

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

⑩ Pathological samples should be pictured with a measuring stick.

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

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

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

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

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

② The maximum number of video clips is 20.

③ The video clip(s) should be playable on both Windows and MAC computers. The video clip(s) should be tested for playback before submission, preferably on computers not used for their creation, to check for any compatibility issues.

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

⑤ Supplemental still images that correspond to the respective video clip(s) should be, but are not always required to be, accompanied by legends. The video clip file name(s) should refer to the corresponding figure number(s).

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

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

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

- Authors of reports of meta-analyses of clinical trials should submit the PRISMA flow diagram. The PRISMA checklist should be submitted as a separate file along with the manuscript. For information regarding PRISMA guidelines, please visit http://www.prisma-statement.org or EQUATOR Network (https://www.equator-network.org/home/). Systematic reviews and meta-analyses of observational studies in epidemiology should be reported according to MOOSE guidelines. For more information regarding MOOSE guidelines, please visit http://www.equator-network.org/reporting-guidelines/meta-analysis-of-observational-studies-in-epidemiology-a-proposal-for-reporting-meta-analysis-of-observational-studies-in-epidemiology-moose-group/.

- No limitation the number of the references.

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

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

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

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

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

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

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

6) Statistical Round
A Statistical Round is a narrative review of the application of contemporary quantitative sciences to issues of concern to anesthesia 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.