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New trends in regional analgesia and anesthesia

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New trends in regional analgesia and anesthesia

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Editorial: New trends in regional analgesia and anesthesia

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Editorial on the Research Topic
New trends in regional analgesia and anesthesia

Two review articles examined six peripheral nerve block techniques after arthroscopic shoulder surgery in terms of efficacy and adverse effects (Liu et al.; Jiangping et al.). Liu et al. presented the first network meta-analysis of postoperative pain regimens after arthroscopic shoulder surgery has been conducted. In comparison to other peripheral nerve blocks, interscalene brachial plexus blocks reduced pain and opioid consumption better, but had a higher rate of adverse events. There is a risk of diaphragmatic paresis due to the location of the interscalene insertion near the phrenic nerve. Jiangping et al. also proposed the same idea. However, Hussain et al. indicated that suprascapular block and interscalene block don't differ clinically in analgesia and suprascapular block has fewer complications (1). In the future, high–quality randomized controlled trials should continue to examine the best multimodal analgesic regimen for perioperative pain after shoulder arthroscopy. In another systemic review article (Fenta et al.), post-spinal anesthetic shivering was evaluated based on injection of local anesthetics into subarachnoid spaces. Fenta et al. found that patients receiving intravenous ketamine had fewer instances of nausea, vomiting, and bradycardia compared with patients receiving intravenous tramadol. Ketamine is a competitive N-methyl-D-aspartate receptor antagonist that plays a major role in inhibiting postoperative shivering, and it is thought that its anti-shivering effect may be through the action on the hypothalamus or through the β-adrenergic effect of norepinephrine. Generally speaking, postoperative shivering is a frequent complication of anesthesia. Shivering is believed to increase oxygen consumption and the risk of hypoxemia, as well as induce lactic acidosis and catecholamine release. Prevention and management of shivering are critical as it may reduce the potential for many adverse effects. However, the precise mechanism by which these medications stop shivering is not well known.

This Research Topic also includes an original study on the impact of pregabalin on the minimum alveolar concentration (MAC) of inhaled anesthetics. Pregabalin is effective as preemptive analgesia for neuropathic pain. Over the past several years, it has increasingly been used perioperatively to reduce postoperative pain intensity, and opioid use, and prevent post-operative pain. Pregabalin is still included in many multimodal perioperative analgesic regimens. Müller et al. presented that administration of 300 mg pregabalin preoperatively lowers the MAC of sevoflurane by 33%, while administration of 150 mg pregabalin did not result in a significant reduction in MAC. Pregabalin, depending on the dose, had a slight decrease in postoperative pain levels, but it also had an increase in side effects, such as nausea and vomiting, dizziness, and headache.The results are consistent with these previous studies indicating that pregabalin spares inhalation anesthetic, maintains hemodynamics, and optimizes postoperative analgesia (2). Obtaining more quality evidence in this field is crucial, as only a few studies exist in this area.

Over the past few years, the opioid epidemic has emerged as one of the world's most critical challenges. Multimodal analgesia (MMA) also falls under this Research Topic. Previous studies have shown that the combination with multimodal analgesia, enhances recovery after surgical procedure, reduces perioperative use of opioids, and later on, their adverse effects (3). Conversely, the Research Topic reported opposing results to the previous study, where the use of the pectoralis nerve block has not significantly reduced the use of perioperative opioids relative to MMA alone in elective breast surgery (Uribe et al.). Most of prospective and retrospective studies, systematic reviews, and meta-analyses published in recent years demonstrated that the combined pectoral nerve block during anesthesia reduces the severity of postoperative pain and the total amount of perioperative opioid. However, following possible analysis, this can be attributed to the intrinsic limitation of a retrospective study, the small sample size and the inability to collect data on opioid use over 24 h. Additionally, dose and regimen of MMA were not consistent across these studies. The use of gabapentinoids in postoperative pain management schemes has linked to a high incidence of adverse events such as conscious disturbances and vertigo that hinder early mobilization and delay recovery.

This Research Subject also comprises one scoping review regarding artificial intelligence (AI) in ultrasound-guided regional anesthesia (Viderman et al.). The theme of AI has become very hot recently because of Nvidia founder Jensen Huang. Viderman et al. indicated that AI solutions could be helpful in identifying anatomical cues, reducing or even avoiding possible complications. AI solutions can assist in identifying anatomical markers and reduce or even prevent potential complications. As a result, strong collaboration between clinicians and engineers is critical. Attracting medical students and talented practitioners to the anesthesia profession will take a multipronged approach and time. Perhaps AI can solve this problem more quickly. In the past, many physicians (except for anesthesiologists with expertise in regional anesthesia) regarded regional anesthesia as too complex and intimidating. Another barrier may be the longer time to perform regional anesthesia than conventional pain management. AI-based devices may potentially facilitate the acquisition and interpretation of ultrasound-guided regional anesthesia images. Such technology could improve the performance of ultrasound for regional anesthesia by non-experts, which could expand patient access to these techniques. More research is required to demonstrate the effectiveness of AI in supporting training and clinical practice.

Author contributions

S-MC prepared the draft. P-KW and J-AL revised the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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The Effect of Pregabalin on the Minimum Alveolar Concentration of Sevoflurane: A Randomized, Placebo-Controlled, Double-Blind Clinical Trial

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Background: Pregabalin is commonly used perioperatively to reduce post-operative pain and opioid consumption and to prevent the development of chronic pain. It has been shown to reduce anesthetic consumption in balanced anesthesia, but studies investigating its effect on the minimum alveolar concentration (MAC) of volatile anesthetics are lacking. The aim of this study was to investigate the effect of two different doses of pregabalin on the MAC of sevoflurane.

Methods: In a randomized, double-blinded, placebo controlled clinical study, 75 patients were assigned to receive placebo, 300 mg pregabalin, or 150 mg pregabalin, as a capsule 1 h before anesthesia induction with sevoflurane only. After equilibration, the response to skin incision (movement vs. non-movement) was monitored. The MAC was assessed using an up- and down-titration method.

Results: The MAC of sevoflurane was estimated as 2.16% (95% CI, 2.07–2.32%) in the placebo group, 1.44% (95% CI, 1.26–1.70%) in the 300 mg pregabalin group, and 1.81% (95% CI, 1.49–2.13%) in the 150 mg pregabalin group. We therefore report a 33% reduction in the MAC of sevoflurane in the 300 mg pregabalin group as compared to placebo. The MAC of the 150 mg pregabalin group was reduced by 16% as compared to placebo but was not statistically significant.

Conclusions: The administration of 300 mg pregabalin reduced the MAC of sevoflurane by 33%, while the administration of 150 mg pregabalin did not significantly reduce the MAC of sevoflurane. Pregabalin use led to a small reduction in post-operative pain levels but increased side effects in a dose-dependent manner.

Keywords: pregabalin, minimum alveolar concentration (MAC), sevoflurane, anesthesia, depth of anesthesia, premedication before anesthesia

INTRODUCTION

Pregabalin is an antiepileptic drug also licensed to treat neuropathic pain and anxiety disorders (1). Pregabalin binds to α2δ subunits of high voltage-activated calcium channels and decreases the release of excitatory neurotransmitters (2). In recent years, it has increasingly been used perioperatively to improve post-operative pain control, reduce post-operative opioid consumption and prevent the development of chronic post-operative pain (3). Although there is ongoing controversy about the clinical benefits vs. risks of its perioperative use, pregabalin is still part of many protocols for multimodal perioperative analgesia (4).

The concept of the minimum alveolar concentration (MAC), which is defined as the volumetric concentration of an inhaled anesthetic that prevents movement in response to a noxious stimulus in 50% of subjects, was introduced more than 50 years ago and remains the most used parameter to guide anesthetic depth during inhalational anesthesia (5). The MAC also enables quantification of the effect of adjunctive drugs on inhalational anesthetics. Despite the widespread use of pregabalin in the perioperative period and sevoflurane being one of the most commonly used inhalational anesthetic agents, studies regarding the effect of pregabalin on the MAC of sevoflurane in humans are lacking. Therefore, the aim of this study was to investigate the effect of pregabalin on the MAC of sevoflurane.

METHODS

This study was performed in accordance with the Declaration of Helsinki, and the CONSORT (Consolidates Standards of Reporting Trials) guidelines were followed during the preparation of this article. We conducted this single-center, prospective, randomized, controlled, double blinded trial between September 2019 and February 2021 at the University Department of Anesthesia, Intensive Care Medicine and Pain Medicine at the Medical University of Vienna, Vienna, Austria. The trial was registered at EudraCT before patient enrolment (EudraCT re. no. 2017-001439-37). Approval by the institutional ethics committee and the regulatory authority was obtained (Ethics Committee of the Medical University of Vienna, Bundesamt für Sicherheit im Gesundheitswesen) before patient enrolment. Patients were included only after written informed consent was obtained.

Study Population

We recruited adult patients with an American Society of Anesthesiologists physical status of 1–2 scheduled for elective surgery under general anesthesia. To standardize the noxious stimulus, we only included patients undergoing breast surgery, as this usually requires a skin incision of 3–5 cm at the trunk (6). The patients' age was restricted to 30–65 years, as the MAC is relatively uniform in this age group (7). We excluded patients unable to understand the study procedure, patients with a need for sedative or analgesic premedication or a history of chronic pain, patients with a known allergy to one of the medications used in this study, pregnant or breastfeeding patients, and patients in whom inhalational induction of anesthesia was contraindicated.

Randomization and Blinding

Patients were randomly assigned to receive placebo, 150 or 300 mg pregabalin. Randomization was performed by a study nurse that was not involved in the experimental part of the study at patient enrolment using the online randomization tool provided by our institution (https://www.meduniwien.ac.at/randomizer/).

To ensure blinding of the patients and the investigators, identical capsules containing the study medication or placebo were provided by the pharmacy of the Vienna General Hospital. The study nurse that had performed the randomization administered the capsule according to randomization results 1 h before the surgery. Based on a pseudonymized patient list that was also only accessible to the study nurse they determined the appropriate sevoflurane concentration for the patient and instructed the investigators on which concentration to target. The investigators therefore were not aware of the patients' randomization results or the corresponding study group. After the determination of the skin movements the investigators informed the study nurse, who updated the patient list to include the newest result.

Anesthesia Induction

Routine anesthetic monitoring, including pulse oximetry, electrocardiography, non-invasive blood pressure, and the bispectral index (BIS monitor A2000 software version 3.3, Aspect Medical Systems, Norwood, MA, USA), was applied in the operating room. Anesthesia was then induced solely by multiple deep inhalation breaths of 8 vol% sevoflurane in pure oxygen (8). A laryngeal mask airway (LMA Supreme Airway, Teleflex Medical Europe Ltd, Dublin, Ireland) was inserted once the BIS value had decreased below 40 and the patients were clinically adequately sedated. We ventilated the patients' lungs with tidal volumes of 6 to 8 ml kg^{-1} at a frequency of 10 to 16 breaths per minute to achieve normocapnia (endtidal CO_2 between 30 and 40 mmHg). Forced air was applied to the lower limbs to maintain normothermia.

Determination of MAC

The MAC of an inhalational anesthetic is defined as "the minimum alveolar concentration of an anesthetic that prevents movement in response to a noxious stimulus in 50% of subjects" (5). We used a standardized skin incision for the noxious stimulus and an up- and down-titration method to assess the MAC of sevoflurane in the study groups, as this approach shows the potential to provide reliable data with relatively few patients, as compared to other methods (9). After induction of anesthesia, the sevoflurane concentration was adjusted to reach a predetermined end-tidal sevoflurane concentration, which was held constant for at least 15 min before the skin incision. The sevoflurane concentration was measured using the gas-measuring unit of a Dräger Primus (Dräger Austria GmbH, Vienna, Austria) that was calibrated every 24 hours. In the first patient in each study group, the end-tidal sevoflurane

concentration was 1.6 vol%. Before the skin incision was made, one investigator ensured unconsciousness of the patients by calling their name, tapping on their shoulders, and asking them to open their eyes. Next, the surgeon was asked to perform a single incision of 3 to 5 cm and then pause for 1 min before continuation of the operation. The response to the skin incision was counted as positive if the patient exhibited "gross purposeful movement of the head or at least one extremity" within 1 min after the skin incision (6). The response to the skin incision was classified as negative if no such movement occurred within 1 min after the skin incision. Coughing, bucking, and straining were not considered gross purposeful movements. One investigator at the head of the operating table observed the response of the patient's head and upper limbs, and a second investigator observed the response of the lower limbs from the foot of the operating table. The end-tidal sevoflurane concentration for the next patient in each study group was either increased by 0.2 vol% if the previous patient in that group had exhibited a positive response to the skin incision or decreased by 0.2 vol% if the previous patient of that group had exhibited a negative response to the skin incision. 0.2 vol% steps were chosen in order to cover a wider range of sevoflurane doses with a smaller number of patients. Smaller steps might have led to decreased power in case the variability in the observed data was larger than expected in the planning phase.

After the response to the skin incision was determined, patients received further anesthetic management at the discretion of the attending anesthetist based on our departmental standards, which include the administration of opioids (i.e., fentanyl and piritramide) and non-opioid analgesics (i.e., metamizole and paracetamol) as well as medical prophylaxis for post-operative nausea and vomiting (i.e., ondansetron and dexamethasone).

Secondary Endpoint Parameters

A venous blood sample was taken immediately before the skin incision to determine the serum concentration of pregabalin. Furthermore, we collected BIS values, systolic blood pressure, and heart rate throughout the study period at 2 min intervals until 2 min after the skin incision. The patients were asked about their pain level using a numeric rating scale (min 0, max 10) and the presence of nausea, vomiting, or intraoperative awareness while they were in the recovery area. The site of the incision and the areas of movement were also recorded.

Measurement of Serum Pregabalin Concentration

Pregabalin concentrations in the serum were assessed with MassTox® TDM Serie A test kits (Chromsystems, Gräfeling, Germany) and liquid chromatography–tandem mass spectrometry (LC–MS/MS) consisting of an LC-20 UFLC (Shimadzu, Kyoto, Japan) and a Triple Quad 4500 (Sciex, Framingham, MA, USA) equipped with a TurboIon Source for electrospray ionization.

Statistical Analysis

The primary endpoint was the MAC of sevoflurane in the three study groups. The MAC values of the sevoflurane concentration of the three groups were estimated using isotonic regression methods (10–12). To further account for the dependence structure in the data due to the up-and-down design, bootstrap methods were used to construct bias-corrected bootstrap confidence intervals for the MAC as well as the differences in MAC values (13). Within each bootstrap step, resamples where randomly generated (separately for the three groups using sampling with replacement) from the sampling distribution (probability of no-reaction for the observed sevoflurane concentrations) and for each resample, the MAC was calculated using isotonic regression and the difference in MAC between groups was calculated. In total, 5,000 resamples were used to generate the bootstrap-distribution. The bootstrap MAC-differences between groups were estimated as the mean over all bootstrap samples and the confidence interval was estimated using the corresponding percentiles of the bootstrap-distribution. For the two main comparisons of the 150 mg and the 300 mg Pregabalin group to placebo 97.5% confidence intervals (Bonferroni-Correction to apply for multiple testing) for the difference in the MAC values were calculated. The comparison between the 300 mg and 150 mg Pregabalin group was performed as a secondary aim. Furthermore, estimators of the MAC and the corresponding 95% confidence intervals were calculated separately for the three groups.

Differences in the secondary endpoint parameters between the groups, including the baseline characteristics, serum pregabalin concentration, BIS, blood pressure, heart rate, systolic blood pressure, post-operative pain scores, and the perioperative doses of opioids and propofol, were investigated with the Kruskal–Wallis test for independent groups. *P*-values were adjusted for multiplicity using a Bonferroni correction, as there were three groups involved. The X^2-test was used to investigate differences in the ASA physical status score; the use of non-opioid analgesics and antiemetics; and the occurrence of negative side effects, including nausea and vomiting, dizziness, headache, and awareness, between the groups. Adjusted $P < 0.05$ were considered statistically significant. The analyses were performed using R (R: A Language and Environment for Statistical Computing, R Core Team, R Foundation for Statistical Computing, Vienna, Austria 2014, https://www.R-project.org) and SPSS 27 (SPSS Statistics, IBM, Armonk, NY, USA). The data are presented as the mean (standard deviation, SD), minimum-maximum, or number (percentage) unless indicated otherwise.

Sample Size Determination

For the determination of the sample size, simulation studies were performed. The assumptions of the dose-response curve for the placebo group were based on a previous study (14). Therefore, for the placebo group, the dose-response model formula of Görges et al. with a MAC of 2 with a standard deviation of 0.3 was assumed (10). Since a reduction of the MAC of about 20% was assumed to be clinically relevant, for the treatment groups a MAC of 1.6 with a standard deviation of 0.3 was assumed for the sample size calculations. Due to the two primary comparisons (high and low dose compared to placebo), the 97.5% confidence intervals were calculated (Bonferroni Correction to apply for multiple testing). In each simulation step, the MAC was estimated using isotonic regression and confidence intervals for the difference in

MAC between groups were constructed using 1,000 bootstrap samples. 10,000 simulation runs were performed to estimate the power. Under the given assumptions, simulation studies showed a power of 80.8% for a per-group sample size of 22 patients per group. Due to some possible drop-outs, the sample size was fixed with 25 per group.

RESULTS

Seventy-eight female patients were recruited for our study (**Figure 1**). Three of these patients did not complete the study procedure because they required intravenous anesthetics for the treatment of laryngeal spasms that occurred during induction.

Patient characteristics, morphometric data and the time from the insertion of the laryngeal mask airway to skin incision were similar in all groups (**Table 1**).

Primary Outcome

The bootstrap estimate of the MAC of sevoflurane was 2.16% (95% CI, 2.07–2.32%) in the placebo group, 1.81% (95% CI, 1.49–2.13%) in the 150 mg pregabalin group, and 1.44% (95% CI, 1.26–1.70%) in the 300 mg pregabalin group (**Figure 2**).

The MAC estimate of sevoflurane in the 300 mg pregabalin group was 33% lower than that in the placebo group. As the confidence intervals of the difference in the MAC values between the placebo group and the 300 mg pregabalin group did not contain 0, this difference in the MAC estimates was statistically significant (97.5% CI for difference: 0.39–1.01%). No significant difference in the MAC estimate was found between the placebo and the 150 mg pregabalin group or the 300 mg pregabalin group and the 150 mg pregabalin group. **Table 2** shows the estimates of the MAC of sevoflurane and the corresponding bootstrap confidence intervals to investigate the MAC within the groups as well as the difference between groups.

Secondary Outcomes

Pregabalin was not detected in the serum of patients in the placebo group. The mean serum pregabalin concentration was 4.2 (SD 1.6) $\mu g\ ml^{-1}$ in the 150 mg pregabalin group and 9 (SD 2.8) $\mu g\ ml^{-1}$ in the 300 mg pregabalin group (**Table 3**).

BIS, Blood Pressure, Heart Rate

The BIS at the time of skin incision was significantly lower in the placebo group than in the 150 mg pregabalin and 300 mg pregabalin groups. No significant differences between the groups were observed regarding systolic blood pressure or heart rate before or after the skin incision (**Table 3**).

Post-operative Pain

The mean post-operative pain score reported on the numeric rating scale and the cumulative dose of post-operative piritramide were significantly higher in the placebo group than in both pregabalin groups (**Table 4**).

Side Effects

Patients in the 150 mg pregabalin group (12%) and the 300 mg pregabalin group (32%) reported negative side effects, such as nausea and vomiting, dizziness and headache, more frequently than patients in the placebo group (4%).

None of the patients in any group reported an event of intraoperative awareness.

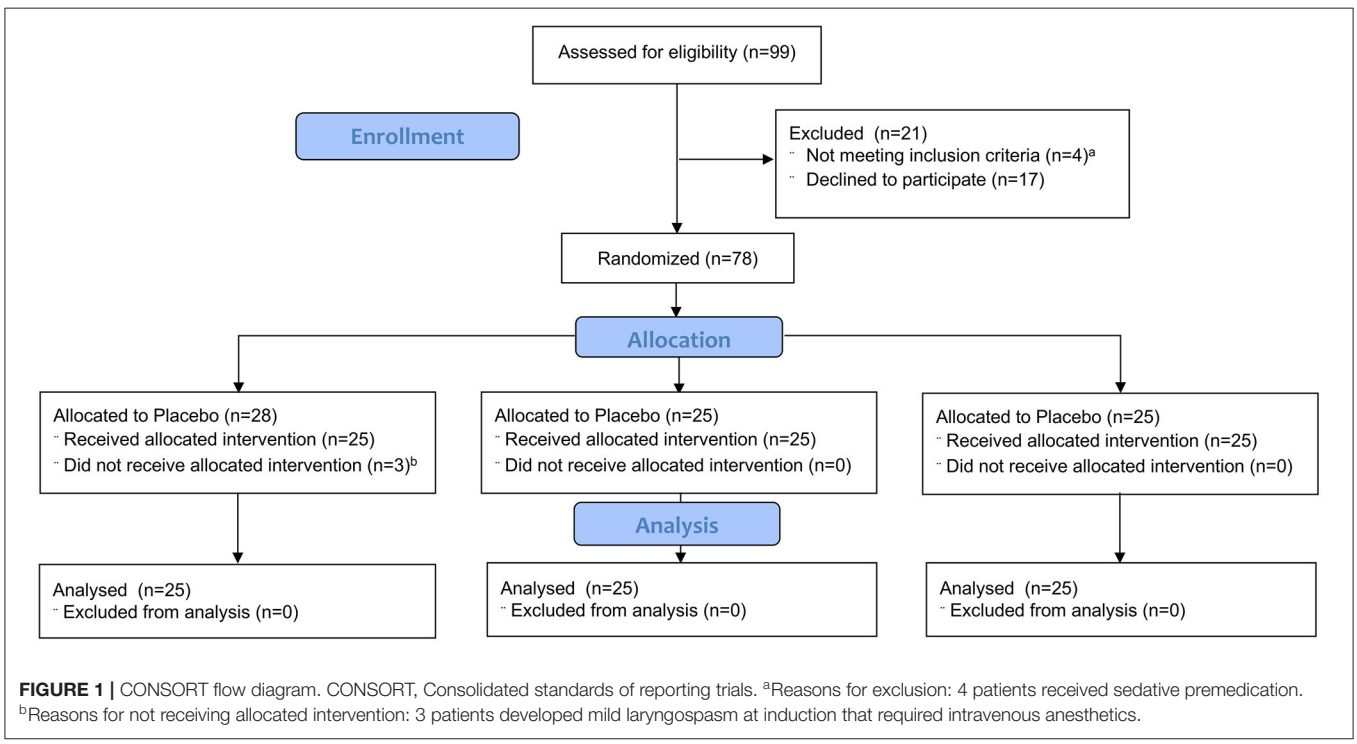

FIGURE 1 | CONSORT flow diagram. CONSORT, Consolidated standards of reporting trials. [a]Reasons for exclusion: 4 patients received sedative premedication. [b]Reasons for not receiving allocated intervention: 3 patients developed mild laryngospasm at induction that required intravenous anesthetics.

TABLE 1 | Subject characteristics and morphometric data.

Group	Placebo ($n = 25$)	300 mg pregabalin ($n = 25$)	150 mg pregabalin ($n = 25$)	
Age, years	48 (8), 31–61	47 (8), 31–65	51 (8), 32–65	$P = 0.193$
Height, cm	166 (4), 154–172	167 (7), 155–185	165 (5), 156–176	$P = 0.612$
Weight, kg	70 (10), 52–85	68 (12), 50–97	69 (11), 53–90	$P = 0.884$
BMI, kg m^2	25 (3), 19–32	25 (4), 19–34	26 (4), 19–34	$P = 0.562$
ASA physical status (*n*)	ASA 1 = 16	ASA 1 = 13	ASA 1 = 14	$P = 0.683$
	ASA 2 = 9	ASA 2 = 12	ASA 2 = 11	
Equilibration time, minutes	21 (7), 15–39	20 (6), 15–41	20 (5), 15–34	$P = 0.337$
Duration of surgery, minutes	74 (44), 19–182	87 (56), 8–225	77 (51), 17–216	$P = 0.679$
Body temperature, °C	36.2 (0.4), 35.4–37.2	36.2 (0.4), 35.6–36.9	36.1 (0.5), 35–36.8	$P = 0.680$

Data are presented as the mean (standard deviation), minimum-maximum, or absolute number (n).

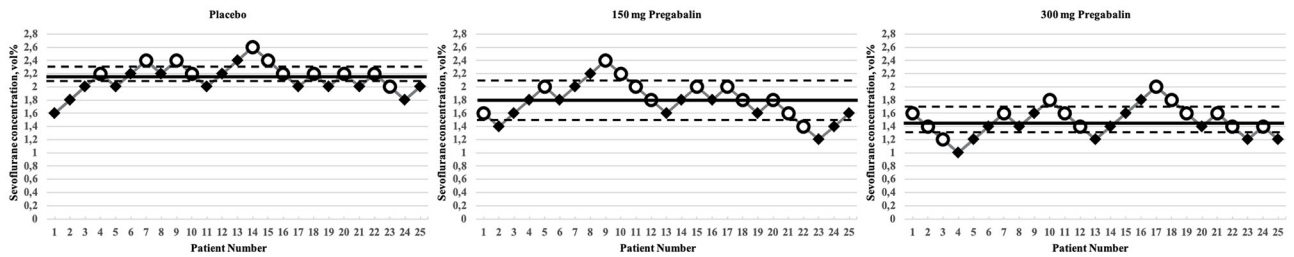

FIGURE 2 | Titration process in the study groups. Circles indicate patients who moved, and rhombi indicate patients who did not move. Solid horizontal lines indicate the bootstrap estimates for the MAC, dashed horizontal lines indicate the 95% confidence intervals. MAC, minimum alveolar concentration.

TABLE 2 | MAC estimates, 95% confidence intervals, and differences in the MAC between the study groups.

	Sample estimates	Bootstrap estimates	Bootstrap lower CI	Bootstrap upper CI
MAC sevoflurane placebo group, vol%	2.13	2.16	2.07	2.32
MAC sevoflurane 300 mg group, vol%	1.40	1.44	1.26	1.70
MAC sevoflurane 150 mg group, vol%	1.86	1.81	1.49	2.13
Difference from the placebo group −150 mg group, vol%	0.27	0.35	−0.04	0.75
Difference from the placebo group −300 mg group, vol%	0.73	0.72*	0.39	1.01
Difference between the 300 and 150 mg groups, vol%	0.46	0.36	−0.09	0.80

**Indicates a statistically significant difference.*

TABLE 3 | Serum pregabalin concentration, bispectral index, blood pressure, and heart rate at different time points in the study groups.

Group	Placebo ($n = 25$)	150 mg pregabalin ($n = 25$)	300 mg pregabalin ($n = 25$)	a	b	c
Serum pregabalin concentration, μg ml^{-1}	0 (0), 0–0	4.2 (1.6), 0–7.0	9 (2.8), 1.2–12.9	$P < 0.001$*	<0.001*	<0.001*	0.001*
BIS at incision	38 (9), 24–57	48 (13), 15–70	51 (10), 29–78	$P < 0.001$*	$P = 0.008$*	$P < 0.001$*	$P = 0.637$
Systolic blood pressure before incision, mmHg	101 (11), 84–125	101 (15), 75–141	103 (15), 82–141	$P = 0.866$			
Systolic blood pressure after incision, mmHg	107 (15), 84–150	101 (18), 56–129	104 (20), 75–155	$P = 0.676$			
Heart rate before incision, bpm	65 (9), 49–82	67 (14), 49–100	64 (9), 53–84	$P = 0.846$			
Heart rate after incision, bpm	73 (16), 44–114	69 (17), 44–107	70 (11), 50–88	$P = 0.897$			

*Data are presented as the mean (standard deviation), minimum-maximum; a = placebo vs. 150 mg pregabalin group, b = placebo vs. 300 mg pregabalin-group, c = 150 mg pregabalin vs. 300 mg pregabalin-group. *$P < 0.05$. BIS, bispectral-index.*

TABLE 4 | Side effects.

Group	Placebo ($n = 25$)	150 mg pregabalin ($n = 25$)	300 mg pregabalin ($n = 25$)		a	b	c
Pain level in the recovery unit, NRS	2.5 (2.2), 0–6	0.7 (1.1), 0–3	1 (1.6), 0–6	$P = 0.003$*	$P = 0.002$*	$P = 0.007$*	$P = 0.636$
Total negative side effects, *n* (percentage)	1 (4)	3 (12)	8 (32)	$P = 0.001$*	$P = 0.001$*	$P = 0.006$*	$P = 0.009$*
Nausea and Vomiting, *n* (percentage)	1 (4)	1 (4)	0 (0)	$P = 0.598$			
Dizziness, n (percentage)	0 (0)	0 (0)	8 (32)	$P < 0.001$*			
Headache	0 (0)	2 (8)	0 (0)	$P = 0.128$			
Awareness, *n* (percentage)	0 (0)	0 (0)	0 (0)	n.a.			
Cumulative propofol dose intra OP, mg	122 (71), 0–290	122 (54), 50–260	139 (71), 40–290	$P = 0.694$			
Cumulative fentanyl dose intra OP, µg	284 (178), 100–850	245 (116), 100–575	238 (83), 100–350	$P = 0.832$			
Number of patients receiving metamizol intra OP, *n* (percentage)	20 (80)	20 (80)	23 (92)	$P = 0.409$			
Number of patients receiving paracetamol intra OP, *n* (percentage)	1 (4)	0 (0)	1 (4)	$P = 0.598$			
Number of patients receiving diclofenac intra OP, *n* (percentage)	7 (28)	3 (12)	2 (8)	$P = 0.125$			
Number of patients receiving dexamethason intra OP, *n* (percentage)	20 (80)	15 (60)	13 (52)	$P = 0.105$			
Number of patients receiving ondansetron intra OP, *n* (percentage)	13 (52)	12 (48)	12 (48)	$P = 0.948$			
Cumulative piritramid dose in the recovery unit, mg	3.3 (3.1), 0–9	1.4 (2.5), 0–9	1.8 (3), 0–9	$P = 0.027$*	0.012*	0.037*	0.675
Number of patients receiving metamizol in the recovery unit, *n* (percentage)	9 (36)	5 (20)	5 (20)	$P = 0.324$			
Number of patients receiving paracetamol in the recovery unit, *n* (percentage)	5 (20)	1 (4)	2 (8)	$P = 0.162$			
Number of patients receiving diclofenac in the recovery unit, *n* (percentage)	5 (20)	1 (4)	1 (4)	$P = 0.080$			

*Data are presented as the mean (standard deviation), minimum-maximum; or absolute number (percentage); a = placebo vs. 150 mg pregabalin-group, b = placebo vs. 300 mg pregabalin group, c = 150 mg pregabalin vs. 300 mg pregabalin-group. *P < 0.05.*

A summary of the secondary outcome parameters is provided in **Table 4**.

DISCUSSION

In this prospective, randomized, controlled, double-blinded study, we assessed the effect of two different doses of pregabalin on the MAC of sevoflurane in female ASA 1 and 2 patients undergoing elective surgery. We found a 33% reduction in the MAC at a dose of 300 mg pregabalin compared to placebo but there was no statistically significant reduction at a dose of 150 mg.

In neuropathic pain, pregabalin seems to "impair the trafficking of α2δ-1 to presynaptic terminals of dorsal root ganglion neurons, which would reduce Ca^{2+} influx and transmitter release in the spinal cord and subsequently reduce spinal sensitization" (15). Although acute pain is caused by different mechanisms than neuropathic pain, pregabalin has been shown to reduce acute pain in various animal models (16, 17). Furthermore, pregabalin has been reported to decrease the isoflurane and sevoflurane requirements during balanced anesthesia (18, 19). There is evidence that sevoflurane acts on gamma-aminobutyric acid-receptors, which increase the release of inhibitory neurotransmitters (20, 21). Similar pharmacological effects of pregabalin and sevoflurane in the context of general anesthesia might therefore be explained by the overlap of pharmacodynamic principles.

Our results are in line with these previous reports indicating an anesthesia-enhancing effect of pregabalin. However, the endpoint of MAC testing (gross purposeful movements in response to a painful stimulus) might be affected not only by pain perception but also by the motor response to painful stimulation. Our study design did not allow us to discriminate between these possible mechanisms, and additional studies are necessary to elucidate the underlying mechanism of the observed MAC reduction.

Various guidelines recommend the use of depth of anesthesia monitors such as the BIS to guide the depth of anesthesia in certain patient groups (22). We found that for the same endpoint of 50% of the patients moving and 50% not moving in response to skin incision, the BIS values were significantly lower in the placebo group than in the pregabalin group. This is not surprising, as the average sevoflurane level in the placebo groups

was higher than that in the pregabalin groups. It seems that pregabalin does not enhance immobility *via* cerebral depressing effects, which should also have decreased the BIS. As inhalational anesthetics produce immobility mainly by acting on the spinal cord, we speculate that pregabalin enhances immobility at the same level, especially since we observed the same degree of immobility at higher BIS levels with pregabalin (23).

We chose to use doses of 300 mg and 150 mg pregabalin, as these doses are most commonly used in the perioperative setting, and found a statistically significant reduction in the MAC in the 300 mg pregabalin group but not in the 150 mg pregabalin group (3). Several explanations for this finding, such as an increased interindividual variation in the MAC caused by variations in the serum pregabalin concentrations or the effect of the initial sevoflurane concentration in this up-and-down design, are possible (24). Most likely, our study was just underpowered to detect minor differences in the MAC, but the clinical relevance of such minor differences in the MAC remains questionable. Nevertheless, given that 150 mg pregabalin is associated with fewer unwanted side effects and shows the potential to reduce the MAC of sevoflurane as well as post-operative pain and opioid consumption, future studies should focus on dosages lower than 300 mg.

Recently, the perioperative usefulness of pregabalin has been questioned, as its effect on post-operative and chronic pain appears to be minimal, and side effects seem to be common (4). Our results suggest that pregabalin reduces post-operative pain and opioid consumption in general but not in a dose-dependent manner. At the same time, side effects were significantly increased with higher doses of pregabalin. In our study, anesthetic procedures that followed the initial skin incision were not standardized. We chose this approach to be able to provide individualized patient care to guarantee the best medical outcome. However, this means that the secondary outcome parameters that refer to post-operative pain or opioid consumption should only be considered in terms of hypothesis generating.

In addition to the limitations mentioned above, we need to mention that only female patients were included in this study. While there is no evidence that the MAC of conventional inhalational anesthetics is affected by sex, we cannot rule out that the effects of pregabalin differ between men and women (25). However, as only female patients undergoing breast surgery were investigated, our study group contained a very uniform patient population, limiting interindividual variation due to surgery or sex.

In conclusion, the preoperative administration of 300 mg pregabalin reduced the MAC of sevoflurane by 33%, while the administration of 150 mg pregabalin did not significantly reduce the MAC. Pregabalin use led to a small reduction in post-operative pain levels but increased side effects in a dose-dependent manner.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethikkommission der Medizinischen Universität Wien, Borschkegasse 8b/E06, 1090 Wien. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JM generated the concept, administered the project, conducted the investigation, provided resources, and wrote the original draft of the manuscript. WP generated the concept, provided resources and guidance in conducting the investigation, and edited the manuscript. PM conducted the investigation and edited the manuscript. AG generated the concept, provided statistical planing, conducted the formal analysis, and edited the manuscript. TS conducted the formal and analytical analysis and edited the manuscript. TH generated the concept, provided resources, wrote the original draft of the manuscript, edited the manuscript, and supervized the project as a whole. All authors contributed to the article and approved the submitted version.

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Median Effective Analgesic Concentration of Ropivacaine in Ultrasound-Guided Interscalene Brachial Plexus Block as a Postoperative Analgesia for Proximal Humerus Fracture: A Prospective Double-Blind Up-Down Concentration-Finding Study

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Background: The innervation of the proximal humerus fracture is complicated and unclear. The use of interscalene nerve block has been effective as postoperative analgesia for patients, but the optimal concentration of usage is unknown.

Method: This study was conducted on 30 patients with ASA I or II, who were planning to undergo a proximal humerus fracture operation. A dosage of 10 ml Ropivacaine was administered for the interscalene brachial plexus block (ISBPB) as determined using the up-and-down sequential method. The initial concentration of Ropivacaine in the first patient to receive ISBPB was 0.3%. After a successful or unsuccessful postoperative analgesia, the concentration of local anesthetic was decreased or increased, respectively, by 0.05% in the next patient. We defined successful postoperative analgesia as a visual analog scale (VAS) score of < 4 at rest, within the initial 8 h after ISBPB. The analytic techniques of linear, linear-logarithmic, exponential regressions, and centered isotonic regression were used to determine the EC50 of Ropivacaine, and the residual standard errors were calculated for the comparison of "goodness of fit."

Results: The concentration of Ropivacaine ranged from 0.1 to 0.35%. The EC50 (95% confidence interval) from 4 different statistical approaches (linear, linear-logarithmic, exponential regressions, and centered isotonic regression) were 0.222% (0.198%, 0.335%), 0.233% (0.215%, 0.453%), 0.223% (0.202%, 0.436%), and 0.232%, respectively. Among all the 4 models, the linear regression had the least residual standard error (0.1676).

Conclusion: The EC50 from the four statistical models for 10 ml Ropivacaine in ultrasound-guided ISBPB for postoperative analgesia was distributed in a narrow range of 0.222–0.233%.

Trial Registration: www.chictr.org.cn/; registration number: ChiCTR2100047231.

Keywords: interscalene brachial plexus block, median effective analgesic concentration, postoperative analgesia, proximal humerus fracture, Ropivacaine

INTRODUCTION

Proximal humeral fractures are common and may account for up to 10% of all fractures in the elderly population over 60 years, with a notably higher incidence in women aged 80 to 89 years (1, 2). Whether to use conservative or surgical treatment mainly depends on the fracture pattern and the functional demands of the patient. At present, for complex, unstable, or severe proximal humeral fractures, surgical is the commonly accepted treatment (3, 4). However, this is often associated with significant pain, with patients often receiving multiple doses of opiate medications, which affects the quality of life and is related to high mortality rates (5).

Traditional proximal humeral surgery generally uses "beach chair position" or "semi-sitting position." To better manage the airway and provide patients with more comfort, general anesthesia is used. This study showed that general anesthesia, combined with interscalene brachial plexus block (ISBPB), could reduce the use of intraoperative opioid drugs, shorten postoperative recovery time, and alleviate postoperative pain (6). For ISBPB, some studies have shown that high concentrations of local anesthetics can increase the incidence of phrenic nerve paralysis and affect respiratory function (7). Therefore, determination of the median effective analgesic concentration (MEAC, EC50 = effective concentration in 50% of patients) is important.

Ropivacaine is one of the commonly used analgesics for nerve block. It has the advantages of fast onset, long-acting time, fewer incidences reported of arrhythmia than bupivacaine, and rare severe central nervous system toxicity and cardiovascular toxicity (8). Studies have found that brachial plexus block with 0.1–0.3% Ropivacaine can achieve separation of sensory and motor, which provides the possibility of early postoperative functional exercise for patients (9).

This study aimed to estimate the MEAC of Ropivacaine used in ultrasound-guided ISBPB for successful postoperative analgesia of proximal humeral fractures.

METHODS

Study Design and Population

This single-armed prospective study was approved by the Ethics Committee of the Sixth People's Hospital of Shanghai (reference No. 2021-144) and registered with the Clinical Trial Registry of China (http://www.chictr.org.cn/; registration No. ChiCTR2100047231; date of registration, June 11, 2021; date of patient enrollment, July 10, 2021). All patients who underwent proximal humerus fracture operation were assessed for eligibility. All eligible patients obtained written informed consent. Inclusion criteria: age between 18 and 70 years old, ASA physical status 1–2, and body mass index (bmi) between 18 and 35 kg/m^2. Exclusion criteria: pregnancy, local infection at the block site, pre-existing neuropathy or coagulopathy, allergy to local anesthetics and opioids, dementia, known history of intravenous (IV) drug abuse, preoperative chronic opioid requirements, chronic pain, psychiatric illness, patients who failed to understand the scoring systems used in the study, uncontrolled hypertension or ischemic heart disease, renal or hepatic dysfunction, and pre-existing neurologic deficits.

Blinding Method

All blocks were performed by one experienced anesthetist (G), using the same high-frequency (6 to 13 MHz) ultrasound probe (Sonosite, Inc., USA). Another anesthetist performed anesthesia management in the operating theater. An independent research assistant evaluated the nerve block. All personnel were blinded to the concentration of local anesthetic injected. A nurse, who did not participate in follow-up research, prepared the local anesthetics depending on the response of the previous patients.

The Technique of Block Administration

Routine monitors (pulse oximeter, non-invasive blood pressure cuff, and electrocardiogram) were used, and intravenous access was established. Patients were positioned supine with the head turned 45 degrees to the non-operative side. After skin disinfection, the brachial plexus at the interscalene groove was identified either by distal-to-proximal (trace-back) approach or by medial-to-lateral approach. After clearly identifying root C5, C6, and C7 in the imaging screen, a 4-cm 22-gauge insulated needle (UniPlex Nanoline; Pajunk, Geisingen, Germany) was inserted using an in-plane technique from the lateral-to-medial direction. The needle tip was ultimately positioned close to each root at the 3 o'clock position, respectively. If paraesthesia was complained of, the needle tip was repositioned before local anesthetic (LA) injection to avoid nerve injury. A total of 10 ml (3–4 ml/root) of Ropivacaine was given, and the spread of local anesthetic was seen. All injections were administered slowly with a repeated aspiration to prevent or detect early intravascular injection. A concentration of 0.3% Ropivacaine was administered in the first patient. The Dixon and Mood's up-and-down study design was followed (10). LA concentration for subsequent patients was determined by success or failure of postoperative analgesia (success of postoperative analgesia: in the initial 8 h after ISBPB, the VAS score was < 4) in the previous patient. Drug concentration was increased by 0.05% in case of failure and decreased by 0.05% in case of success.

Block Evaluation

Final needle removal time was noted as "block time". Block assessment was done at 5-min intervals by an independent observer who was blinded to LA concentration until 30 min after block time. Sensory blockade was assessed on the deltoid and

lateral upper arm according to a 3-point qualitative scale with a pinprick sensation test using a sharp 25 G needle: 0 = no block (compared with the contralateral side); 1 = incomplete block (a non-sharp sensation, touch or pressure); 2 = complete block (unable to recognize pinprick sensation). The motor block was assessed using a 3-point modified Bromage score: 0 = no motor block at full extension and flexion of all upper extremity joints; 1 = decreased motor strength with the ability to move only the fingers; 2 = complete motor block with the inability to move the elbow, wrist, and fingers.

Clinical Procedures

General anesthesia was induced with propofol (1–2 mg/kg), sufentanil (0.1–0.15 μg/kg), and a laryngeal mask airway was placed at the proper position. Volatile anesthetics sevoflurane was used for maintenance, with end-expiratory sevoflurane concentration above 0.7 MAC (minimum alveolar concentration) and ETCO2 between 35 and 45 mmHg.The patient's spontaneous breathing was observed. During the operation, the anesthesiologist would use 0.1 μg/kg sufentanil intravenously if any signs indicated insufficient anesthesia (an increase of more than 20% in the heart rate and/or blood pressure compared to before anesthesia, rapid shallow breathing with a spontaneous respiratory rate greater than 20 breaths per minute). All patients received Postoperative nausea and vomiting (PONV) prophylaxis droperidol IV before emergence. When the surgical operation was completed, the patients were transferred to the post anesthesia care unit (PACU), and then, to the wards for discharge. For excluded patients, endotracheal intubation general anesthesia was performed. They were provided with a patient-controlled analgesia pump (sufentanil 1 ug/ml, background infusion 1ml/h, bolus 2 ug, and lockout 15 min) for 48 h postoperatively. Besides, an oral paracetamol 1 g or ibuprofen 400 mg could be given every 6 h after the surgery.

Pain Assessment and Management

Patients were instructed to record their pain using the visual analog scale (VAS) (0–10, 0 = no pain, 10 = worst imaginable pain). VAS of rest pain and movement-related pain was measured immediately after resuscitation, right before discharging from the PACU, and at 4, 6, 8, and 24 h after the block time. The timing and dosage of analgesics were recorded. Twenty-four hours after the block time, patients were questioned for VAS, time of the first operative limb pain, and satisfaction with the ISBPB (0–3, 0 = very unsatisfied; 3 = very satisfied). In addition, patients were telephone-interviewed if they suffered a late complication such as nerve injury and pain radiating to the arm and forearm related to ISBPB after discharging from the hospital.

UDM

A concentration of 0.3% of 10-ml Ropivacaine was administered in the first patient. After successful postoperative analgesia (in the initial 8 h after ISBPB, the VAS score was < 4), the concentration of local anesthetic in the next patient was decreased by 0.05%. However, if the block was unsuccessful, then the local anesthetic concentration was increased by 0.05% in the next patient. All patients received < 3 mg/kg of Ropivacaine to avoid local anesthetic toxicity.

Adverse Effect

Complications include hematoma, Horner's syndrome, hoarseness, nausea, vomiting, local anesthetic systemic toxicity (blurred vision, hearing impairment, sleep disturbances, dizziness, muscle twitching, and arrhythmia), respiratory distress, and hypoxemia, which were also assessed during this study.

Statistical Analysis

In most cases, the exact sample size for Dixon's Up-and-down method (UDM) could not be determined in advance. When six cross-overs (conversion from successful block to unsuccessful block or vice versa) had occurred, we ceased to recruit patients (11). We determined that at least 20–40 patients would be required to provide reliable estimates of the target dose in our simulation studies in anesthesia trials using Dixon's UDM. Our study recruited 30 patients to achieve this goal.

To explore the target dose of EC50, four statistical approaches were used, including 3 parametric estimates of the dose-responsive curve (12): linear, linear-logarithmic and exponential regressions, and one nonparametric model: the centered isotonic regression, which was only for assuming a nondecreasing dose and response relationship (11).

The residual standard errors, a statistical tool to determine the goodness of fit, which analyzes how well a set of data points fit with the actual model, were calculated for all four statistical approaches. We also calculated Pearson's correlation coefficient (r) to find the association between the time to the first analgesic request and administered local anesthetic volume.

For the continuous variables, data were presented as mean ± SD or median (interquartile range) depending on the distribution of the data. For all categorical variables, frequency/percentage was calculated. The Mann–Whitney U test was used for statistical analysis of skewed continuous variables or ordered categorical data. Chi-square or Fisher exact test was applied to find out the association between subgroup and categorical variables.

RESULTS

All 30 patients in this study met the screening criteria, and no patients were excluded during the study. All patients were selected with eight independent up-down deflections (**Figure 1**). There was no significant difference in sex, age, BMI, ASA status, and duration of surgery between the upper and lower cases ($P < 0.05$). **Table 1** shows the surgical characteristics of these patients.

The Median Effective Analgesic Concentration of Local Anesthetic

The illustration of the sequence of successful and unsuccessful postoperative analgesia is shown in **Table 2**. The linear model estimator led to an EC50 of 0.222%, the linear-logarithmic model resulted in an EC50 value of 0.233%, the exponential regression gave an EC50 of 0.223%, and the centered isotonic regression (a nonparametric method) yielded an EC50 of 0.232% (see

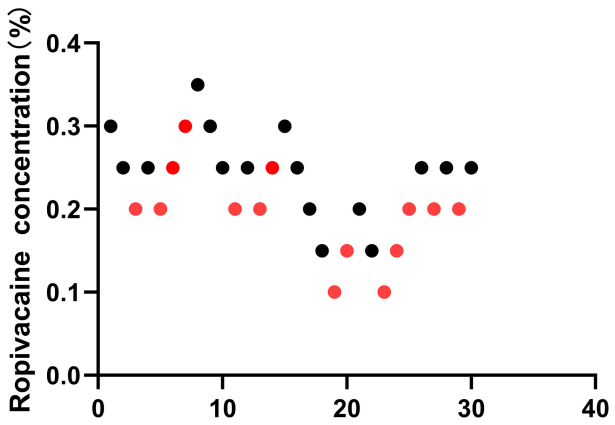

FIGURE 1 | Sequential block results of ultrasound-guided Interscalene Brachial Plexus Block using 10 ml ropivacaine according to the Dixon and Massey up-and-down method.

TABLE 1 | Patient characteristic.

Characteristic	Mean ± SD or No. (%)
Sex (male/female)	23/7
Age (yr)	36.2 ± 6.34
Body mass index (kg/m^2)	22.7 ± 3.07
ASA physical status (I/II)	14/16
Duration of surgery (min)	67.9 ± 18.89
sufentanil consumption (μg)	8.3 ± 2.71
Time to 1st rescue analgesic (h)	7.4 ± 2.36
Time to remove the laryngeal mask (min)	9.8 ± 3.54
Onset time of sensory block (min)	5.0 ± 1.96
Onset time of motor block (min)	11.9 ± 2.73
Duration of motor block (h)	8.8 ± 2.20
Analgesic satisfaction (1/2/3)	0/10/20

ASA, American Society of Anesthesiologists.

TABLE 2 | The mean effective concentration and 95% confidence interval of the different models.

Model	ED 50 (%)	95%CI(%)	Residual standard error
Centered isotonic			
Regression	0.232		
Linear	0.222	0.198, 0.335	0.1676
Linlog	0.233	0.215, 0.453	0.1823
Exponential	0.223	0.202, 0.436	0.1907

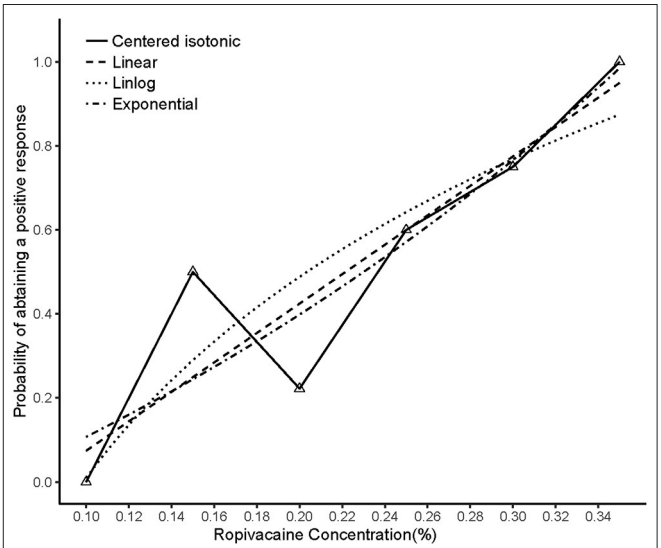

FIGURE 2 | Estimated ropivacaine–Interscalene Brachial Plexus Block relationship for a given dose level and probability of successful block. Median estimators for each model are plotted. The numbers of measurements at each ropivacaine concentration are represented by numbered triangles.

Figure 2). The 95% confidence intervals for the 3 parametric models (linear, linear-logarithmic, and exponential) were 0.198%, 0.335%; 0.215%, 0.453%; and 0.202%, 0.436%, respectively (**Table 2**), and they showed similar fitted probabilities within the range of the EC50, while the 95% confidence intervals from these models successfully covered all observed data. **Table 2** also shows the results of residual standard deviations for the goodness of fit of each model. The exponential regression has the least residual standard error (0.1676) among all models.

Block Performance Characteristics

The mean onset time for the sensory block to reach grade 1 was 5.8 ± 3.33 min and the mean onset time for the motor block to reach grade 2 was 12.9 ± 2.81 min. The onset time of sensory block and motor block was not significantly different between patients having successful and failed blocks ($p = 0.5890$, $p = 0.7012$, respectively). All patients achieved grade 1 or 2 with motor block within 8 h after surgery. The average duration of the motor block was 7.5 ± 1.32 h. No difference occurred in the duration of the motor block between successful and unsuccessful blocks ($p = 0.6500$).

Postoperative Pain and Rescue Analgesia Required

Out of the total patients included in the study, 16 patients had a successful block. All patients with a successful block had a postoperative visual analog scale score of < 4 in the initial 8 h (**Figures 3A,B**). The average intraoperative sufentanil consumption was 10.8 ± 3.33 μg. Intraoperative sufentanil consumption between successful and unsuccessful blocks ($p = 0.6676$) showed no difference. However, the mean time to first rescue analgesia was 9.2 ± 2.71 h. The time to 1st rescue analgesia between successful and unsuccessful blocks ($p < 0.0001$) was significantly different. The time to 1st analgesic request was moderately positively correlated with administered local anesthetic concentration, with the Spearman rank correlation (r) being 0.4351. This value of r was found to be statistically significant ($p = 0.0163$) (**Figures 3C,D**).

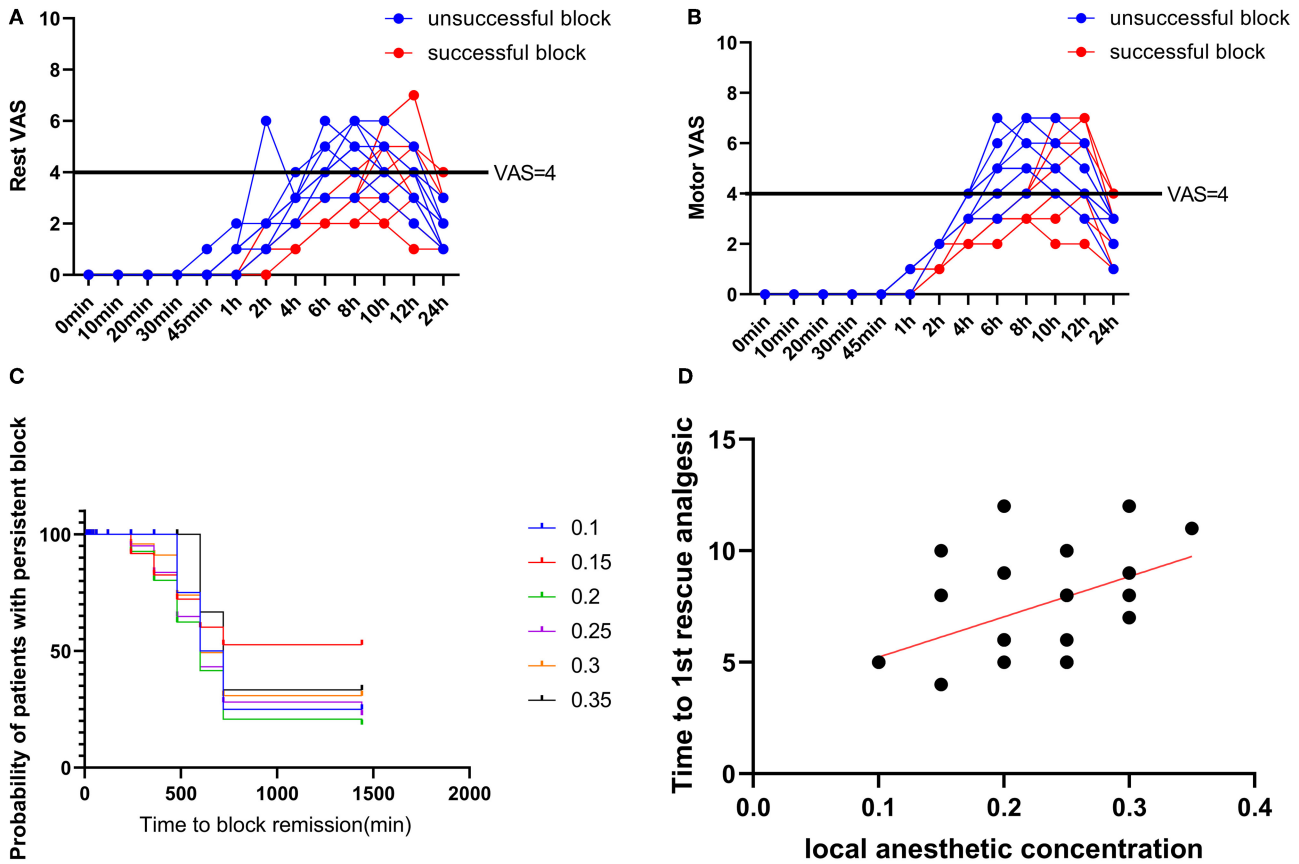

FIGURE 3 | Postoperative pain scores. **(A)** Rest pain score 24 h after surgery. **(B)** Motor pain score 24 h after surgery. **(C)** Duration of the Interscalene Brachial Plexus Block with different concentrations of ropivacaine. **(D)** Correlation between ropivacaine concentration and time to first rescue analgesic in interscalene brachial plexus block.

Postoperative Adverse Events

A female patient complained of chest tightness on the blocked side after returning to the ward, suggesting phrenic nerve block and unilateral lung function decline. This was relieved by nasal cannula oxygen inhalation, without hypoxemia occurrence. No other complications were noted.

DISCUSSION

In this study, we have found the median EC50 was 0.222% (95% CI, 0.202 to 0.436%).

The ISBPB can provide dense analgesia and anesthesia to the upper extremity from the shoulder to the fingers, depending on the indication and approach utilized. The use of ultrasound has made the block more accessible and safer to perform. There is evidence to suggest that the use of ultrasound reduces the total volume of anesthetic required, decreases complications such as pneumothorax and vascular injury, and increases block success (13). Therefore, general anesthesia combined with ultrasound-guided nerve block is the preferred method compared to general anesthesia alone, particularly when general anesthesia with a laryngeal mask that preserves the patient's spontaneous breathing (14). Compared with endotracheal intubation, it can reduce or circumvent irritation to the soft tissues of the pharynx and tracheal wall, and improve the hemodynamic stability of anesthesia induction and recovery period. Meanwhile, the amount of medicine required by the laryngeal mask has also been reduced in contrast to the endotracheal intubation. Compared with simple intravenous anesthesia, considering the special "beach chair position" or "semi-sitting position," sedative analgesics can be used more safely under the premise of a laryngeal mask, which improves the safety of airway and patient comfort.

With regard to proximal humerus fracture operation, ISBPB is effective in postoperative pain control and reducing opiate intraoperative use in patients. Various approaches can be considered, such as a suprascapular nerve block (SSNB) or a superior trunk block (15, 16). Several randomized controlled trials have compared ISBPB with SSNB, but the evidence is conflicting. Some have found ISBPB to be superior, whereas others have shown that SSNB provides non-inferior analgesia (17). A review suggested that there are no clinically meaningful analgesic differences between ISBPB and SSNB except that ISBPB does provide better pain control during recovery room stay

(18). The superior trunk block can potentially cause diaphragm sparing, but further research is needed to determine the efficacy (16). Thus, ISBPB is the most popular and frequently used approach for proximal humerus fracture operation.

Ropivacaine is one of the commonly used drugs for nerve block. It has the characteristics of motor-sensory block separation at low concentrations meaning the sensory function of the corresponding body parts is temporarily lost, while the motor function can be partially or completely retained. Studies have found that brachial plexus block using 0.10–0.25% Ropivacaine can achieve the separation of sensory and motor (9). Patients undergoing proximal humerus fracture operation are required for early functional exercises. Therefore, a brachial plexus block with a low concentration of Ropivacaine is an ideal method of anesthesia and postoperative analgesia.

When performing ISBPB, there is a high risk of causing ipsilateral hemidiaphragmatic paralysis *via* phrenic nerve palsy (19). For patients without basic respiratory diseases before surgery, even if diaphragmatic paralysis occurs, the postoperative respiratory function of patients can still be well-tolerated (20). Therefore, none of the patients enrolled in this study had preoperative pulmonary disorders. A large number of studies have shown that the incidence of phrenic nerve block is 100% when the volume of Ropivacaine used in ISBPB exceeds 15 ml (21). Meanwhile, It has been reported that when 0.75% Ropivacaine is used for ISBPB, an average of 1.7 ml of local anesthetic for each nerve root can meet the needs of a single nerve block (22). Therefore, in this study, due to the expected low target concentration of Ropivacaine, a total volume of 10 ml LA was used to block the brachial plexus. To achieve a more satisfactory blocking effect, 3–4 ml drug was injected around the three roots, respectively, and all blocks were completed under ultrasound guidance to ensure the accuracy of the injection site. Previously, it has been reported that the EC50 of surgical operation under nerve block using Ropivacaine alone is 0.2675% (23). Thus, an initial concentration of 0.3% for ISBPB was selected.

The Dixon and Mood up-and-down sequential method is used to assess the dose-response of medications. It proved to be an effective method with reduced samples compared to classic studies of multiple groups with fixed concentrations. In this study, the linear model was used to calculate the EC50 of Ropivacaine for postoperative analgesia of proximal humerus fracture after general anesthesia combined with ISBPB. The EC50 measured by other methods is not much different from this result and is less than commonly used clinical doses. Therefore, during general anesthesia combined with a nerve block, the concentration of Ropivacaine can be appropriately reduced.

Also, this study has certain limitations, although we strictly abide by the entry standards, follow the operating specifications, and conduct the experiments by the blind method. There may be selection bias due to the small sample size in the study; thus, the experimental results still need to be further verified by large samples and multi-center studies. In addition, a VAS score < 4 points within 8 h after the operation was defined as a standard for a successful block in this study; otherwise, it is recognized as unsuccessful. The VAS score test is highly subjective and may affect the experimental results.

In conclusion, we found that the median EC50 of Ropivacaine is 0.222%.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Sixth People's Hospital of Shanghai. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CX and YL wrote the manuscript. JL designed the research. CX, FG, RC, and CW performed the research. CX and CW analyzed the data. FG and RC contributed new reagents and analytical tools. All authors agree to the submission of this manuscript.

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Perineural Administration of Dexmedetomidine in Axillary Brachial Plexus Block Provides Safe and Comfortable Sedation: A Randomized Clinical Trial

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Dexmedetomidine prolongs the duration of regional block while its systemic sedative effect when administered perineurally is unknown. We aimed to evaluate the systemic sedative effect of perineural dexmedetomidine in patients after axillary brachial plexus block (ABPB). This single-blinded prospective randomized control trial included 80 patients undergoing wrist surgery receiving ABPB. Patients were randomized into two groups – Control group (CG, $N = 40$) and dexmedetomidine group (DG, $N = 40$). Both groups received ABPB with 20 ml of 0.5% Bupivacaine and 10 ml of 2% Lidocaine. Additionally, patients in DG received 100 mcg of dexmedetomidine perineurally. Depth of sedation was evaluated using Narcontrend Index (NI) and Ramsay Sedation Scale (RSS) immediately after ABPB and in several time points up to 120 min. Duration of block as well as patient satisfaction with sedation was evaluated using a postoperative survey. Our results showed that NI and RSS statistically differed between groups, presenting a deeper level of sedation during the first 90 min in DG compared to controls, $P < 0.001$. In the first 10 to 60 min after ABPB the median RSS was 4 (IQR within median) and median NI was 60 (IQR 44–80) in DG group, in contrast to CG patients where median RSS was 2 (IQR within median) and median NI was 97 (IQR 96–98) throughout surgery. The level of sedation became equal in both groups 90 and 120 min after ABPB when the median NI value was 98 (97–99) in DG and 97.5 (97–98) in CG, $P = 0.276$, and the median RSS was 2 (IQR within median) in both groups, $P = 0.128$. No significant intergroup differences in hemodynamic or respiratory parameters were found. Patients in DG expressed satisfaction with sedation and 86.5% noted that the sensation was similar to ordinary sleep. In DG mean duration of motor block was 13.5 ± 2.1 h and sensory block was 12.7 ± 2.8 h which was significantly longer compared to CG 6.3 ± 1.5 h, $P < 0.001$ and 6.4 ± 1.8 h, $P < 0.001$. We found that beside prolongation of analgesia, perineural administration of dexmedetomidine might provide rather safe and comfortable sedation with no significant effect on hemodynamic or respiratory stability and yields a high level of patient satisfaction.

Keywords: dexmedetomidine, axillary plexus brachialis block, sedation, wrist surgery, patient satisfaction

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INTRODUCTION

The use of peripheral nerve blocks (PNB) has seen widespread adoption with the recent advancements of ultrasound-controlled techniques (1, 2). PNB provide adequate anesthesia for surgery, provide postoperative analgesia and decrease opioid requirements (3–7). Axillary brachial plexus block (ABPB) is the preferable option of anesthesia for wrist and hand surgery since it avoids the side effects of general anesthesia (8, 9).

Sedation is commonly applied in regional anesthesia. It is particularly useful for those who experience anxiety or restlessness and would prefer not to be awake during surgery (10). In order to choose the appropriate sedative agent, its side effects on spontaneous breathing and cardiovascular stability must be considered. Although midazolam is traditionally the most used sedative agent during regional anesthesia, alternative sedatives are emerging. dexmedetomidine is a highly selective α2 blocker which has recently gained widespread popularity due to its mild to moderate sedative, anxiolytic, and analgesic properties (11). During the last few years, increasing attention has been paid to reports demonstrating dexmedetomidine as a safe and effective sedative agent for intensive care (ICU) patients.

When dexmedetomidine is administered perineurally alongside local anesthetics it increases the duration of motor and sensory block (12–15). Curiously, previous reports have noted a systemic sedative effect after the perineural administration of dexmedetomidine (13, 16, 17) which was initially classified as an adverse effect.

We hypothesized that the systemic sedative effect produced by perineural Dexmedetomidine might have clear advantages during surgery under regional anesthesia. However, there is very limited data in previous literature on the systemic sedative effect of perineural dexmedetomidine. Therefore, our aim was to assess the systemic sedative effects of perineural administration of dexmedetomidine in patients receiving axillary brachial plexus block.

MATERIALS AND METHODS

The study protocol and the informed consent form were approved by the Ethics Committee of Riga East Clinical University hospital (Approval Number ZD/08-06/01-21/4). Written informed consent was obtained from every patient.

Patient Selection and Patient Groups

Between 1st of January and 31st of May 2021, 86 consecutive adult patients were included in this single-blinded prospective randomized controlled study. All patients were admitted to the Latvian Microsurgery Center at Riga East University hospital, Riga, Latvia, to undergo urgent or elective wrist surgery.

The inclusion criteria: 18 years of age or older; ASA score of I–II. The exclusion criteria: pregnancy; history of mental or sleep disorders; sinus bradycardia (<50/min) just before performing ABPB; failed regional block (inadequate block 30 min after the attempt) and conversion to general anesthesia.

There were five patients excluded due to conversion to general anesthesia and one patient due to unexpected adverse effects related to the local anesthetics.

Simple randomization was performed by the researchers to allocate patients into two groups: control group (CG, $N = 40$) and dexmedetomidine group (DG, $N = 40$). The patients were included either in CG or DG group in a single-blinded manner.

Perioperative Management

All patients received a premedication of 7.5 mg of oral midazolam (Dormicum®, F. Hoffman-La Roche AG, Switzerland) 30 min before transfer to the operating room. All patients underwent regional anesthesia with ABPB. The block was performed with the concurrent use of ultrasound and nerve stimulation guidance. The block was provided using 20 ml of 0.5% bupivacaine (Bupivacaine-Grindeks, AS Grindeks, Latvia) and 10 ml of 2% lidocaine (Lidocaine-Grindeks, AS Grindeks, Latvia) perineurally for patients in both groups. Additionally, patients in DG received 100 mcg of dexmedetomidine (Dexdor®, Orion Corporation, Finland) in 1 ml of normal saline perineurally. Standard monitoring with non-invasive blood pressure, pulse oximetry and heart rate was applied during surgery. The entire process of ABPB administration and intraoperative monitoring was carried out by a designated group of three experienced anaesthesiologists. Depth of sedation was continuously monitored using Narcotrend (Narcotrend Compact M, MT MonitorTechnik GmbH & Co. KG, Germany) which displays a derived electroencephalographic parameter referred to as the Narcotrend Index (NI). The Narcotrend Index is measured from 0 to 100 with values below 79 considered as light to moderate sedation and values below 64 considered as deep sedation or level of general anesthesia (18). Ramsay sedation scale (RSS) was also used to evaluate depth of sedation. RSS scores were assigned in the following manner: 1 point—patient is agitated; 2 points—patient is oriented and tranquil; 3 points—patient is arousable to verbal command; 4 points—patient is arousable to mild sensory stimulus; 5 points—patient has an incomplete reaction to painful stimulus; 6 points—patient has no reaction to painful stimulus. Values of Narcotrend Index (NI) and RSS score were obtained immediately after block, 10, 20, 30, 60, 90 and 120 min after the block as well as at the end of surgery.

The following conditions were defined as adverse effects: hypertension (systolic blood pressure >180 mmHg); tachycardia (heart rate >100/min at least 5 min); hypotension (mean arterial pressure <60 mmHg); bradycardia (heart rate <50/min at least 5 min); low oxygen saturation (SpO_2 <90%). During surgery, patients with bradycardia (<50/min) received 0.5 mg of Atropine (Atropine Sopharma, Sopharma AD, Bulgaria) intravenously. Patients with low oxygen saturation (SpO_2 <90%) were stabilized by securing the airway with head positioning and received oxygen *via* a nasal cannula or oxygen mask. Low oxygen saturation (SpO_2 <90%) was the only designated indication for initiation of oxygen support.

A written postoperative survey was conducted on the first day after surgery after full recovery from sedation. The survey contained questions regarding the satisfaction with sedation and

TABLE 1 | Demographic and clinical course characteristics of patients scheduled for wrist surgery undergoing axillary brachial plexus block.

	Dexmedetomidine group *N* = 40	Control group *N* = 40	*P*-Value
Age, years	48.9 ± 17.3	48.0 ± 12.6	0.654
Sex, female, *n* (%)	22 (55)	20 (50)	0.779
Body mass index	24.1 ± 4.0	25.7 ± 6.3	0.159
ASA score:			
I class, *n* (%)	18 (45)	10 (25)	0.061
II class, *n* (%)	22 (55)	30 (75)	
Wrist surgery type			
Urgent, *n* (%)	8 (20)	10 (25)	0.592
Elective, *n* (%)	32 (80)	30 (75)	
Duration of block procedure (min)	10.0 ± 3.3	10.2 ± 3.1	0.764
Time to incision (min)	16.3 ± 3.4	20.8 ± 3.1	<0.001
Duration of block (h)			
Motory block	13.5 ± 2.1	6.4 ± 1.8	<0.001
Sensory block	12.7 ± 2.8	6.3 ± 1.5	<0.001

Data are presented as mean ± SD or number (n) and percentage (%) and median (interquartile range).
SD, Standard Deviation; ASA, American Society of Anesthesiologists.

its similarity to ordinary sleep, the presence of postoperative nausea and the duration of sensory and motor block.

Statistical Analysis

Statistical analysis was performed using the SPSS 26.0 (*Statistical Package for Social Sciences*). The Kolmogorov–Smirnov test was used to evaluate whether datasets conformed to normal distribution. Continuous variables were presented as mean ± standard deviation (SD) and categorical variables were presented as median ± IQR. Differences in data distribution between the groups were evaluated using Mann–Whitney *U* test for non-parametric datasets, and two-sample *t*-test or ANOVA for datasets conforming with normal distribution. Chi-square test was used for sets of nominal variables. Statistical significance was assumed if two-tailed $P < 0.05$.

RESULTS

Clinical Course

In total 80 consecutive patients consisting of 38 men and 42 women were included. The mean age was 48.5 ± 14.9 years. All patients included in the study were scheduled for urgent or elective wrist surgery. There were no differences in age, gender distribution or ASA score, or body mass index between the groups, as depicted in **Table 1**. There were no significant intergroup differences in mean duration of block procedure either. Although, patients in the DG group had a shorter mean time to incision, the median time from end of block procedure to end of surgery was 120 min in both groups, with no significant intergroup difference, $P = 0.096$. As shown in **Table 1**, the CG had a significantly lower mean duration of postoperative sensory and motor block when compared to DG, $P < 0.001$.

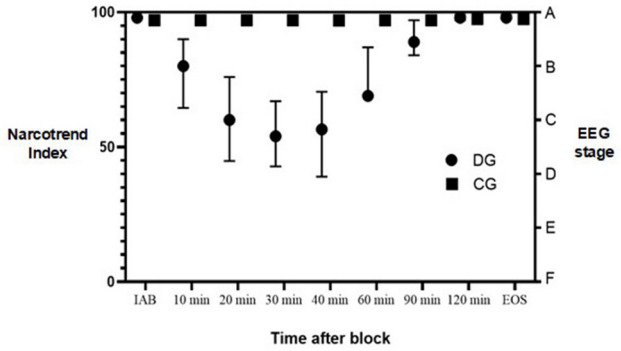

FIGURE 1 | Narcotrend Index during surgery. DG, dexmedetomidine group; CG, control group; IAB, initially after block; EOS, end of surgery; EEG, electroencephalography. Dots represent median values. Lines represent interquartile range.

Dominantly, patients were scheduled for elective wrist surgery. However, few urgent surgical cases were conformed to the study inclusion criteria. There was no significant difference in the proportion of elective and urgent patients between both groups, $P = 0.790$.

Variables of Systemic Sedation Effect

As shown in **Figure 1**, median values of NI were significantly lower in 10, 20, 30, 40 and 60 min after the ABPB in DG compared to controls, $P < 0.001$. Patients receiving dexmedetomidine perineurally demonstrated a median NI 98 (IQR, 97–99) immediately after the block. In 10 min, the median NI decreased to 80 (64.5–90), representing mild sedation. In the next 20 to 60 min median NI further decreased to a median of 57 (44–76), representing moderate to deep sedation. In 90 min, the median NI increased to 89 (84–97) when patients were mostly awake or mildly sedated. In contrast, patients in the CG remained wakeful and had a median NI of 97 (IQR 96–98) all throughout surgery. There ceased to be any statistically significant intergroup differences in NI values after 90 and 120 min.

Concomitantly, the intergroup statistical difference in median RSS score was found in 20–60 min after the ABPB, $P < 0.001$. Patients in the DG demonstrated RSS score 2 initially after block and then it increased to 4 in 20–60 min after block with the patient being sedated but easily awoken with verbal stimulus. Finally, in 90 min the median RSS score returned to 2. In contrast, patients in CG had a median RSS score of 2 initially after block and throughout surgery. There was no statistical difference in RSS score between the groups after 90 and 120 min.

Variables of Respiratory and Hemodynamic Stability

We found no differences in mean heart rate or mean arterial blood pressure (MAP) between the two groups all throughout the surgery. However, brief episodes of bradycardia were observed in 4 (10%) subjects from DG and 2 (5%) subjects from CG, $P =$

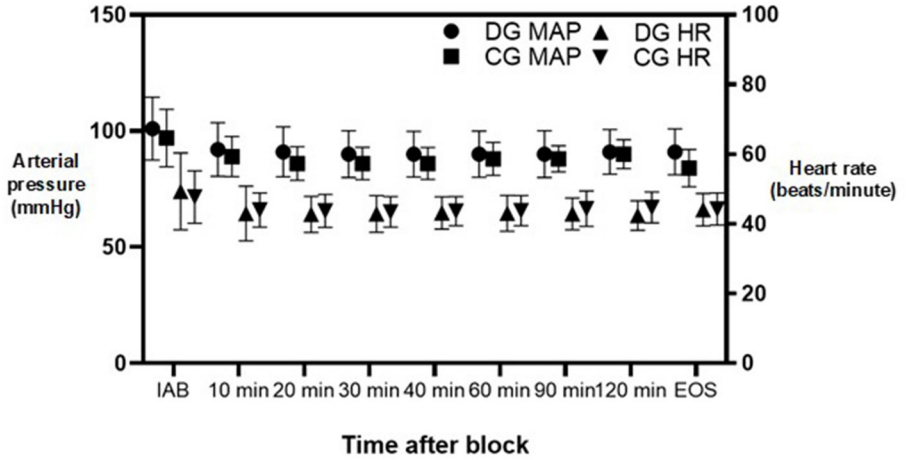

FIGURE 2 | Mean arterial pressure and heart rate changes during surgery. DG, dexmedetomidine group; CG, control group; MAP, mean arterial pressure; HR, heart rate; IAB, initially after block; EOS, end of surgery. Dots represent median values. Lines represent standard deviation.

0.396. Changes in mean heart rate and MAP throughout surgery can be appreciated in detail in **Figure 2**.

Desaturation was rare in both groups. There was no statistical difference in median oxygen saturation all throughout surgery. However, a larger subset of subjects in the DG needed oxygen support by face mask to maintain adequate oxygenation (40% vs. 12.5%; $P = 0.005$).

Patient Satisfaction

The survey revealed that 92.5% of subjects in the DG described falling asleep during surgery. Only 12.5% of patients in the CG recall sleeping during surgery. All patients in the DG expressed satisfaction with sedation and 86.5% of subjects found it comparable to ordinary sleep.

DISCUSSION

Dexmedetomidine has been recently proven to be an effective adjuvant to regional anaesthesia (12–15) Perineural administration of dexmedetomidine alongside local anesthetics is advantageous for prolonged surgery and provides long-duration postoperative analgesia (12, 17, 19). In the present study, DG patients demonstrated safe and comfortable systemic sedative effect after 100 mcg of dexmedetomidine added perineurally in ABPB for wrist surgery. Our most compelling finding was that NI and RSS statistically differed between both groups, suggesting a deeper level of systemic sedation during surgery in the first 90 min in DG patients compared to controls. Moreover, we noticed no significant events of hemodynamic instability in DG, confirming safe systemic sedation of dexmedetomidine when being administered perineurally. But so far, we suggest the proper monitoring must be applied since a larger subset of subjects in the DG needed oxygen support by face mask, especially if sicker patient is treated.

Dexmedetomidine was initially approved by the European Medicines Agency for use as a sedative in ICU setting (EMEA/H/C/002268). It has an acceptable tolerability profile, and its sedative effect is noninferior to other commonly used sedative agents in the ICU (20). At the same time, the administration of dexmedetomidine as an adjuvant to PNB is still considered as an off-label indication. This implies that both the local and systemic effects of perineural administration are yet to be fully examined.

Nevertheless, multiple authors have previously proposed adding dexmedetomidine as an adjuvant to local anesthetics for prolongation of sensory and motor blockade (14, 17). A systematic review by El-Boghdadly and co-authors found perineural dexmedetomidine to be a more effective adjuvant than Clonidine (14). In contrast, Albrecht and co-authors found that perineural dexmedetomidine was a less effective adjuvant than dexamethasone (21). The previously stated publications on perineural dexmedetomidine have noted the appearance of side effects such as systemic sedation and bradycardia (14, 16, 17, 21). The intravenous administration of dexmedetomidine has also been proven to be equally effective as compared to perineural dexmedetomidine with respect to onset and duration of block and duration of analgesia but has greater hemodynamic instability (22). We attempted to demonstrate that the systemic sedative effect of perineural dexmedetomidine can be objectively measured and is in fact beneficial in the context of regional anesthesia. Furthermore, we attempted to demonstrate that patient safety and satisfaction might be achieved with the appropriate dosing strategy.

Several studies have focused on multiple dosing strategies. A meta-analysis of 32 studies by Vorobeichik and co-authors suggest 50–60 mcg of perineural dexmedetomidine to be the optimal dose for prolongation of sensory blockade while avoiding hemodynamic instability (17). A meta-analysis of 12 studies by Dai and co-authors did not find a significant difference in incidence of hemodynamic or respiratory instability between doses <50 mcg and >50 mcg (23). It has been found that a dexmedetomidine plasma concentration of 0.2–0.3 ng/ml provides moderate systemic sedation (11). A prospective study by Fritsch and co-authors revealed that 150 mcg of perineural

dexmedetomidine led to a plasma concentration of 0.37 ng/ml in 90 min (12) which exceeds the previously stated plasma concentration for moderate sedation. So far, a study by Keplinger and co-authors has concluded that the 100 mcg dose level for perineural dexmedetomidine may represent an optimal balance between efficacy and sedation (16). Based on previous reports, we considered that 100 mcg of perineural dexmedetomidine might provide safe systemic sedation during surgery and would not have any marked effects on hemodynamic or respiratory stability.

Two randomized groups were included in our study and proved to be indistinguishable by population characteristics, ASA score and surgical factors and thus further comparisons were not at risk of confounding factors.

In our study the Narcotrend Index (NI) was used as objective criteria to assess the depth of sedation. As far as we know, there is only one study that uses NI to explore the sedative effect of dexmedetomidine in the context of continuous epidural anesthesia (24). There are no previous studies which have used NI to measure the systemic sedative effect of perineural dexmedetomidine in PNB.

When assessing patient satisfaction, we found that every patient in the DG expressed satisfaction with sedation and most of patients compared the systemic sedative effect to ordinary sleep. Clinicians often report that it would be preferable if during the sedation the patient could be easily awoken with verbal stimulus and be oriented and cooperative. Such effects of dexmedetomidine have already been elucidated in previous studies (19, 25). This implies that perineural dexmedetomidine has a high potential for patient and clinician satisfaction. It must be noted that in our study most subjects spent a considerable amount of surgical time with no sedation since the duration of sedation provided by perineural Dexmedetomidine using this dosing strategy was only 90 min. Admittedly, the surgery ended in less than 90 min after the PNB in only 20% of cases. Furthermore, 20–60 min after ABPB the NI and RSS indicated moderate to deep sedation which may exceed the necessary depth of sedation for surgery under regional anesthesia. Therefore, it is too early to conclude that 100 mcg is the optimal dose for effective and safe systemic sedation since in some cases the time from block until end of surgery exceeds 90 min.

Previous data on the systemic complications of perineural dexmedetomidine are similar to those observed with its intravenous administration, with the main complications being hypotension and bradycardia. No serious adverse effects of 100 mcg perineural dexmedetomidine were noted in our study. As mentioned before, a larger subset of subjects in the DG received oxygen support *via* face mask which may emphasize the need for diligent monitoring of SpO_2 during the sedative effect, although no significant events of respiratory instability requiring airway establishment were otherwise noted. There was no statistical difference in median oxygen saturation, mean heart rate or MAP all throughout surgery. Our observations are consistent with recent findings of investigators, who reported that hemodynamic changes caused by perineural dexmedetomidine were not found to be dose-dependent and were not severe enough to warrant the use of hemodynamic support (23). Moreover, a systematic review by Barends et al. (25) showed that intravenous dexmedetomidine during procedural sedation has advantages over midazolam in terms of reliability, analgesia and patients' and clinicians' satisfaction while maintaining a similar cardio-respiratory safety profile as well.

Additionally, we found perineural dexmedetomidine to prolong the duration of sensory block by 6.4 h and motor block by 7.1 h. A meta-analysis by Vorobeichik and co-authors revealed a more substantial prolongation of duration of sensory block 7.7–11.5 h and motor block 6.9–10.1 h (17). Apart from the previously known fact that dexmedetomidine prolongs PNB, this discrepancy might be partially explained by the fact that the duration of sensory and motor block was evaluated by the postoperative survey instead of an objective assessment by the clinician.

Limitations

Our study was not conducted in a double-blind manner, therefore, clinician awareness of Dexmedetomidine administration may have influenced some of our results. However, this might be slightly mitigated by the fact that the entire process of ABPB administration and intraoperative monitoring was carried out by a designated team of three experienced anaesthesiologists instead of just a single clinician. Moreover, NI as an objective criterion was used to assess the depth of sedation.

Another limitation is the fact that the duration of sensory and motor block was provided by the subject filling the postoperative survey instead of an objective assessment by the clinician. This might have affected the results, reporting shorter duration of sensory and motor block since the patient might have felt a subjective regain of function while there still might be objective signs of residual blockade.

Since it is our common practice to provide premedication with 7.5 mg of oral midazolam, we should take into consideration the fact, that all patients received premedication, also in DG. Thus, the subsequent sedative effect from perineural dexmedetomidine might be slightly affected by the residual effects of the premedication. We speculate that possible side effects, particulary on hemodynamic function, of perineural 100 mcg dexmedetomidine could be more harmful in patients with pre-existing conditions or advanced age, since only ASA I and II patients were included in our study. Therefore, the dose and indication for dexmedetomidine sedation effect should be individually evaluated.

Despite these limitations, our results indicate that 100 mcg of perineural dexmedetomidine provides rather safe and effective sedation without significantly affecting respiratory or hemodynamic stability. Moreover, with this dose of dexmedetomidine, subjects had no additional requirement for intravenous sedation during surgery. Patients most commonly associate this type of sedation with the sensation of ordinary sleep and express a high level of satisfaction.

In conclusion, we found that perineural administration of 100 mcg of dexmedetomidine in axillary brachial plexus block might provide rather safe systemic sedation with no significant effect on

hemodynamic or respiratory stability and yields a high level of patient satisfaction.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Riga East Clinical University hospital (Approval Number ZD/08-06/01-21/4). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AO, RR, and MA designed and directed the trial. DR and MA performed the trial and collected data. RR performed statistical analysis. AO and RR developed the theoretical framework and wrote the manuscript in consultation with PN and BM. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Network Meta-Analysis of Perioperative Analgesic Effects of Different Interventions on Postoperative Pain After Arthroscopic Shoulder Surgery Based on Randomized Controlled Trials

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Background: Shoulder arthroscopic surgery is a common surgical method used in orthopedics. However, severe postoperative pain can significantly limit the early joint movement of patients and adversely affect the impact of the surgery. At present, there is no consistent and effective analgesic scheme for the management of postoperative pain after arthroscopic surgery of the shoulder.

Purpose: The aim of this study was to search for the most effective analgesic scheme to control pain in the perioperative period of arthroscopic surgery of the shoulder.

Study Design: Network meta-analysis.

Methods: We searched 5 different databases (i.e., Medline, PubMed, Embase, Web of Science, and the Cochrane Library) from January 2011 to January 2021 for English literature. Thereafter, we sifted out randomized controlled trials (RCTs), which compared different intervention schemes for pain management after shoulder arthroscopy and selected only 12 h, 24 h, or 48 h after the patient leaves the operating room as an optimal period for administration of analgesic intervention schemes. Only patients with shoulder disease who have undergone arthroscopic shoulder surgery were included in this study. The Cochrane "risk of bias" was used for the quality assessment. Moreover, some additional tests were performed to enhance the credibility of the results.

Results: Twenty-nine RCTs involving 1,885 patients were included in this frequentist network meta-analysis (NMA). These articles mainly were divided into two distinct groups, namely, the nerve block group and the non-nerve block group. Regarding the nerve block group, at postoperative 12 h, the intervention suprascapular nerve block + interscalene nerve block (SSNB + INB) was ranked first, whereas INB + intra-articular injection (INB + IAI) was ranked first at 24 h and 48 h postoperation. In the non-nerve block group, external application (EA) was ranked first at postoperative 12 h, but oral administration (OA) exhibited a better analgesic effect at postoperative 24 h and postoperative 48 h.

Conclusion: We conclude that the analgesic effect of SSNB+INB was the best at postoperative 12 h, and INB+IAI was the best at postoperative 24 h and 48 h in the nerve block group. For the non-nerve block group, the effect of EA was the best at postoperative 12 h, and the analgesic effect of OA at postoperative 24 h and 48 h was significantly better than any other interventions.

Systematic Review Registration: https://www.crd.york.ac.uk/prospero/, identifier: CRD42021286777.

Keywords: arthroscopic shoulder surgery, postoperative pain, network meta-analysis, randomized controlled trials, pair-wise meta-analysis

INTRODUCTION

Shoulder pain has become a common musculoskeletal disease, in which the rotator cuff gets torn, and a frozen shoulder is commonly observed. Despite the well-documented postoperative pain, a disturbing sensory and emotional experience linked with actual or potential tissue damage can occur, which might develop within the first 48 h (1). Shoulder arthroscopic surgery is one of the most frequently performed surgeries in orthopedics with multitudinous surgical indications, such as rotator cuff tears, instability, and frozen shoulder (2–4). Postoperative pain can significantly limit the early activity of patients, thereby affecting the clinical effect of the operation. Thus, effective pain management after arthroscopic shoulder surgery can allow patients to get discharged earlier, reduce the risk for readmission, and thereby improve the ultimate outcome after surgery (5, 6). Currently, two main measures, i.e., subjective pain scales and quantity of postoperative narcotic consumption, are used to assess the patient pain levels. At present, the pain scales used in the mainstream include the visual analog scale (VAS) and numeric rating scale (NRS), which are both repeatable and reliable, depending on the subjective patient reporting (7, 8).

A number of previous studies have evaluated different kinds of available postoperative pain management strategies after arthroscopic surgery of the shoulder (3, 5, 9, 10). These include oral administration (OA), intra-articular injection (IAI), external application (EA), intravenous administration (IVA), and regional nerve block, which can yield different analgesic conclusions. For instance, Toma et al. (10) recommended that interscalene brachial plexus blockade could be the first-choice regional analgesic technique. Michell Ruiz-Suarez and Barber (5) reported that postoperative pain management should include three distinct stages, namely, preoperative, intraoperative, and postoperative.

Moreover, preemptive analgesia with oral medications can be taken before operation (11), a regional nerve block can be used during operation (12), and an analgesic pump can be used after operation (13). At present, two kinds of analgesia, namely, single analgesia and multimode analgesia are mainly used; however, which analgesic scheme among these two has the best effect remains unclear.

Some traditional systematic reviews have focused on this topic, but they have only included two therapies or did not effectively compare the analgesic efficacy of a combination of the numerous intervention measures due to limitations in the methodology used (3, 14–16). In addition, there are also some meta-analyses that have been examined on this topic. Changjiao et al. (16) and Kay et al. (17) have reported that the analgesic effect of interscalene nerve block (INB) was significantly better than suprascapular nerve block (SSNB), and SSNB can be an

TABLE 1 | Interventions on postoperative pain after arthroscopic shoulder surgery studied in this network meta-analysis.

	Nerve block group	Non-nerve block group
Interventions	SSNB+ANB	IAI
	INB+SSNB	OA
	INB+OA	IVA
	INB+IAI	EA
	INB	-
	CEB	
	SGB	
	CCB	
	ANB	
	SCNB	
	SSNB	
	HTESPB	
	ICSCB	

INB, interscalene nerve block; SCNB, supraclavicular nerve block; SSNB, suprascapular nerve block; HTESPB, high thoracic erector spinae plane block; CEB, cervical epidural block; SGB, stellate ganglion block; ICSCB, infraclavicular-suprascapular blocks; CCB, costoclavicular blocks; ANB, axillary nerve block; IAI, intra-articular injection; OA, oral administration; EA, external application; IVA, intravenous administration.

Abbreviations: INB, interscalene nerve block; SCNB, supraclavicular nerve block; SSNB, suprascapular nerve block; HTESPB, high thoracic erector spine plane block; CEB, cervical epidural block; SGB, stellate ganglion block; ICSCB, infraclavicular-suprascapular block; CCB, costoclavicular block; ANB, axillary nerve block; IAI, intra-articular injection; PL, placebo; OA, oral administration; EA, external application; IVA, intravenous administration; SUCRA; surface under the cumulative ranking curve; VAS, visual analog scale; NRS, numeric rating scale; M ± SD = mean ± standard deviation; MD and 95%CI, mean difference and 95% confidence interval; SMD, standard mean difference; RCT, randomized controlled trial; NMA, network meta-analysis.

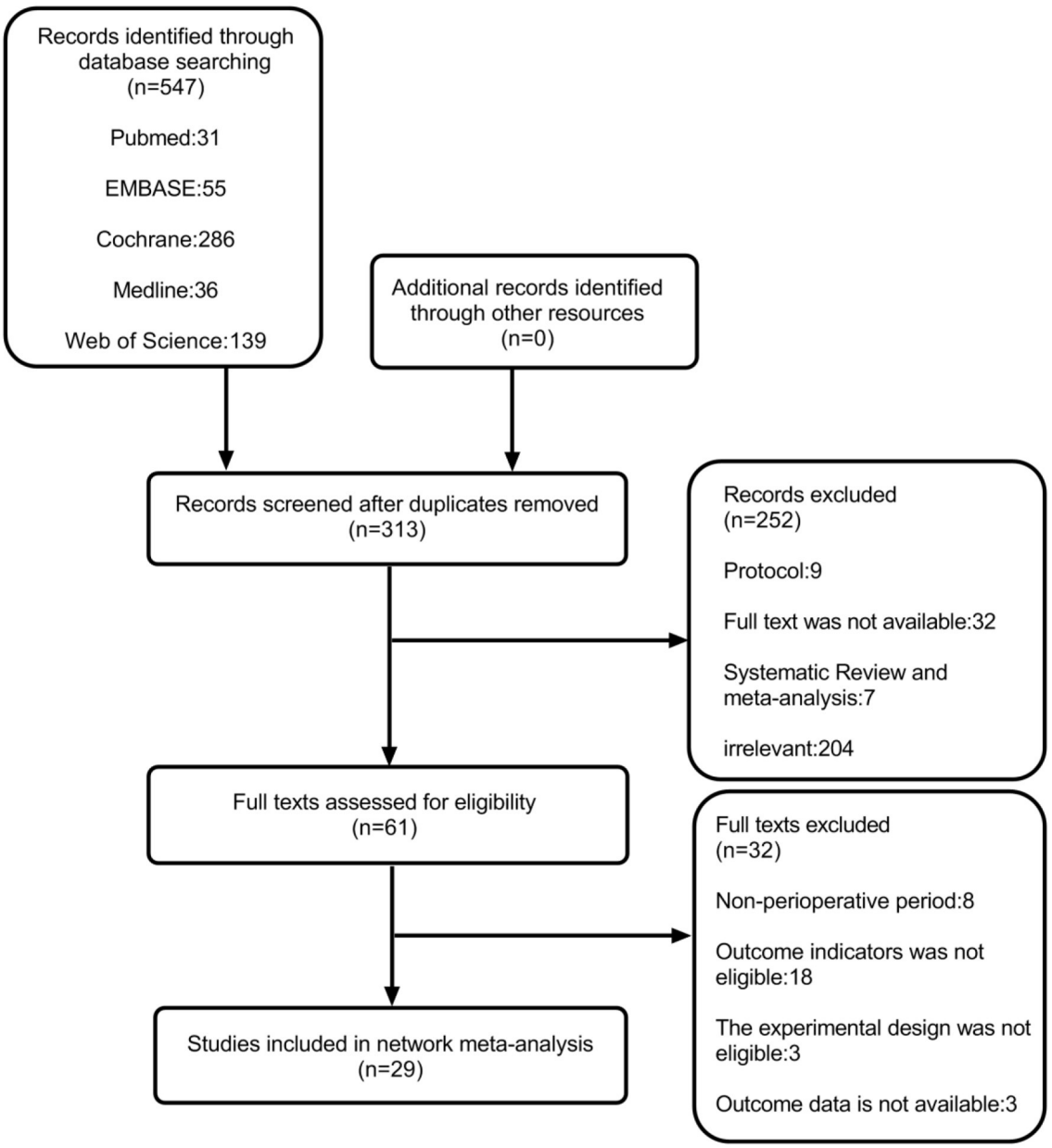

FIGURE 1 | PRISMA flowchart of study selection.

alternative to INB. Ul Huda et al. (15) suggested that preoperative use of gabapentin might effectively reduce the incidence of postoperative nausea and vomiting, whereas White et al. (14) reported that anterior SSNB could display fewer complications than INB. The latter also suggested that anterior SSNB could be more suitable for shoulder arthroscopic surgery in terms of complications. However, there was no accepted and consistent conclusion reached based on all these prior studies. This study aimed to explore the most effective analgesic scheme that can be employed in the perioperative period of shoulder arthroscopy through network meta-analysis (NMA).

METHODS

This NMA was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (18), and our review was registered with PROSPERO (CRD42021286777).

Eligibility Criteria

We included RCTs of patients with shoulder disease for comparing the different interventions used in pain management after shoulder arthroscopy. The selected intervention types

TABLE 2 | Characteristics of the included studies.

Study	Design	Patients	Sample size (T1/T2 or T1/T2/T3)	Age (years, T1/T2 or T1/T2/T3, M ± SD)	Gender (T1/T2 or T1/T2/T3; M/F)	Intervention	Pain score	Outcome time point (post-operative time)
Sowoon et al. (11)	RCT	Arthroscopic shoulder surgery (Bankart or rotator cuff repair)	30/30	55 ± 9/51 ± 12	(13/17)/(13/17)	OA/PL	NRS	24h; 48h
Auyong et al. (33)	RCT	Unilateral shoulder arthroscopic surgery (rotator cuff or Bankart repair)	63/63/63	54 ± 13/53 ± 14/55 ± 14	(38/25)/(39/24)/(42/21)	INB/SCNB	NRS	24h
Bahadir et al. (36)	RCT	Unilateral arthroscopic shoulder surgery	30/30	47.6 ± 13.01/49 ± 10.26	(10/20)/(16/14)	HTESPB/PL	VAS	24h; 48h
Lee et al. (43)	RCT	Arthroscopic rotator cuff repair (rotator cuff tear)	24/24	57.4 ± 9.6 /57.3 ± 12.0	(12/12)/(8/16)	INB+SSNB/SSNB	VAS	12h; 24h; 48h
Lee et al. (12)	RCT	Arthroscopic rotator cuff repair (rotator cuff tear)	15/15	48.9 ± 11.7/51.6 ± 10.6	(11/4)/(10/5)	SSNB/PL	VAS	12h; 24h
Merivirta et al. (19)	RCT	Arthroscopic surgery (reparable rotator cuff tear)	30/30	52 ± 9/54 ± 9	(11/19)/(14/16)	EA/IAI	NRS	12h; 24h; 48h
Merivirta et al. (20)	RCT	Arthroscopic surgery (subacromial impingement disease)	39/43	53 ± 9/55 ± 6	(24/15)/(34/9)	IAI/PL	NRS	12h; 24h
Anneleen et al. (45)	RCT	Elective arthroscopic shoulder surgery	50/48	54 ± 10/51 ± 10	(28/22)/(18/30)	INB/SSNB+ANB	NRS	24h
Park et al. (47)	RCT	Arthroscopic shoulder operations	19/19/19	52 ± 13/53 ± 9/54 ± 7	not mentioned	INB/IAI	NRS	24h; 48h
Sethi et al. (49)	RCT	Arthroscopic rotator cuff repair surgery	25/25	not mentioned	not mentioned	INB+IAI/INB	VAS	24h; 48h
Thompson et al. (50)	RCT	Arthroscopic Bankart repair	40/40	29.9 ± 10.1/32.6 ± 10.8	(27/13)/(25/15)	INB+OA/INB	VAS	24h
Verdecchia (51)	RCT	Arthroscopic rotator cuff repair	42/42	58.2 ± 7.2/56.2 ± 7.8	(15/27)/(15/27)	INB+IAI/INB	NRS	24h; 48h
Woo (53)	RCT	Arthroscopic shoulder operations	20/20	42.85 ± 18.97/49.65 ± 14.11	(15/5)/(12/8)	INB+IVA/INB	NRS	12h; 24h; 48h
Aksu et al. (30)	RCT	Arthroscopic shoulder surgery	20/20/20	45.1 ± 15.5/44.2 ± 15.9/43.4 ± 13.5	(13/7)/(12/8)/(13/7)	INB/IAI	VAS	12h; 24h
Choi et al. (35)	RCT	Arthroscopic rotator cuff repair	20/20	47.3 ± 13.3/49.1 ± 11.1	(11/9)/(10/10)	SGB/PL	VAS	12h; 24h; 48h
Jeske et al. (40)	RCT	Arthroscopic subacromial decompression	15/15	59.1 ± 6.1/63.6 ± 9.0	(9/6)/(8/7)	SSNB/PL	VAS	24h; 48h
Lee et al. (42)	RCT	Arthroscopic rotator cuff repairs(rotator cuff tears)	21/21	54.0 ± 8.0/55.8 ± 8.0	(14/7)/(14/7)	SSNB+ANB/SSNB	VAS	12h; 24h; 48h
Liu et al. (44)	RCT	Arthroscopic rotator cuff repair(rotator cuff tear)	31/31	59.74 ± 5.85/56.77 ± 7.29	(17/14)/(15/16)	INB/PL	VAS	12h; 24h; 48h
Derya OZKAN (2020)	RCT	Arthroscopic shoulder surgery	22/21	58.5 ± 7.9/53.7 ± 16.5	(7/15)/(10/11)	SSNB+ANB/IAI	NRS	12h; 24h
Tuba Berra Saritas et al. (48)	RCT	Arthroscopic rotator cuff repair	30/30	39.8 ± 9.2/41.6 ± 10.4	(17/13)/(14/16)	IAI/PL	VAS	12h; 24h
Julian Aliste et al. (32)	RCT	Arthroscopic shoulder surgery	20/20	50.6 ± 8.0/57.9 ± 9.3	(11/9)/(9/11)	INB/ICSCB	NRS	12h; 24h
Aliste (32)	RCT	Arthroscopic shoulder surgery	20/20	54.72 ± 12.1/53.5 ± 10.4	(10/12)/(8/14)	INB/CCB	VAS	12h

(Continued)

TABLE 2 | Continued

Study	Design	Patients	Sample size (T1/T2 or T1/T2/T3)	Age (years, T1/T2 or T1/T2/T3, M ± SD)	Gender (T1/T2 or T1/T2/T3; M/F)	Intervention	Pain score	Outcome time point (post-operative time)
Cabaton et al. (34)	RCT	Arthroscopic rotator cuff repair	52/51	57.67 ± 10.67/59 ± 8.38	(32/20)/(27/24)	SCNB/INB	NRS	24h; 48h
Dhir et al. (38)	RCT	Arthroscopic shoulder surgery	30/29	51.3 ± 14.2/46.5 ± 14.5	(26/4)/(22/7)	INB/SSNB+ANB	NRS	24h
Gurger et al. (39)	RCT	Arthroscopic rotator cuff repair	43/42	58.47 ± 7.18/58.21 ± 7.67	(18/25)/(20/22)	PL/INB	VAS	12h; 24h
Kumara et al. (41)	RCT	Arthroscopic shoulder surgeries	30/30	not mentioned	not mentioned	INB/SSNB	VAS	24h
Rothe et al. (25)	RCT	Arthroscopic subacrimial decompression	27/23	53 ± 10.5/54 ± 10.5	(11/16)/(11/12)	ANB/PL	VAS	24h
Wiesmann et al. (52)	RCT	Arthroscopic shoulder surgery	56/58	53.0 ± 13/52.7 ± 13	(34/22)/(34/24)	SCNB/INB	NRS	24h
Demir (37)	RCT	Arthroscopic shoulder surgery	30/30	48.03 ± 11.79/46.73 ± 12.50	(14/16)/(18/12)	INB/INB+IVA	VAS	12h; 24h; 48h

INB, interscalene nerve block; SCNB, supraclavicular nerve block; SSNB, suprascapular nerve block; HTESPB, high thoracic erector spinae plane block; CEB, cervical epidural block; SGB, stellate ganglion block; ICSCB, infraclavicular-suprascapular blocks; CCB, costoclavicular blocks; ANB, axillary nerve block; IAI, intra-articular injection; OA, oral administration; EA, external application; IVA, intravenous administration; VAS, visual analog scale; NRS, numeric rating scale; M ± SD, mean ± standard deviation; RCT, randomized controlled trial; PL, placebo.

included the following: eight regional nerve blocks, IAI, IVA, OA, and EA. Regional nerve block included INB, SSNB, axillary nerve block (ANB), supraclavicular nerve block (SCNB), stellate ganglion block (SGB), infraclavicular-suprascapular block (ICSCB), and costoclavicular block (CCB). In addition to the analgesic methods of high thoracic erector spine plane block (HTESPB), CEBs have been found to be similar to regional nerve block methods, and therefore, they were also classified as the regional nerve block group. IAIs of narcotic drugs, such as bupivacaine, magnesium sulfate, and liposomal bupivacaine, were also considered. It has been established that the subacromial injection anesthetics can communicate with the joint during surgery; therefore, we also attributed subacromial injection to IAIs, such as Merivirta et al. (19, 20). IVA included intravenous ketoprofen and intravenous ketamine, oral drugs included oral ibuprofen or pregabalin, EA included fentanyl patch, and some interventions were a combination of the above. Refer to **Table 1** for the intervention groups in detail, and we have classified all the interventions into two distinct types, including the nerve block group with nerve block during the surgery and the non-nerve block group without nerve block in one surgery.

The inclusion criteria consisted of the following:

Patient

Those who have been diagnosed with shoulder joint diseases, such as rotator cuff tears, instability, and frozen shoulder, and underwent shoulder arthroscopic surgery, regardless of age, sex, course of the disease, underlying diseases, and other differences among the various groups in the same study.

Experimental Design

It consisted of the comparison of the two intervention measures (**Table 1**).

Outcome Measures

The determination of VAS or the NRS at postoperative 12 h, 24 h, and 48 h.

Study Design

RCTs that have reported different intervention measures in the management of postoperative pain.

Systematic Search

We extensively searched English articles in Medline, PubMed, Embase, Web of Science, and the Cochrane library using the following keywords: arthroscopic shoulder surgery, postoperative pain, pain, therapeutics, and randomized controlled trial (RCT). The search was carried out by using the combination of the keywords above and their free words, and all databases were set from January 2011 to January 2021.

Study Selection

We (W.J.P. and D.Z.B.) assessed the credibility of these potential articles with the above criteria and resolved the differences after consulting and discussing with the senior author (N.M.). Finally, useful data were extracted independently and reviewed by the senior author.

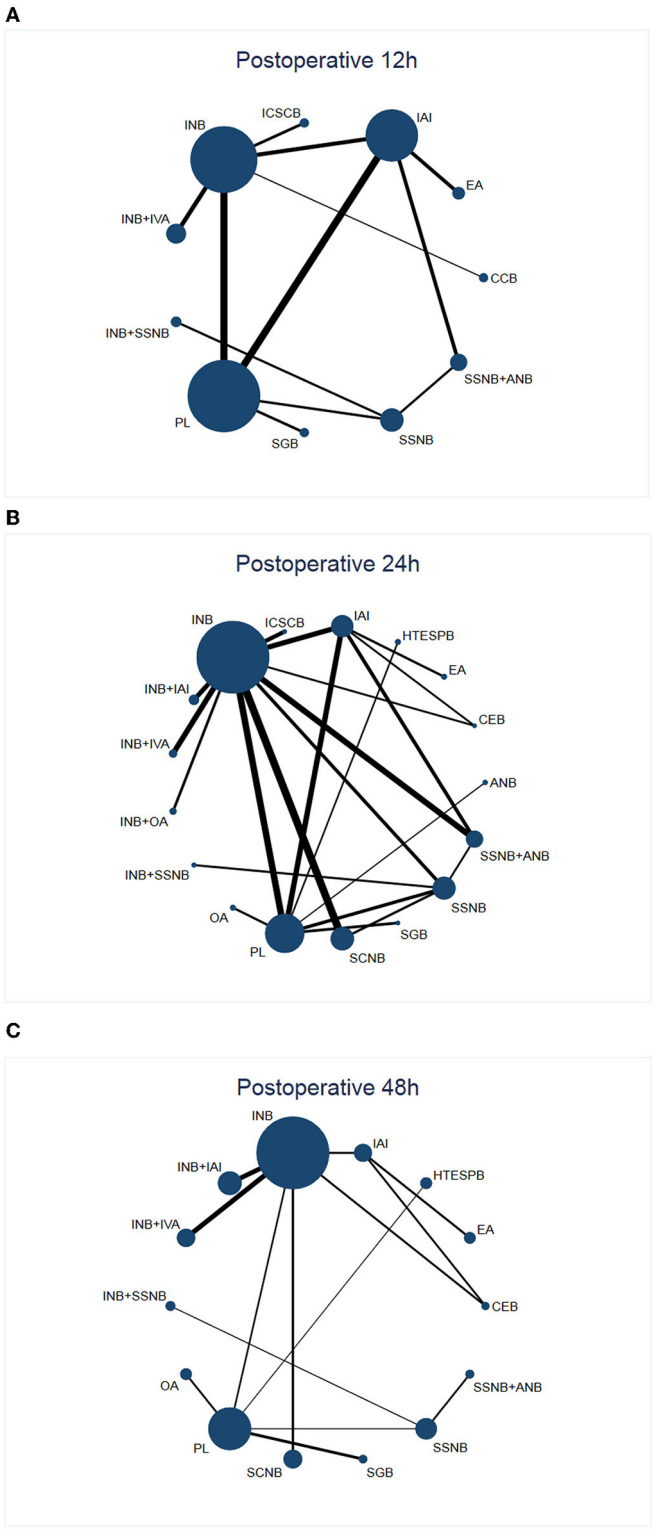

FIGURE 2 | Network plot of treatment comparisons. **(A)** (Network 1) Network plot of treatment comparisons for postoperative 12 h. The size of the blue area indicates the sample size of each group, and the thickness indicates the results of comparisons between two groups. **(B)** (Network 2) Network plot of treatment comparisons for postoperative 24 h. The size of the blue area indicates the sample size of each group, and the thickness indicates the results of comparisons between two groups. **(C)** (Network 3) Network plot of treatment comparisons for postoperative 48 h. The size of the blue area indicates the sample size of each group, and the thickness indicates the results of comparisons between two groups. INB, interscalene nerve block; SSNB, suprascapular nerve block; SCNB, supraclavicular nerve block; ICSCB, infraclavicular-suprascapular blocks; CCB, costoclavicular blocks; ANB, axillary nerve block; IAI, intra-articular injection; EA, external application; IVA, intravenous administration; SGB, stellate ganglion block; PL, placebo; HTESPB, high thoracic erector spinae plane block; CEB, cervical epidural block; ANB, axillary nerve block; OA, oral administration.

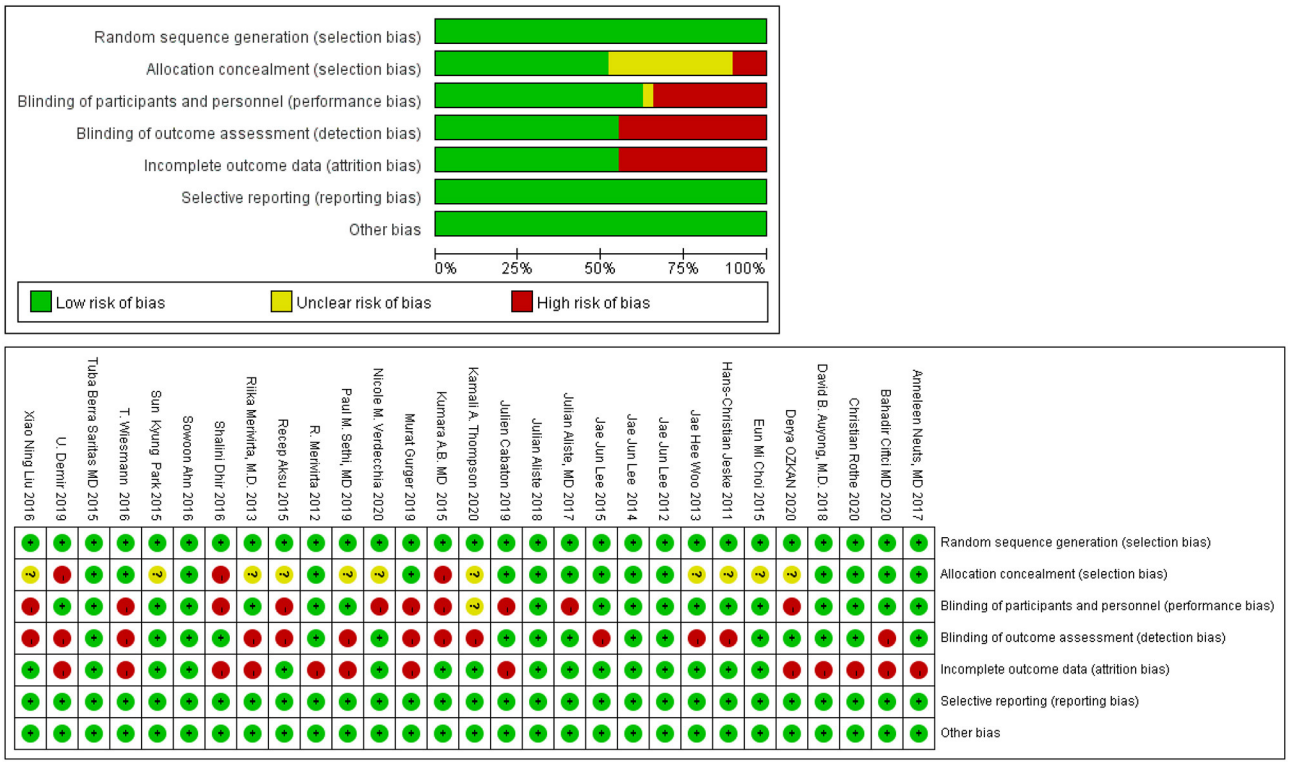

FIGURE 3 | Quality assessment.

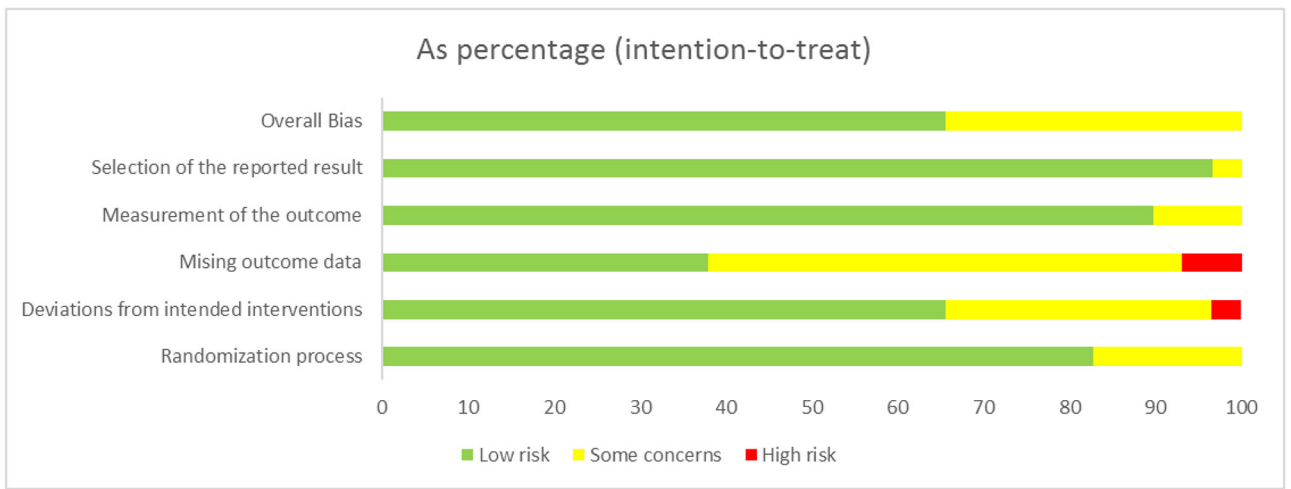

FIGURE 4 | Quality assessment (ROB2.0).

Data Extraction

The extracted data included publication time, author, article and intervention type, the characteristics of the subjects, mean patient age, the ratio of the male to female, the number of patients in each arm, male percentage, outcome representation method, and time point of outcome index. The outcome index selected by us was the value of postoperative pain score, which was divided into three distinct groups, namely, postoperative 12 h, postoperative 24 h, and postoperative 48 h, according to the time point of the outcome, and the outcome was expressed as mean ± standard difference (M ± SD). Both VAS and NRS were scored 0–10, so it was deemed appropriate to include them in the same meta-analysis (15).

TABLE 3 | Quality assessment (ROB2.0).

Intention–to–treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	Sowoon et al. (11)	NA	NA	NA	NA	1	+	+	+	+	+	+
	Auyong et al. (33)	NA	NA	NA	NA	1	+	+	!	+	+	+
	Bahadir et al. (36)	NA	NA	NA	NA	1	+	+	!	+	+	+
	Lee et al. (43)	NA	NA	NA	NA	1	+	+	+	+	+	+
	Lee et al. (12)	NA	NA	NA	NA	1	+	+	+	+	+	+
	Merivirta et al. (19)	NA	NA	NA	NA	1	+	!	!	+	+	!
	Merivirta et al. (20)	NA	NA	NA	NA	1	+	+	!	+	+	!
	Anneleen et al. (45)	NA	NA	NA	NA	1	+	+	!	+	+	+
	Park et al. (47)	NA	NA	NA	NA	1	!	!	+	+	+	!
	Sethi et al. (49)	NA	NA	NA	NA	1	!	!	-	!	+	!
	Thompson et al. (50)	NA	NA	NA	NA	1	+	+	!	!	+	+
	Verdecchia (51)	NA	NA	NA	NA	1	+	!	!	+	+	!
	Woo (53)	NA	NA	NA	NA	1	+	!	!	+	+	+
	Aksu et al. (30)	NA	NA	NA	NA	1	+	!	!	+	+	+
	Choi et al. (35)	NA	NA	NA	NA	1	+	!	-	!	!	!
	Jeske et al. (40)	NA	NA	NA	NA	1	+	+	+	+	+	+
	Lee et al. (42)	NA	NA	NA	NA	1	+	+	!	+	+	+
	Liu et al. (44)	NA	NA	NA	NA	1	!	+	+	+	+	+
	Özkan et al. (46)	NA	NA	NA	NA	1	+	+	!	+	+	+
	Tuba Berra Saritas et al. (48)	NA	NA	NA	NA	1	+	+	+	+	+	+
	Julian Aliste et al. (32)	NA	NA	NA	NA	1	+	+	+	+	+	+
	Aliste (32)	NA	NA	NA	NA	1	+	+	+	+	+	+

(Continued)

TABLE 3 | Continued

Intention–to–treat	Unique ID	Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
	Cabaton et al. (34)	NA	NA	NA	NA	1	+	+	+	−	+	−
	Dhir et al. (38)	NA	NA	NA	NA	1	−	−	−	+	+	−
	Gurger et al. (39)	NA	NA	NA	NA	1	+	−	−	+	+	+
	Kumara et al. (41)	NA	NA	NA	NA	1	−	!	−	+	+	−
	Rothe et al. (25)	NA	NA	NA	NA	1	+	+	−	+	+	−
	Wiesmann et al. (52)	NA	NA	NA	NA	1	+	+	−	+	+	+
	Demir (37)	NA	NA	NA	NA	1	+	+	+	+	+	+

+ *Low risk,* − *Some concerns,* ! *High risk. D1 Randomisation process, D2 Randomisation process, D3 Missing outcome data, D4 Measurement of the outcome, D5 Selection of the reported result.*

Quality Assessment

The Cochrane "risk of bias" tool was used to evaluate the methodological quality of the selected articles (21).

Statistical Analysis

Pooling the different instruments that report on a common domain typically is conducted by converting each instrument to SD units and combining their effects across the studies as the standardized mean difference (SMD). However, this approach has major limitations, including difficulties in interpretation and vulnerability to the baseline heterogeneity of enrolled patients (22, 23). Therefore, by using the linear transformation and assuming that instruments reporting on the shared domains might have similar measurement properties, we converted all the measures of pain intensity and physical functioning to 10-cm VASs (24), such as Rothe et al. (25).

Initially, we performed a conventional pairwise meta-analysis by using a DerSimonian–Laird random-effects model and then conducted a frequentist NMA by using the methodology of the multivariate meta-analysis by assuming a common heterogeneity parameter (26), using the mv-meta command and the network suite in Stata (SE 15.1) (27). The results were expressed by mean difference (MD) and 95% CI.

In addition, the ranking probabilities for all the different protocols were calculated, and the results were reported as the (surface under the cumulative ranking curve) (28): 100% meant the best treatment, whereas 0% meant the worst treatment. We ranked the analgesic effects of the various intervention measures, after combining them with the outcomes of the NMA.

Inconsistency Analysis

We calculated the inconsistency between the direct and indirect evidence at home and abroad by evaluating the potential differences in all the closed loops of the network and by comparing the suitability and conciseness of consistency and inconsistency of the models (27), which was assessed using the node-splitting method (29).

Additional Analysis

Publication bias was analyzed by using Egger's test. We screened the studies with a sample size of <40 patients in order to conduct the sensitivity analyses and calculated the rank probabilities again. The results were considered reliable in case of the insignificant difference between the latter and the former outcomes. A comparison-adjusted funnel plot was then plotted to evaluate the risk of bias as an asymmetric plot can only indicate a small study effect (28).

RESULTS

Eligible Studies

After a systematic search, 547 records were found, among which we included only 29 reports that were published between 2011 and 2021 (**Figure 1**) (11, 12, 19, 20, 25, 30–53). Among these 29 articles, the average number of patients per article was 65 (range, 30–114), and the average age varied from 29 to 63 years. Generally

TABLE 4 | Quality of evidence according to the GRADE criteria.

Outcomes	No. of studies	Characteristics of the included studies					Overall GRADE quality score
		Risk of bias	Inconsistency[a]	Indirectness	Imprecision	Publication bias	
VAS at postoperative 12h	15	Not serious	Not serious	Not serious	serious	None	⊕⊕⊕O Moderate
VAS at postoperative 24h	28	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕ Advanced
VAS at postoperative 48h	14	Serious	Not serious	Not serious	Not serious	None	⊕⊕⊕O Moderate

VAS, Visual Analog Scale Score. [a]Indicates studies differed in the age of participants and in the detailed postoperative interventions.

TABLE 5 | Results of treatment comparisons for postoperative 24 h.

A				*N* = 1;0.00 (−0.62; 0.62)						
0.45 (0.04;5.05)	B	*N* = 1;0.05 (−0.46; 0.56)								
0.52 (0.11;2.51)	1.16 (0.18;7.33)	C		*N* = 1;0.00 (−0.88; 0.88)			*N* = 3;−0.39 (−0.71; −0.08)			*N* = 1;−0.79 (−1.41; −0.17)
1.29 (0.18;9.26)	2.87 (0.20;40.92)	2.47 (0.36;16.78)	D	*N* = 1;0.13 (−0.49; 0.75)						
1.00 (0.31;3.20)	2.24 (0.27;18.73)	1.92 (0.67;5.56)	0.78 (0.16;3.84)	E	*N* = 2;−0.08 (−1.20; 1.05)		*N* = 3;−0.94 (−1.49; −0.39)			
1.23 (0.27;5.68)	2.74 (0.26;28.49)	2.36 (0.56;10.00)	0.96 (0.15;6.26)	1.23 (0.45;3.32)	F					
5.42 (0.51;58.14)	12.09 (0.81;181.01)	10.41 (1.43;75.58)	4.21 (0.31;57.43)	5.41 (0.68;42.83)	4.41 (0.45;43.54)	G			*N* = 1;−1.34(−1.97;−0.71)	
0.30 (0.08;1.23)	0.68 (0.09;5.01)	0.58 (0.27;1.27)	0.24 (0.04;1.40)	0.30 (0.14;0.66)	0.25 (0.07;0.87)	0.06 (0.01;0.38)	H	*N* = 1;0.58 (−0.06; 1.21)	*N* = 1;−0.21 (−0.92; 0.51)	
0.11 (0.01;0.87)	0.24 (0.02;3.00)	0.21 (0.04;1.16)	0.08 (0.01;0.88)	0.11 (0.02;0.61)	0.09 (0.01;0.64)	0.02 (0.00;0.23)	0.36 (0.08;1.65)	I		
0.54 (0.08;3.60)	1.21 (0.12;12.04)	1.04 (0.27;4.11)	0.42 (0.05;3.75)	0.54 (0.12;2.41)	0.44 (0.07;2.64)	0.10 (0.02;0.42)	1.79 (0.50;6.40)	5.00 (0.68;36.72)	J	*N* = 1;−0.81 (−1.44; −0.18)
2.59 (0.35;19.48)	5.79 (0.56;59.49)	4.98 (1.19;20.77)	2.02 (0.20;19.98)	2.59 (0.50;13.46)	2.11 (0.31;14.32)	0.48 (0.07;3.21)	8.52 (1.98;36.69)	23.86 (2.88;197.92)	4.77 (1.36;16.69)	K

1. Lower–left triangle presents the findings (MD with 95%CI) of the network meta–analysis conducted using Stata 15.1. Upper–right triangle presents the findings (SMD with 95% CI) of the pair–wise meta–analyses conducted using STATA 15.1 and N refers to the numbers of RCTs which compared the 2 interventions directly. 3. A positive MD favors the lower–right intervention; a negative MD favors the upper–left intervention.4. Statistically significant findings are shaded. A, ANB (axillary nerve block); B, CEB (cervical epidural block); C, EA (external application); D, HTESPB (high thoracic erector spinae plane block); E, IAI (intra–articular injection); F, ICSCB (infraclavicular–suprascapular blocks); G, INB (interscalene nerve block); H, INB+IAI (interscalene nerve block + intra–articular injection); I, INB+IVA (interscalene nerve block + intravenous administration); J, INB+OA (interscalene nerve block + oral administration); K, INB+SSNB (interscalene nerve block + suprascapular nerve block); L, OA (oral administration); M, PL (placebo); N, SCNB (supraclavicular nerve block); O= SGB (stellate ganglion block); P, SSNB (suprascapular nerve block); Q, SSNB+ANB (suprascapular nerve block + axillary nerve block).
Red represents the code of intervention measures and green represents the significant difference between two intervention measures with statistical significance.

speaking, we included 1,885 patients, and in **Table 2**, we have summarized the key details of each article. Of these 29 articles, 12 articles used the NRS 0–10 score scale, 16 articles used the VAS 0–10 score scale, and 1 article used NRS 0–100 score scale (25). The results of 15 articles described the pain scores at postoperative 12 h, 28 articles included scores at postoperative 24 h, and 14 articles included scores at 48 h after the surgery (**Figure 2**). The network for eligible comparisons of the three different groups is presented in **Figure 2**.

Quality Assessment

We found that no study was highly risky for the random sequence generation and selective reporting after being assessed for the quality. A total of 52% were considered to have a low risk for allocation concealment, whereas 45% of the studies had a high risk for incomplete results, and none of the studies displayed a high risk for selective reporting. A total of 62% of the literature implemented blind methods for experimenters and subjects, 55% of the recorders were blind, and among them, 38% of the articles

TABLE 6 | Results of treatment comparisons for postoperative 24 h.

A											*N* = 1;−1.17 (−1.78; −0.57)				
2.74 (0.49;15.36)	B			*N* = 1;−2.23 (−3.36; −1.09)		*N* = 1;1.42 (0.40; 2.44)									
0.65 (0.09;4.71)	0.24 (0.04;1.58)	C		*N* = 1;−0.16 (−0.67; 0.35)											
1.06 (0.19;5.94)	0.39 (0.06;2.31)	1.62 (0.21;12.36)	D								*N* = 1;−0.80 (−1.33; −0.27)				
0.47 (0.12;1.80)	0.17 (0.05;0.58)	0.73 (0.17;3.12)	0.45 (0.11;1.85)	E		*N* = 2;−0.44 (−1.09; 0.20)					*N* = 3;−0.40 (−0.71; −0.09)				*N* = 1;−0.15 (−0.75; 0.45)
1.03 (0.09;11.65)	0.38 (0.04;4.04)	1.58 (0.12;21.38)	0.98 (0.08;11.56)	2.17 (0.25;18.84)	F	*N* = 1;−0.24 (−0.86; 0.38)									
0.53 (0.14;1.96)	0.19 (0.06;0.65)	0.81 (0.16;4.09)	0.50 (0.12;2.02)	1.11 (0.55;2.26)	0.51 (0.07;3.93)	G	*N* = 2;−1.05 (−2.82; 0.73)	*N* = 2;−0.43 (−1.16; 0.31)	*N* = 1;0.16 (−0.28; 0.60)		*N* = 3;−0.42 (−1.24; 0.39)	*N* = 3;0.17 (−0.07; 0.40)		*N* = 2;−0.03 (−0.38; 0.33)	*N* = 2;−0.44 (−0.98; 0.11)
3.48 (0.66;18.36)	1.27 (0.26;6.20)	5.34 (0.79;36.25)	3.30 (0.58;18.58)	7.35 (2.12;25.46)	3.38 (0.35;33.00)	6.60 (2.39;18.25)	H								
1.27 (0.23;7.03)	0.46 (0.09;2.38)	1.95 (0.28;13.79)	1.21 (0.20;7.10)	2.69 (0.73;9.89)	1.24 (0.12;12.48)	2.42 (0.81;7.18)	0.37 (0.08;1.62)	I							
0.35 (0.05;2.68)	0.13 (0.02;0.92)	0.54 (0.06;5.08)	0.33 (0.04;2.68)	0.75 (0.14;4.08)	0.34 (0.03;4.43)	0.67 (0.14;3.14)	0.10 (0.02;0.64)	0.28 (0.04;1.83)	J						
1.32 (0.19;9.20)	0.48 (0.07;3.31)	2.03 (0.23;17.94)	1.25 (0.17;9.23)	2.79 (0.55;14.12)	1.28 (0.10;16.46)	2.51 (0.54;11.63)	0.38 (0.06;2.40)	1.04 (0.16;6.83)	3.74 (0.42;32.95)	K				*N* = 1;−0.62 (−1.20; −0.04)	
5.78 (0.91;36.61)	2.11 (0.31;14.16)	8.86 (1.05;74.93)	5.47 (0.81;36.80)	12.20 (2.57;58.03)	5.61 (0.44;72.36)	10.97 (2.35;51.27)	1.66 (0.26;10.55)	4.54 (0.69;30.03)	16.36 (1.85;144.95)	4.38 (0.53;35.80)	L	*N* = 1;−1.49 (−2.06; −0.91)			
0.35 (0.11;1.14)	0.13 (0.04;0.45)	0.54 (0.11;2.64)	0.33 (0.09;1.18)	0.74 (0.39;1.40)	0.34 (0.04;2.85)	0.67 (0.37;1.21)	0.10 (0.03;0.33)	0.28 (0.08;0.96)	0.99 (0.19;5.19)	0.27 (0.06;1.25)	0.06 (0.01;0.25)	M	*N* = 1;0.11 (−0.51; 0.73)	*N* = 2;−0.13 (−0.63; 0.38)	
0.33 (0.07;1.53)	0.12 (0.03;0.52)	0.51 (0.08;3.10)	0.31 (0.06;1.56)	0.70 (0.24;2.04)	0.32 (0.04;2.91)	0.63 (0.27;1.44)	0.09 (0.03;0.35)	0.26 (0.07;1.02)	0.94 (0.16;5.40)	0.25 (0.05;1.36)	0.06 (0.01;0.32)	0.94 (0.35;2.53)	N		*N* = 1;0.30 (−0.20; 0.79)
0.28 (0.04;2.02)	0.10 (0.01;0.78)	0.44 (0.05;4.08)	0.27 (0.04;2.03)	0.60 (0.11;3.27)	0.28 (0.02;3.88)	0.54 (0.10;2.89)	0.08 (0.01;0.58)	0.22 (0.03;1.66)	0.81 (0.08;7.88)	0.22 (0.02;1.95)	0.05 (0.01;0.41)	0.81 (0.17;3.90)	0.86 (0.13;5.51)	O	

(Continued)

TABLE 6 | Continued

0.49 (0.13;1.88)	0.18 (0.05;0.67)	0.75 (0.14;3.99)	0.46 (0.11;1.93)	1.03 (0.45;2.35)	0.47 (0.06;4.00)	0.92 (0.49;1.75)	0.14 (0.04;0.47)	0.38 (0.11;1.36)	1.38 (0.26;7.32)	0.37 (0.09;1.48)	0.08 (0.02;0.41)	1.38 (0.71;2.70)	1.47 (0.56;3.87)	1.71 (0.31;9.40)	P	*N* = 1;−0.52 (−1.13; 0.10)
1.12 (0.25;4.99)	0.41 (0.10;1.70)	1.72 (0.30;9.89)	1.06 (0.22;5.09)	2.37 (0.91;6.21)	1.09 (0.12;9.85)	2.13 (0.93;4.87)	0.32 (0.09;1.20)	0.88 (0.22;3.48)	3.18 (0.55;18.31)	0.85 (0.16;4.42)	0.19 (0.04;1.06)	3.20 (1.27;8.02)	3.40 (1.08;10.67)	3.94 (0.64;24.31)	2.31 (0.96;5.57)	Q

1. Lower–left triangle presents the findings (MD with 95%CI) of the network meta–analysis conducted using Stata 15.1. Upper–right triangle presents the findings (SMD with 95% CI) of the pair–wise meta–analyses conducted using STATA 15.1 and N refers to the numbers of RCTs which compared the 2 interventions directly. 3. A positive MD favors the lower–right intervention; a negative MD favors the upper–left intervention. 4. Statistically significant findings are shaded. A, CEB (cervical epidural block); B, EA (external application); C, HTESPB (high thoracic erector spinae plane block); D, IAI (intra–articular injection); E, INB (interscalene nerve block); F, INB+IAI (interscalene nerve block + intra–articular injection); G, INB+IVA (interscalene nerve block + intravenous administration); H, INB+SSNB (interscalene nerve block + suprascapular nerve block); I, OA (oral administration); J, PL (placebo); K, SCNB (supraclavicular nerve block); L, SGB (stellate ganglion block); M, SSNB (suprascapular nerve block); N, SSNB+ANB (suprascapular nerve block + axillary nerve block).

Red represents the code of intervention measures and green represents the significant difference between two intervention measures with statistical significance.

applied the blind method for all the participants. The detailed results are shown in **Figure 3**. We also used the ROB2.0 risk assessment tool to assess the quality of incorporated references, the detailed results are shown in **Figure 4** and **Table 3**. Finally, we used GRADE criteria to assess the quality of evidence (**Table 4**).

Pair-Wise Meta-Analysis

We entered all the data that were suitable for the traditional pairwise meta-analysis into STATA 15.1, developed random-effects models, and then evaluated the SMDs and 95% CIs.

All the data, which were suitable for the conventional pairwise meta-analysis, were entered into STATA 15.1, and then the random-effects models were developed. Thereafter, the SMDs and 95% CIs were evaluated. In the postoperative 12 h group, 17 pairs of pain score comparisons were performed among which 9 had 95% CIs beyond the null value, thus suggesting significant differences, as follows: 1 pair of INB + SSNB vs. SSNB (SMD −1.34, 95% CI −1.97 to −0.71), 3 pairs of IAI vs. placebo (PL) (SMD −0.39, 95% CI −0.71 to −0.08), 3 pairs of INB vs. PL (SMD −0.94, 95% CI −1.49 to −0.39), 1 pair of SSNB+ANB vs. SSNB (SMD −0.81, 95% CI −1.44 to −0.18), and 1 pair of SSNB+ANB vs. IAI (SMD −0.79, 95% CI −1.41 to −0.17). The differences in the remaining 8 comparisons were considered insignificant. Regarding the postoperative 24 h group, 34 pairs of pain score comparisons were performed while 9 of which had 95% CIs beyond the null value, thus suggesting significant differences, as follows: 1 pair of OA vs. PL (SMD −1.49, 95% CI −2.06 to −0.91), 1 pair of HTESPB vs.PL (SMD −0.80, 95% CI −1.33 to −0.27), 1 pair of INB + SSNB vs. SSNB (SMD −0.62, 95% CI 0.40 to 2.44), 3 pairs of IAI vs.PL (SMD −0.40, 95% CI −0.71 to −0.09), 1 pair of CEB to IAI (SMD −2.23, 95% CI −3.36 to −1.09), 1 pair of INB vs. CEB (SMD 1.42,95% CI 0.40 to 2.44), and 1 pair of ANB vs. PL (SMD −1.17, 95% CI −1.78 to −0.57). We found no significant differences in the remaining 25 comparisons. Regarding the postoperative 48 h group, 16 pairs of pain score comparisons were performed among which 7 had 95% CIs beyond the null value, thus suggesting significant differences, as follows: 1 pair of OA vs. PL (SMD −0.94, 95% CI −1.47 to −0.40), 1 pair of HTESPB vs. PL (SMD −0.80, 95% CI −1.32 to −0.27), 1 pair of INB + SSNB vs. SSNB (SMD −0.93, 95% CI −1.53 to −0.33), 1 pair of INB vs. IAI (SMD −1.88, 95% CI −2.98 to −0.78), 1 pair of CEB vs. IAI (SMD −2.27, 95% CI −3.45 to −1.09), and 2 pairs of INB + IAI vs. INB (SMD −0.64, 95% CI −0.98 to −0.29). We found no significant differences in the remaining 9 comparisons. We have shown the results in the upper triangle of **Tables 5**–**7**, and the significant differences have been shaded.

Network Meta–Analysis

All the differences of the possible comparisons were evaluated, and the results as the MDs and 95% CIs were obtained, which have been listed in the lower triangle of **Tables 5**–**7** with the various significant differences being shaded.

Regarding the postoperative 12 h group, among the significant results, INB + SSNB vs. SSNB, INB vs. PL, SSNB + ANB vs. SSNB, and SSNB + ANB vs. IAI exhibited similar results to those

TABLE 7 | Results of treatment comparisons for postoperative 48 h.

A		*N* = 1,−2.27 (−3.45;−1.09)	*N* = 1,0.38 (−0.55;1.31)									
0.12 (0.02,0.77)	B		*N* = 1,0.00 (−0.51;0.51)									
0.80 (0.10,6.17)	6.51 (0.57,74.22)	C							*N* = 1,−0.80 (−1.32; −0.27)			
0.12 (0.03,0.44)	1.00 (0.27,3.77)	0.15 (0.02,1.18)	D	*N* = 1,−1.88 (−2.98; −0.78)								
0.71 (0.19,2.57)	5.76 (0.91,36.43)	0.88 (0.18,4.34)	5.76 (1.60,20.74)	E	*N* = 2,−0.64 (−0.98; −0.29)	*N* = 2,−0.53 (−1.58;0.53)			*N* = 1–0.34 (−0.84;0.16)	*N* = 1,−0.34 (−0.84;0.16)		
2.73 (0.54,13.80)	22.28 (2.76,179.75)	3.42 (0.53,22.14)	22.29 (4.45,111.72)	3.87 (1.45,10.29)	F							
1.81 (0.34,9.70)	14.72 (1.74,124.72)	2.26 (0.33,15.48)	14.73 (2.76,78.59)	2.56 (0.87,7.52)	0.66 (0.15,2.83)	G						
0.80 (0.08,8.00)	6.51 (0.46,92.69)	1.00 (0.16,6.17)	6.52 (0.65,64.99)	1.13 (0.17,7.65)	0.29 (0.03,2.50)	0.44 (0.05,3.99)	H				*N* = 1,−0.93 (−1.53; −0.33)	
1.96 (0.22,17.14)	16.01 (1.27,202.40)	2.46 (0.48,12.67)	16.01 (1.84,139.19)	2.78 (0.49,15.89)	0.72 (0.10,5.31)	1.09 (0.14,8.47)	2.46 (0.35,17.34)	I	*N* = 1,−0.94 (−1.47; −0.40)			
0.44 (0.08,2.55)	3.57 (0.40,32.22)	0.55 (0.19,1.56)	3.57 (0.62,20.64)	0.62 (0.19,2.06)	0.16 (0.03,0.75)	0.24 (0.05,1.22)	0.55 (0.12,2.43)	0.22 (0.06,0.79)	J	*N* = 1,0.03 (−0.59;0.65)	*N* = 1,0.18 (−0.54;0.90)	
1.29 (0.19,8.54)	10.50 (1.05,105.29)	1.61 (0.20,13.27)	10.50 (1.59,69.19)	1.82 (0.46,7.27)	0.47 (0.09,2.57)	0.71 (0.12,4.12)	1.61 (0.15,17.07)	0.66 (0.07,6.07)	2.94 (0.47,18.35)	K		
0.42 (0.04,4.32)	3.40 (0.23,49.82)	0.52 (0.08,3.35)	3.40 (0.33,35.09)	0.59 (0.08,4.16)	0.15 (0.02,1.36)	0.23 (0.02,2.15)	0.52 (0.06,4.45)	0.21 (0.03,1.56)	0.95 (0.20,4.44)	0.32 (0.03,3.55)	L	
0.40 (0.05,3.07)	3.23 (0.28,36.93)	0.50 (0.11,2.18)	3.24 (0.42,24.93)	0.56 (0.11,2.76)	0.15 (0.02,0.94)	0.22 (0.03,1.51)	0.50 (0.17,1.43)	0.20 (0.04,1.04)	0.91 (0.32,2.58)	0.31 (0.04,2.54)	0.95 (0.15,6.13)	M	*N* = 1,−0.38 (−0.99;0.23)
0.65 (0.06,7.19)	5.33 (0.35,82.37)	0.82 (0.12,5.68)	5.33 (0.49,58.46)	0.93 (0.12,7.01)	0.24 (0.03,2.27)	0.36 (0.04,3.60)	0.82 (0.16,4.22)	0.33 (0.04,2.62)	1.49 (0.29,7.63)	0.51 (0.04,5.90)	1.57 (0.17,14.80)	1.65 (0.47,5.76)	N

1. Lower-left triangle presents the findings (MD with 95%CI) of the network meta-analysis conducted using Stata 15.1. Upper-right triangle presents the findings (SMD with 95% CI) of the pair-wise meta-analyses conducted using STATA 15.1 and N refers to the numbers of RCTs which compared the 2 interventions directly. 3. A positive MD favors the lower-right intervention; a negative MD favors the upper-left intervention. 4. Statistically significant findings are shaded. A, CEB (cervical epidural block); B, EA (external application); C, HTESPB (high thoracic erector spinae plane block); D, IAI (intra-articular injection); E, INB (interscalene nerve block); F, INB+IAI (interscalene nerve block + intra-articular injection); G, INB+IVA (interscalene nerve block + intravenous administration); H, INB+SSNB (interscalene nerve block + suprascapular nerve block); I, OA (oral administration); J, PL (placebo); K, SCNB (supraclavicular nerve block); L, SGB (stellate ganglion block); M, SSNB (suprascapular nerve block); N, SSNB+ANB (suprascapular nerve block + axillary nerve block).

Red represents the code of intervention measures and green represents the significant difference between two intervention measures with statistical significance.

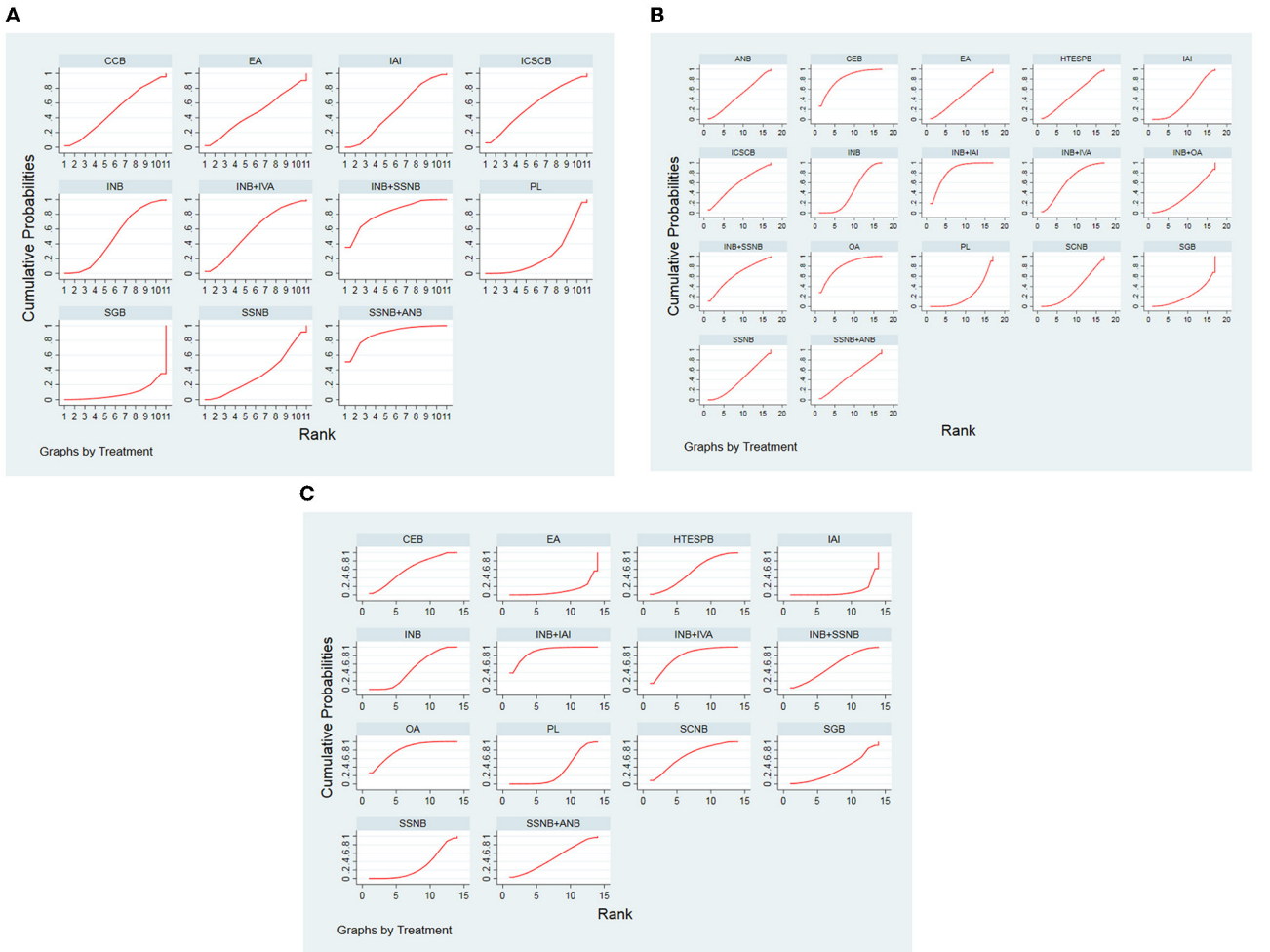

FIGURE 5 | (A) SUCRA for results of postoperative 12 h. **(B)** SUCRA for results of postoperative 24 h. **(C)** SUCRA for results of postoperative 48 h. The area under the curve represents the cumulative rank probability of each treatment; with larger areas signifying higher probabilities. INB, interscalene nerve block; SCNB, supraclavicular nerve block; SSNB, suprascapular nerve block; HTESPB, high thoracic erector spinae plane block; CEB, cervical epidural block; SGB, stellate ganglion block; ICSCB, infraclavicular-suprascapular blocks; CCB, costoclavicular blocks; ANB, axillary nerve block; IAI, intra-articular injection; OA, oral administration; EA, external application; IVA, intravenous administration; PL, placebo.

of the above traditional meta–analysis. However, 1 comparison–AI vs. PL–had no significant difference, which is the difference between the NMA and the traditional meta–analysis, in which the difference between different interventions vs. PL was compared, and it was found that the top two interventions were SSNB + ANB (MD 0.06, 95% CI 0.01 to 0.38) and INB + SSNB (MD 0.12, 95% CI 0.03 to 0.51).

Regarding the postoperative 24 h group, among the significant results, OA vs. PL, CEB vs. IAI, and INB vs. CEB exhibited similar results to those of the above–discussed traditional meta–analysis. In addition, 4 distinct comparisons that included HTESPB vs. PL, INB + SSNB vs. SSNB, IAI vs. PL, and ANB vs. PL exhibited no significant differences, which may be due to the variation between the NMA and the traditional meta–analysis. Among these results, the differences between the various interventions vs. PL were also compared, and it was found that the top two interventions were OA (MD 0.06, 95% CI 0.01 to 0.25) and INB + IAI (MD 0.10, 95% CI 0.03 to 0.33).

Regarding the postoperative 48 h group, among the observed significant results, OA vs. PL, INB vs. IAI, CEB vs. IAI, and INB+IAI vs. INB exhibited similar results to those of the above–reported traditional meta–analysis. Moreover, 2 comparisons that consisted of HTESPB vs. PL and INB + SSNB vs. SSNB exhibited no significant differences, which might be due to the variation between the NMA and the traditional meta–analysis. We adapted the above steps and found that the top two interventions were INB + IAI (MD 0.16, 95% CI 0.03 to 0.75) and OA (MD 0.22, 95% CI 0.06 to 0.79).

Rank Probability

The order of the curative effect of the intervention measures was obtained after the calculation. Based on the area under the

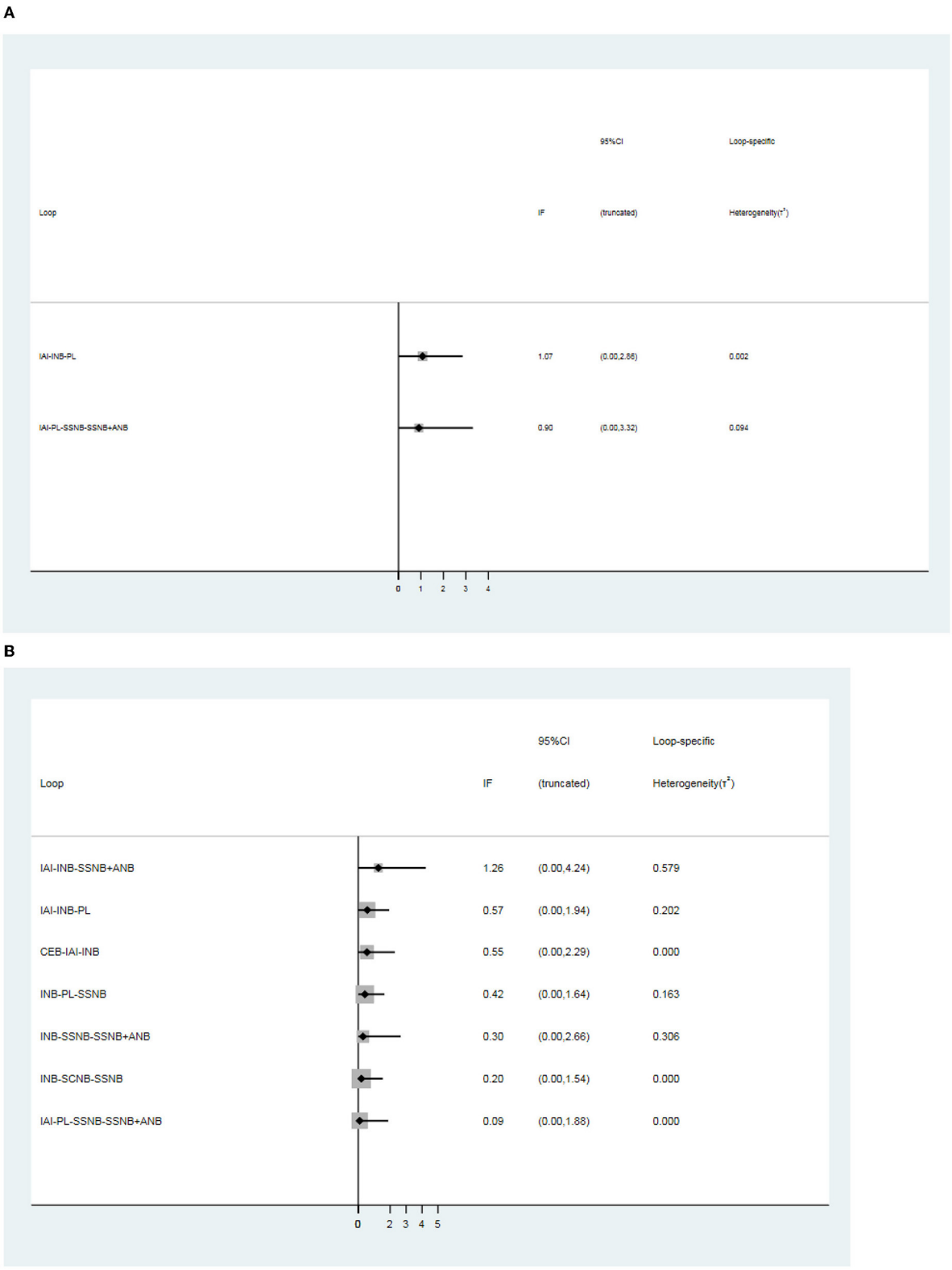

FIGURE 6 | Loops analysis for inconsistency of network meta-analysis. [**(A)** postoperative 12 h., **(B)** postoperative 24 h]. When the 95% confidence interval (CI) includes 0; it means that inconsistency is low risk. INB, interscalene nerve block; SCNB, supraclavicular nerve block; SSNB, suprascapular nerve block; CEB, cervical epidural block; ANB, axillary nerve block; IAI, intra-articular injection; PL, placebo.

curve, we could find out about intervention, which was the most effective (**Figure 5**).

For the postoperative 12 h group, the best analgesic effect was found in SSNB + ANB, whereas in the non–nerve block group, EA was ranked first.

Regarding the postoperative 24 h and 48 h group, the analgesic effect of INB + IAI was best among other treatment options in the nerve block, but OA ranked first at postoperative 12 h.

Inconsistency Analyses

There was 1 quadrilateral loop (IAI–PL–SSNB–SSNB + ANB) and 1 triangle loop (IAI–INB–PL) in network 1. In network 2, 1 quadrilateral loop (IAI–PL–SSNB–SSNB + ANB) and 6 different triangle loops (IAI–INB–PL, IAI–INB–SSNB + ANB, CEB–IAI–INB, INB–PL–SSNB, INB–SSNB–SSNB + ANB, and INB–SCNB–SSNB) were found. In network 3, 1 triangle loop (CEB–IAI–INB) was found, but the triangle loop (CEB–IAI–INB) was disregarded, which was derived from the same article, and testing inconsistency in network 3 was not needed. The evaluation of inconsistency of network 1 and network 2 at the global showed no significant inconsistency, with p–values of 0.86 and 0.99, respectively. There was no consistency observed in these loops of network 1 and network 2 (**Figure 6**). In addition, no inconsistency was found between any comparison pairs in network 1 and network 2 through the node–splitting test (**Tables 8**, **9**).

TABLE 8 | Node–splitting test for inconsistency of network meta–analysis (postoperative 12 h).

Side	Direct		Indirect		Difference		P>|z|
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	
A E*	0.00	0.59	−0.65	10.73	0.65	10.75	0.95
B C*	−0.15	0.94	1.30	185.01	−1.45	185.01	0.99
C E	0.01	1.03	−0.89	0.63	0.90	1.21	0.46
C H	0.60	0.46	0.24	1.23	0.36	1.31	0.78
C K	−2.05	0.98	−0.97	1.19	−1.08	1.54	0.48
D E*	0.25	0.81	0.00	120.49	0.25	120.50	1.00
E F*	−0.21	0.51	−0.03	71.53	−0.17	71.53	1.00
E H*	1.25	0.41	−0.17	1.94	1.42	1.98	0.47
G J*	2.30	0.73	1.22	107.55	1.08	107.56	0.99
H I*	1.03	0.78	−2.38	104.35	3.41	104.35	0.97
H J	−0.30	0.79	−1.38	1.32	1.08	1.54	0.48
J K	−1.30	0.77	−2.38	1.34	1.08	1.54	0.48

A, CCB (costoclavicular blocks); B, EA (external application); C, IAI (intra–articular injection); D, ICSCB (infraclavicular–suprascapular blocks); E, INB (interscalene nerve block); F, INB+IVA (interscalene nerve block + intravenous administration); G, INB+SSNB (interscalene nerve block + suprascapular nerve block); H, PL (placebo); I, SGB (stellate ganglion block) J, SSNB (suprascapular nerve block); K, SSNB+ANB (suprascapular nerve block + axillary nerve block).

**All the evidence about these contrasts comes from the trials which directly compare them.*

Additional Analysis

The publication bias of the 3 distinct networks was evaluated by using Egger's tests, and the result is shown in **Table 10**. The publication bias was only detected in network 2 (**Table 6**) due to the small amount of the subjects present in the studies included in this analysis. The rank possibility was recalculated by excluding these studies with < 40 people. The results in postoperative 12 h changed significantly (**Figures 7A–C**). The small sample might produce bias, which can lead to the wrong ranking of ANB + SSNB (27). At present, it is considered that the larger sample size is more reliable for analysis. Moreover, in the network comparison, INB + SSNB was significantly better than ANB + SSNB, so it could be concluded that the analgesic effect of INB + SSNB ranked first in the 12 h group after the operation. A little asymmetry was found in the comparison–adjusted funnel plot, which suggested that there were small–study effects in the primary analysis (**Figure 8**).

DISCUSSION

In this NMA, all the RCTs that focused on the different intervention measures in the treatment of pain after shoulder arthroscopy were included. The analgesic effects of the different interventions at postoperative 12 h, 24 h, and 48 h were analyzed, respectively. The intervention measures were divided into two distinct categories, namely, the nerve block group and the non–nerve block group. The results of SUCRA showed that, first, the analgesic effect of the nerve block group was significantly better than that of the non–nerve block group at the three time points after the operation. Among them, the first regimen related to the nerve was SSNB + INB at postoperative 12 h, INB + IAI at 24 h after operation, and INB + IAI at 48 h after surgery. For the non–nerve block group, the effect of EA was found to be the best in the 12 h after operation, and the analgesic effect of OA at postoperative 24 h and 48 h was significantly better than that of other intervention measures.

There was no intervention reported with INB + IAI and OA in the original data in the postoperative 12 h group (**Figure 2**), which might be the reason for the difference in results between 12 h and 24 h after operation. In addition, in the network comparison, the analgesic effect of OA at 24 h after operation was found to be significantly better than that of other intervention measures; however, SUCRA was ranked third in the 24 h group after the operation. The possible reasons could be related to the inadequate sample size of the experiments, the environment in which each experiment was carried out, and other external conditions, which might have exerted a variable impact on the experiment and so on.

Clinical Implications

On the one hand, shoulder arthroscopic surgery is currently carried out successfully in a large number of affected patients. Thus, it can be implied that there are numerous patients undergoing shoulder arthroscopic surgery, and the postoperative pain can adversely slow down the recovery speed of the patients and affect the surgical effect on the patients. On the other hand, there is no unified and optimal scheme for postoperative analgesia after shoulder arthroscopic surgery. At present, the use of INB as the best nerve block has been recommended for postoperative pain after arthroscopic surgery (10), and it has been suggested to take analgesic drugs before and after shoulder

TABLE 9 | Node–splitting test for inconsistency of network meta–analysis (postoperative 24 h).

Side	Direct		Indirect		Difference		P>|z|
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	
A M*	1.05	0.60	0.40	8.08	0.65	8.10	0.94
B E*	2.07	0.68	0.30	1.48	1.77	1.63	0.28
B G*	1.32	0.69	3.09	1.47	−1.77	1.63	0.28
C E*	0.32	0.74	1.50	123.05	−1.18	123.05	0.99
D M*	1.10	0.65	2.09	84.13	−0.99	84.13	0.99
E G*	−0.51	0.54	0.24	0.50	−0.75	0.74	0.31
E M	0.44	0.38	−0.13	0.67	0.57	0.77	0.46
E Q	−0.38	0.96	−1.05	0.59	0.67	1.13	0.55
F G*	0.67	1.04	1.28	176.14	−0.61	176.14	1.00
G H*	−1.89	0.52	−1.24	84.76	−0.65	84.76	0.99
G I*	−0.88	0.56	−1.27	88.58	0.38	88.58	1.00
G J*	0.40	0.79	−1.28	161.37	1.68	161.37	0.99
G M	0.47	0.42	0.31	0.49	0.15	0.65	0.81
G N*	0.45	0.46	0.69	1.51	−0.24	1.56	0.88
G P	−0.03	0.48	0.18	0.49	−0.21	0.69	0.76
G Q	−1.04	0.59	−0.43	0.65	−0.61	0.88	0.49
K P*	1.00	0.71	1.44	101.21	−0.44	101.21	1.00
L M*	2.80	0.73	2.09	117.02	0.71	117.02	1.00
M O*	0.21	0.80	−2.09	118.29	2.30	118.29	0.98
M P	−0.10	0.47	−0.61	0.53	0.51	0.71	0.47
N P	−0.59	0.76	−0.23	0.68	−0.35	1.02	0.73
P Q	−0.70	0.71	−0.95	0.62	0.25	0.94	0.79

A, ANB (axillary nerve block); B, CEB (cervical epidural block); C, EA (external application); D, HTESPB (high thoracic erector spinae plane block); E, IAI (intra–articular injection); F, ICSCB (infraclavicular–suprascapular blocks); G, INB (interscalene nerve block); H, INB+IAI (interscalene nerve block + intra–articular injection); I, INB+IVA (interscalene nerve block + intravenous administration); J, INB+OA (interscalene nerve block + oral administration); K, INB+SSNB (interscalene nerve block + suprascapular nerve block); L, OA (oral administration); M, PL (placebo); N, SCNB (supraclavicular nerve block); O= SGB (stellate ganglion block); P, SSNB (suprascapular nerve block); Q, SSNB+ANB (suprascapular nerve block + axillary nerve block).

**All the evidence about these contrasts comes from the trials which directly compare them.*

arthroscopy. Moreover, IVA of dexamethasone can markedly increase the duration of anesthesia, reduce the use of anesthetic drugs, and alleviate the pain rebound after the disappearance of the anesthetic effect. Patients with pain can use opioid analgesics as per their requirements (3).

Dexamethasone or dexmedetomidine (54, 55), magnesium sulfate (56), or clonidine (57) can also be added to nerve block drugs, and intravenous anesthesia adjuvant drugs, such as ketamine (58), can also be injected into patients before and after the nerve block. A number of studies reported in the literature have been found to only block the upper trunk of the brachial plexus, which can achieve an effective analgesic effect equivalent to INB and can effectively reduce unilateral diaphragm paralysis (59). Moreover, the effect of continuous intermuscular sulcus nerve block has been found to be better than that of the single injection of intermuscular sulcus nerve block (60), and increasing drug concentration might effectively improve the anesthetic effect (61). Moreover, different types, concentrations, and volumes of local anesthetics may lead to significant clinical heterogeneity. Therefore, this point cannot be ignored in practical application.

Overall, the conclusion was drawn from this study that in the nerve block group, the analgesic effect of SSNB + INB was the best at postoperative 12 h, whereas INB + IAI was superior at postoperative 24 h and 48 h. For the non–nerve block group, the effect of EA was the best in the postoperative 12 h, and the analgesic effect of OA at postoperative 24 h and 48 h was significantly better as compared with other intervention measures.

In addition, in the non–nerve block group, patients can choose oral medicine before and after operation (11, 50), they can receive pain management education before operation (62), patients used an analgesic pump device after operation (13), and opioid analgesics were used after the operation, such as topical analgesic patch (19). Stellate ganglion block was not

TABLE 10 | Egger's test for publication bias of pairwise meta–analysis.

Group	Std_Eff	Coef.	Std. Err.	t	P>|t|	95% Conf. Interval
Postoprative 12 h	Slope	−1.05	0.71	−1.49	0.16	(−2.56; 0.45)
	Bias	2.12	2.34	0.91	0.38	(−2.87; 7.11)
Postoprative 24 h	Slope	0.27	0.37	0.75	0.46	(−0.47; 1.02)
	Bias	−2.09	1.32	−1.58	0.12	(−4.8; 0.60)
Postoprative 48 h	Slope	0.05	0.48	0.10	0.93	(−0.99; 1.08)
	Bias	−1.90	1.65	−1.15	0.27	(−5.43; 1.64)

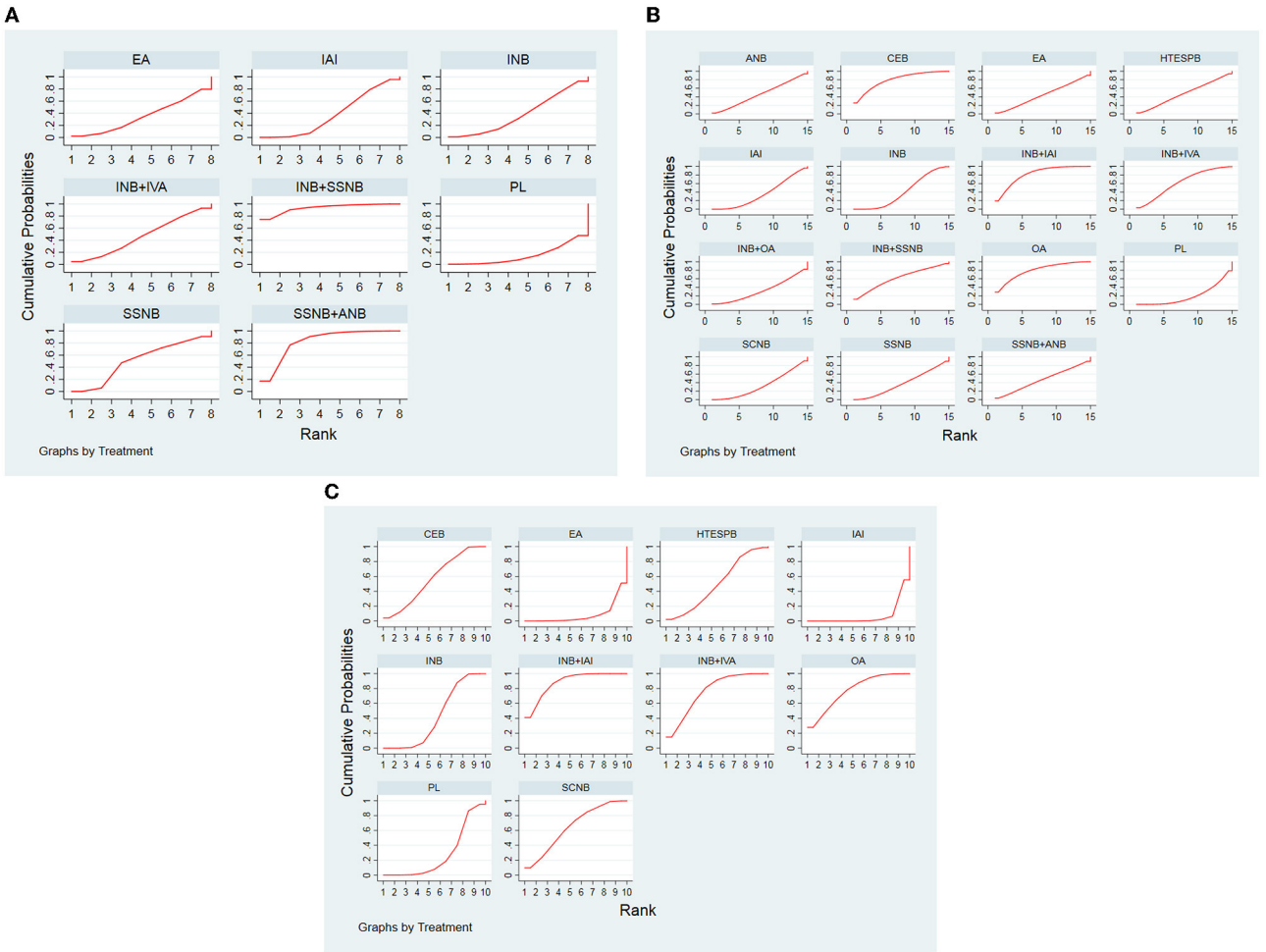

FIGURE 7 | (A) SUCRA for results of postoperative 12 h. **(B)** SUCRA for results of postoperative 24 h. **(C)** SUCRA for results of postoperative 48 h. (*After removing the article with less than 40 people*). The area under the curve represents the cumulative rank probability of each treatment; with larger areas signifying higher probabilities. INB, interscalene nerve block; SCNB, supraclavicular nerve block; SSNB, suprascapular nerve block; HTESPB, high thoracic erector spinae plane block; CEB, cervical epidural block; ANB, axillary nerve block; IAI, intra-articular injection; OA, oral administration; EA, external application; IVA, intravenous administration; PL, placebo.

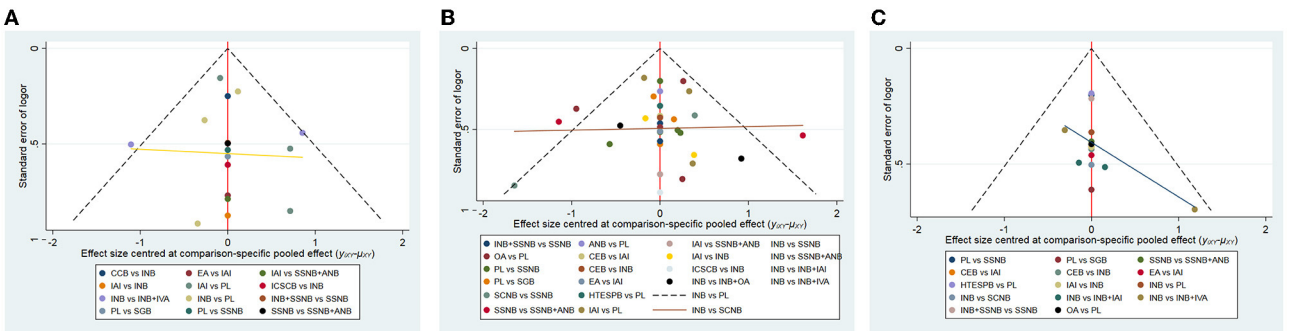

FIGURE 8 | The comparison-adjusted funnel plot of network meta-analyses. [**(A)** postoperative 12 h, **(B)** postoperative 24 h, **(C)** postoperative 48 h]. INB, interscalene nerve block; SCNB, supraclavicular nerve block; SSNB, suprascapular nerve block; HTESPB, high thoracic erector spinae plane block; CEB, cervical epidural block; SGB, stellate ganglion block; ICSCB, infraclavicular-suprascapular blocks; CCB, costoclavicular blocks; ANB, axillary nerve block; IAI, intra-articular injection; OA, oral administration; EA, external application; IVA, intravenous administration; PL, placebo.

recommended because its analgesic effect was found to be significantly lower than that of other intervention strategies, and we recommended the application of a combination of multiple interventions to maximize the analgesic effect and reduce the side effects of a single drug.

However, this study does not include the various complications in the analysis, and the lowest incidences of complications in SSNB + ANB and INB + IAI intervention programs were unknown. In addition, it has been shown that injecting anesthetics into the articular cavity might damage the cartilage of patients and cause unexpected damage (63), so one should try to avoid injecting anesthetics directly on the surface of the cartilage and minimize the trauma.

Implications for Future Research

According to the meta–analysis, the best analgesic effects were that of SSNB + INB, INB + IAI, and INB + IAI at the 3 time points after the operation, respectively. However, at postoperative 12 h, it was not clear whether the analgesic effect of SSNB + INB or INB + IAI was better, and hence clinical trials are needed to verify their efficacies in the future.

In addition, in the intervention control measures of each experiment, there were some other routine intervention measures used, which were not included in this NMA, such as the use of the postoperative analgesic pump, postoperative ice compress wound (64), and so on. Therefore, in addition to the above conclusions, we proposed that analgesics can be taken in advance before operation and use of nerve block such as INB plus IAI analgesics combined with postoperative analgesics, and cryotherapy in the ward, which may be the best analgesic intervention measures at the present.

In the future, high–quality RCTs should continue to be conducted to analyze the best multimode analgesic regimen for perioperative pain after shoulder arthroscopy.

Limitations

This study is also associated with a few limitations. First, this article did not describe the possible side effects of each intervention, but we can conduct another relevant meta–analysis in the future to address this issue. Second, the lack of blind methods in some studies may lead to potential deviations in the effect. In addition, the risk that results may be influenced by the quality of the included RCTs of this article cannot be completely avoided, like any other meta–analysis. Moreover, the bias can also be introduced by the loss of patients during the follow–up, so it might be possible that the major complications were not properly reported. Finally, the inclusion of the various surgical methods and shoulder diseases in the literature is complex, and the meta–analysis of the surgical methods is not subdivided, which may cause potential bias. These can be further subdivided in the future when there are several other related clinical trials have been conducted.

CONCLUSION

The analgesic effect of SSNB + INB was the best at postoperative 12 h, and INB + IAI was the best at postoperative 24 h and 48 h in the nerve block group. For the non–nerve block group, the effect of EA was the best at postoperative 12 h, and the analgesic effect of OA at postoperative 24 h and 48 h was significantly better than any other interventions.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

WJ and QX collected data and wrote and revised the articles. LX, HS, YX, SG, NM, GT, DZ, SH, and XZ revised the articles. All authors contributed to the article and approved the submitted version.

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Efficacy of PECS block in addition to multimodal analgesia for postoperative pain management in patients undergoing outpatient elective breast surgery: A retrospective study

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Background: Pectoralis nerve blocks (PECS) have been shown in numerous studies to be a safe and effective method to treat postoperative pain and reduce postoperative opioid consumption after breast surgery. However, there are few publications evaluating the PECS block effectiveness in conjunction with multimodal analgesia (MMA) in outpatient breast surgery. This retrospective study aims to evaluate the efficacy of PECS's blocks on perioperative pain management and opioid consumption.

Methods: We conducted a retrospective study to assess the efficacy of preoperative PECS block in addition to preoperative MMA (oral acetaminophen and/or gabapentin) in reducing opioid consumption in adult female subjects undergoing outpatient elective breast surgery between 2015 and 2020. A total of 228 subjects were included in the study and divided in two groups: PECS block group (received PECS block + MMA) and control Group (received only MMA). The primary outcome was to compare postoperative opioid consumption between both groups. The secondary outcome was intergroup comparisons of the following: postoperative nausea and vomiting (PONV), incidence of rescue antiemetic medication, PACU non-opioid analgesic medication required, length of PACU stay and the incidence of 30-day postoperative complications between both groups.

Results: Two hundred and twenty-eight subjects (n = 228) were included in the study. A total of 174 subjects were allocated in the control group and 54 subjects were allocated in the PECS block group. Breast reduction

and mastectomy/lumpectomy surgeries were the most commonly performed procedures (48% and 28%, respectively). The total amount of perioperative (intraoperative and PACU) MME was 27 [19, 38] in the control group and 28.5 [22, 38] in the PECS groups ($p = 0.21$). PACU opioid consumption was 14.3 [7, 24.5] MME for the control group and 17 [8, 23] MME ($p = 0.732$) for the PECS group. Lastly, the mean overall incidence of postsurgical complications at 30 days was 3% ($N = 5$), being wound infection, the only complication observed in the PECS groups ($N = 2$), and hematoma ($N = 2$) and wound dehiscence ($N = 1$) in the control group.

Conclusion: PECS block combined with MMA may not reduce intraoperative and/or PACU opioid consumption in patients undergoing outpatient elective breast surgery.

KEYWORDS

nerve block, breast surgery, analgesics, opioid, PECS, regional anesthesia

Introduction

Breast surgery is one of the most common type of surgery worldwide (1). Around 30–60% of patient undergoing breast surgery reports moderate to severe acute pain and up to 43% of them experience persistent postoperative pain lasting 2–18 weeks, regardless of the surgical technique and/or the use of multimodal analgesia (MMA) (1–12). Effective management of acute postoperative pain has a significant impact on patient's immediate and long-term recovery and/or quality of life (2, 3, 13). A poorly controlled perioperative pain management strategy on this surgical population, may result in delayed functional recovery, delayed post anesthesia care unit (PACU) discharge and/or extended length of hospital stay with subsequent financial burden (1). In addition, inadequate postoperative pain management is recognized as one of the most relevant risk factors for the development of chronic postoperative breast pain (2, 3, 13).

Despite the implementation of novel surgical techniques and MMA regimens, postoperative pain remains one of the main perioperative concerns in patients undergoing breast surgeries (12). Consequently, regional blocks (thoracic epidural and paravertebral blocks) for breast surgery have been implemented as "gold standard" analgesic techniques in the perioperative settings despite their association to several adverse events (1, 12, 14, 15). These regional blocks have been associated with reduced surgical stress response, perioperative opioid consumption, and postoperative pain scores, which have had a significant impact on other perioperative outcomes, such as postoperative nausea and vomiting (PONV), pulmonary complications and PACU length of stay (1, 14, 15). Numerous studies have been published describing the effectiveness of Pectoralis nerves (PECS) blocks on postoperative pain and postoperative opioid consumption after cancer breast surgery (12, 16–28). However, there are few published reports evaluating the PECS block's effectiveness in non-cancer related breast surgery (28–31). PECS block I was first described in 2011 by *Blanco et al.* as an interfascial regional block for breast surgery that administers local anesthetic at the level of the third rib on the anterior chest wall between the pectoralis major and pectoralis minor muscles, targeting the medial and lateral pectoral nerves (15, 32). PECS II block involves the injection technique used in PECS I and a second injection of local anesthetic over the fourth rib on the anterior chest wall in the fascial plane between the serratus anterior muscle and pectoralis minor muscles, targeting the lateral branches of the T2–6 intercostal nerves; this variation allows PECS II to have an extended dermatome coverage anesthetizing the whole breast and axilla (15, 21, 28, 33, 34). We summarized the characteristics of PECS I and PECS II in Table 1.

Furthermore, for the last two decades there has been an increasing emphasis on promoting the use of MMA, particularly in the context of postoperative enhance recovery after surgery (ERAS) protocols, reducing perioperative opioid consumption and, subsequently, their side effects (35–37). The use of oral gabapentinoids and acetaminophen alone or in conjunction with regional anesthesia as part of MMA, has shown an adequate reduction on pain scores and opioid consumption (38, 39). Controversially, recent literature suggests that the reduction of opioid consumption associated to the use of perioperative gabapentinoids is not often clinically relevant (40).

Abbreviations: PECS, pectoral nerve block; MMA, multimodal analgesia; PACU, post-anesthesia care unit; MME, oral morphine milligram equivalents; EMR, electronical medical records; PONV, postoperative nausea and vomiting; MAC, minimum alveolar concentration; BMI, body mass index; ASA, American Society of Anesthesiologists physical status; LOS, length of stay; NSQIP, National Surgical Quality Improvement Program; IV, Intravenous.

TABLE 1 Characteristics of PECS I and II blocks.

PECS Type	Nerves blocked	Muscular fascial planes involved	Indications
PECS I	Lateral pectoral nerve Medial pectoral nerve	Pectoralis major muscle Pectoralis minor muscle	Subpectoral prosthesis/breast expanders/implant insertion Subpectoral ICD or pacemaker insertion Adjunct to paravertebral block following mastectomy
PECS II	Lateral pectoral nerve Medial pectoral nerve Lateral and anterior branch of T2–T6 spinal nerves Antero-cutaneous branches of intercostal nerves 3–6 Long thoracic nerve (C5–C7) Thoracodorsal nerve (C6–C8)	Pectoralis major and minor muscles Serratus anterio Axillary region: Teres major, Subscapularis, Latissimus dorsi	Mastectomy with or without reconstruction/subpectoral implant insertion Wide local excision of breast. Sentinel node biopsy. Axillary clearance. Submuscular breast prosthesis Pacemakers and implantable cardiac defibrillators Shoulder surgeries (involving armpit) Arteriovenous fistula formation high up in the arm/armpit

T, thoracic; C, cervical; ICD, internal cardioverter defibrillators.

Therefore, our study hypothesized that the use of a PECS block in combination with MMA will reduce perioperative opioid consumption in patients undergoing outpatient elective breast surgery. Considering the limited evidence on the use of PECS block in combination with MMA on breast surgery, we conducted a retrospective chart review to compare postoperative opioid consumption (oral morphine milligram equivalents [MME]) in subjects undergoing outpatient elective breast surgery under general anesthesia, preoperative oral MMA (with acetaminophen and/or gabapentin) and with or without PECS block.

Methods

After full-board protocol review and approval (Protocol #2019E0641) from our Institutional Review Board (IRB), Office of Responsible Research Practices (ORRP)—The Ohio State University, we conducted a retrospective, single-center, observational, electronic medical record (EMR) review to assess the efficacy of using preoperative PECS block in addition to preoperative MMA with oral acetaminophen and/or gabapentin to reduce perioperative opioid consumption in adult female subjects undergoing outpatient elective breast surgery under general anesthesia at The Ohio State Wexner Medical Center (OSUWMC) between July 1, 2015 and June 26, 2020.

The decision of performing the PECS block prior to surgery was at the surgeon's and anesthesia care provider's discretion.

Study population

The study included 228 female subjects, ≥18 years of age who underwent outpatient elective breast surgery and received preoperative MMA with oral acetaminophen and/or gabapentin as preventive analgesia, with or without PECS block. Subjects were excluded if they met any of the following criteria: chronic use of opioids due to any medical/surgical conditions, opioid consumption within 48 h prior to surgery, use of gabapentin within 30 days prior to surgery, use of acetaminophen within 7 days prior to surgery, pregnant women, subjects under legal protection, prisoners, and subjects scheduled for non-elective breast surgery. Eligible subjects were allocated into one of two groups: PECS block Group (both, PECS and MMA were administered) and control group (only MMA was administered).

Clinical outcomes

The primary outcome was to compare MME in subjects who underwent outpatient elective breast surgery and received oral MMA with or without the use of preoperative PECS block. Secondary outcomes included the length of surgery, length of anesthesia, and length of PACU stay, incidence of PONV, rescue antiemetic medication requirements, amount of non-opioid analgesic medication required during surgery and PACU, and incidence of 30-day postoperative complications.

Anesthesia/analgesia technique

Preoperative MMA with oral acetaminophen 975 mg and/or gabapentin 600 mg as preventive analgesia was given within 2 h prior to surgery. The anesthesia technique followed institutional recommended guidelines. Induction was conducted with intravenous (IV) fentanyl 1.5–2.5 μg/kg and lidocaine 40–100 mg, followed by IV propofol 2.0–2.5 milligrams per kilo (mg/kg) as a hypnotic agent and IV rocuronium 0.6–1.0 mg/kg for the neuromuscular blockade to facilitate endotracheal intubation. Anesthesia maintenance was achieved with sevoflurane in a 45/55% oxygen/air mixture to attain and average minimum alveolar concentration (MAC) of 1 throughout the intraoperative period. Intraoperative opioids included intravenous fentanyl and hydromorphone, while oral oxycodone was prescribed after PACU/hospital discharge.

PECS block technique

The ultrasound-guided PECS block was performed following institutional recommended guidelines, immediately after anesthesia induction. A local anesthetic infiltration was performed at the levels of 3rd and 4th ribs, along the mid-axillary line from each side. PECS I was performed by introducing the needle in plane from medial to lateral and injecting 20–30 ml of 0.5% ropivacaine in the interfascial plane between pectoralis minor and pectoralis major muscles form each side. PECS II blocks consisted of the same steps as PECS I block, but with the bilateral infiltration of the local anesthetic between the pectoralis minor and serratus anterior muscles.

Statistical analysis

Patient demographic and clinical characteristics were summarized for the two study groups using descriptive statistics. Comparisons between the control and PECS block groups included baseline demographics, pre-operative/intra-operative medications, surgery types, postoperative opioid consumption, and patient outcomes. Categorical variables were compared between groups using either a Chi-square test or a Fisher's Exact test, and continuous variables were compared using either a two-sample *t*-test or a Wilcoxon Rank Sum test. Linear regression analysis was also used to assess the association of overall opioid consumption between both groups, adjusted by length of surgery and type of procedure. Secondary objectives (time to first opioid dose, incidence of PONV, total PACU stay length) were compared between the two groups using either a Chi-square test, Fisher's Exact test, two-sample *t*-test, or a Wilcoxon Rank Sum test, where appropriate. All data analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC) or Stata 14 (StataCorp LLC, College Station, TX).

Results

Study participants and clinical characteristics

A total of 685 subjects that underwent outpatient elective breast surgery under general anesthesia at The Ohio State Wexner Medical Center (OSUWMC) between July 1, 2015 and June 26, 2020 were screened to confirm eligibility criteria. Consequently, a total of 457 subjects were excluded due age <18 years, pregnant women, prisoners, subjects who underwent other type of surgical procedures, patient that did not receive any type of MMA and subjects who relevant information was missing. Therefore, a total of 228 eligible subjects were included in the study for statistical analysis. Fifty-four ($n = 54$) subjects were allocated into the PECS group and 174 subjects were allocated in the control group (Figure 1).

Demographics and surgical variables are summarized in Table 2. The average age of subjects was 48 ± 15.1 years old, with subjects in the control group slightly older in age than in the PECS group [50.4 ± 14.2 versus (vs.) 40.3 ± 15.7; $p < 0.001$]. The groups were comparable with respect to body mass index (BMI) (30 [6.2]). The PECS group had fewer American Society of Anesthesiology physical status (ASA) classification of 3 (9.3 vs. 27.6%; $p = 0.001$) and more ASA 1 classification of 1 (33.3 vs. 14.3%; $p = 0.001$) when compared with the control group. ASA classification of two subjects was similar in both groups.

Regarding the preoperative MMA administration, 140 (80%) subjects in the control group and 49 subjects (89%) in the PECS group received a combination of acetaminophen and gabapentin ($p = 0.155$); the remaining subjects in each group received either acetaminophen or gabapentin alone. The median dose of acetaminophen and gabapentin for all subjects was 975 [650–975] mg. and 600 [300–900] mg, respectively.

In the PECS group, the PECS II technique was the most used among subjects compared to PECS I (79.6 vs. 9.3%, respectively, $p < 0.001$). Moreover, a bilateral PECS block was performed in most subjects with only 5% of the PECS II group subjects having a unilateral PECS block.

Among the PECS group, the most common surgeries performed were breast reduction (78%), mastopexy (9%), and breast augmentation (4%). On the other hand, the most common surgeries performed on the control group were breast reduction (39%), mastectomy/lumpectomy (34%) and breast reconstruction (10%).

The median length of surgery time was significantly prolonged in the PECS group in comparison with the control group (153 [128–182] min and 125 [77–168] min, $p < 0.001$). Consequently, the median duration of anesthesia was also longer in the PECS group when compared with the control group (190 [53–293] min and 163 [34–717] min, $p = 0.04$). Lastly, the median length of PACU stay was similar between the control and

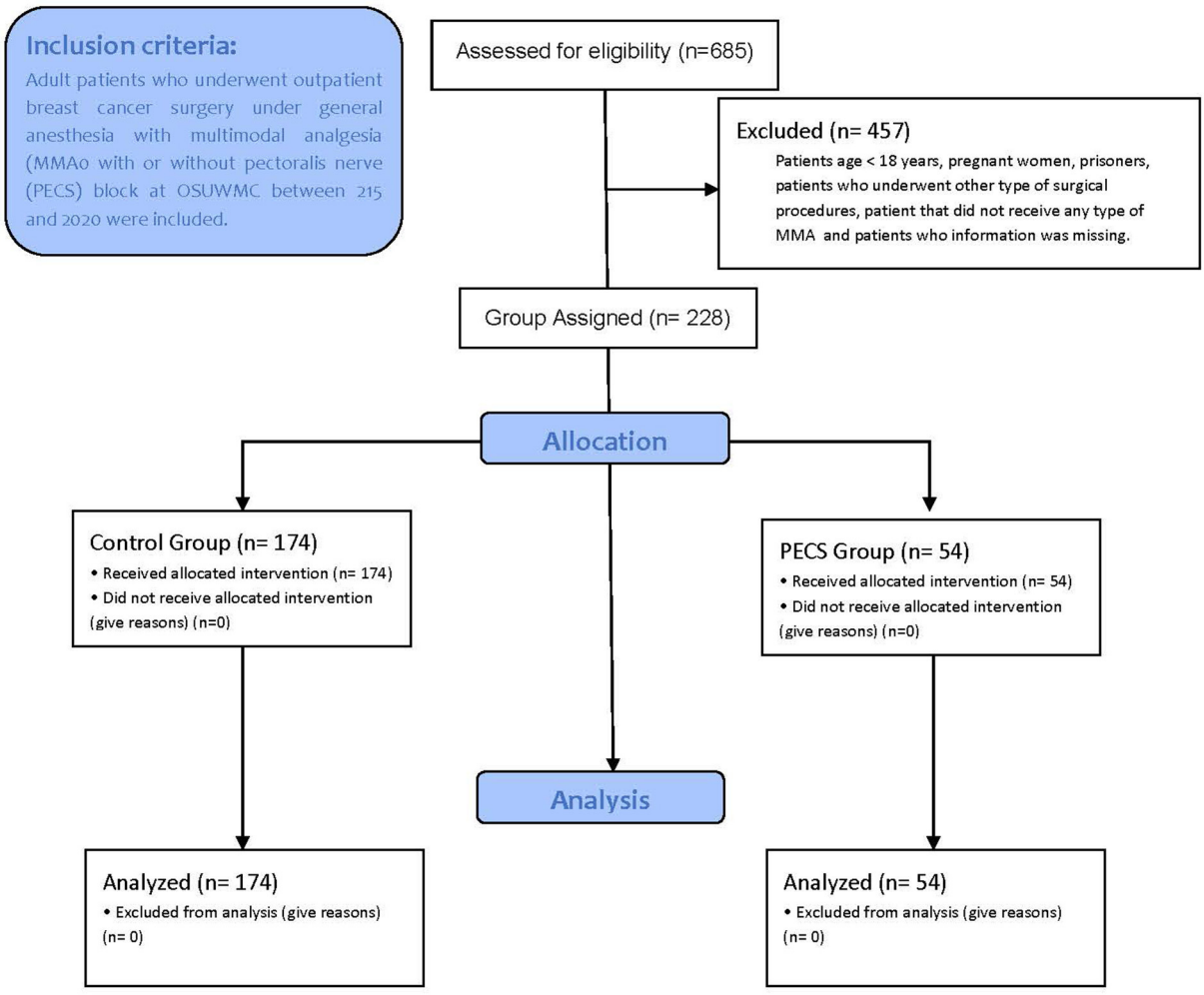

FIGURE 1
CONSORT flow diagram for subjects included in the study. N, number of participants; MMA, multimodal analgesia.

PECS groups (146 [125–186] min vs. 141 [122–168], p: 0.501; respectively).

Primary outcome

Intraoperative median MME was similar in both groups with a median value of 27 (19–38) mg in the control group and 28.5 (22–38) mg in the PECS group ($p = 0.21$). No significant differences between both groups were observed for PACU opioid consumption (14.3 [7–24.5] mg in the control group and 17 [8–23] mg in the PECS group; $p = 0.732$). Overall, there were not significant differences for opioid consumption during the entire perioperative period (i.e., intraoperative and PACU) between groups, (43.5 [31–61] mg in the control group and 45.5 [38–58.3] mg in the PECS group; $p = 0.284$) (Table 3).

Lastly, an additional linear regression analysis was conducted to assess the association of overall opioid consumption between both groups, adjusted by length of surgery and type of procedure. This analysis showed no differences between groups. Table 4 summarizes the adjusted OR, 95% CI, and associated p-values.

Secondary outcomes

There were a few differences on the use of intraoperative medications (Table 2). The use of intraoperative ketorolac (IV 30 mg) and dexamethasone (IV 8 mg) were significantly higher in the PECS group than in the control group (19 vs. 8%; $p = 0.029$ and 98 vs. 88%; $p = 0.032$, respectively).

The overall incidence of PONV in PACU was 18% and was slightly higher in the PECS group compared to the control group

TABLE 2 Demographics and clinical variables.

Variables	Control ($N = 174$)	PECS Block ($N = 54$)	Total ($N = 228$)	*P*-value
Age, years, mean (SD)	50.4 (14.2)	40.3 (15.7)	48 (15.1)	**<0.001**
Weight, kg, mean (SD)	80.2 (17.5)	80.2 (15)	80.2 (16.9)	0.996
Height, meters, mean (SD)	1.6 (0.1)	1.6 (0.1)	1.6 (0.1)	0.219
BMI, kg/m^2, mean (SD)	29.9 (6.5)	30.3 (5.4)	30 (6.2)	0.652
ASA physical status, *N* (%)				**0.001**
I	25 (14.3%)	18 (33.3%)	43 (18.9%)	
II	101 (58%)	31 (57.4%)	123 (53.9%)	
III	48 (28%)	5 (9%)	53 (23%)	
History of PONV or motion sickness, *N* (%)	42 (24%)	9 (17%)	51 (22%)	0.25
MMA pre-op with gabapentin alone, *N* (%)	3 (1.7%)	1 (1.9%)	4 (1.8%)	0.132
MMA pre-op with acetaminophen alone, *N* (%)	31 (17.8%)	5 (9.3%)	36 (15.8%)	0.95
MMA pre-op gabapentin + acetaminophen, *N* (%)	140 (80%)	48 (89%)	188 (82%)	0.155
MMA pre-op gabapentin dose, mg, median (IQR)	600 [300, 900]	600 [300, 900]	600 [300, 900]	**0.132**
MMA pre-op acetaminophen dose, mg, median (IQR)	650 [650, 975]	975 [650, 975]	975 [650, 975]	**0.95**
Intraoperative intravenous medication				
Dexamethasone, *N* (%)	153 (88%)	53 (98%)	206 (90%)	**0.032**
Dexamethasone, mg, median (IQR)	8 (4, 8)	8 (4, 8)	8 (4, 8)	0.859
Ondansetron, *N* (%)	166 (95%)	53 (98%)	219 (96%)	0.69
Ondansetron, mg, median (IQR)	4 (4, 4)	4 (4, 4)	4 (4, 4)	0.599
Ketamine, *N* (%)	18 (10%)	7 (13%)	25 (11%)	0.56
Ketamine, mg, median (IQR)	30 [30, 50]	50 [30, 50]	40 [30, 50]	0.824
Fentanyl, *N* (%)	170 (98%)	53 (98%)	223 (98%)	0.341
Fentanyl, ucg, median (IQR)	125 [100, 200]	150 [100, 200]	125 [100, 200]	0.341
Hydromorphone, *N* (%)	66 (38%)	27 (50%)	93 (41%)	0.115
Hydromorphone, ucg, median (IQR)	1 [1, 2]	1 [1, 2]	1 [1, 2]	0.202
Ketorolac, *N* (%)	14 (8%)	10 (19%)	24 (11%)	**0.029**
Ketorolac, mg, median (IQR)	30 [30, 30]	30 [30, 30]	30 [30, 30]	0.074
Pectoral nerves (PECS) block type, *N* (%)				
PECS I bilateral		5 (9.3%)		
PECS II bilateral		38 (70.4%)		
PECS II unilateral		5 (9.3%)		
PECS (unknown type)—bilateral		6 (11.1%)		
Type of surgery				
Breast reduction, *N* (%)	67 (39%)	42 (78%)	109 (48%)	**<0.001**
Mastectomy/lumpectomy, *N* (%)	60 (34%)	3 (6%)	63 (28%)	
Mastopexy, *N* (%)	14 (8%)	5 (9%)	19 (8%)	
Breast augmentation, *N* (%)	16 (9%)	2 (4%)	18 (8%)	
Breast reconstruction, *N* (%)	17 (10%)	2 (4%)	19 (8%)	
Length of surgery, min, mean (SD)	125 [77, 168]	153 [128, 182]	132 [93, 174.5]	**0.001**
Length of anesthesia, min, mean (SD)	163 [110, 211]	190 [164, 231]	175 [127, 221.5]	**0.004**
Length of PACU stay, min, mean (SD)	146 [125, 186]	141 [122, 168]	144 [124, 184.5]	0.501

N, number; SD, standard deviation; PECS, pectoralis nerve block; BMI, body index mass; ASA, American Society of Anesthesiology physical status classification; PONV, postoperative nausea and vomiting; mg, milligram; IQR, interquartile range; ucg, microgram; PACU, Post-Anesthesia Care Unit; min, minutes; ucg, microgram; kg, kilogram; kg/m2, Kilogram-Meter Squared. Bold values indicate statistically significant results.

(17 and 22%, respectively; $p = 0.41$). PONV rescue medication was required in 19.3% of subjects who experienced PONV. Ondansetron was used in 14% of these subjects as a PONV rescue medication, whereas haloperidol was administered in the remaining 5% with no statistical differences between groups (Table 5). Lastly, the mean overall incidence of postsurgical

TABLE 3 Perioperative opioid consumption.

Variables	Control ($N = 174$)	PECS block ($N = 54$)	Total ($N = 228$)	*P*-value
Intraoperative opioid consumption, oral morphine mg, mean (SD)	27 [19, 38]	28.5 [22, 38]	27 [19, 38]	0.21
PACU opioid consumption, oral morphine mg, mean (SD)	14.3 [7, 24.5]	17 [8, 23]	15 [8, 23.8]	0.732
Overall opioid consumption, oral morphine mg, mean (SD)	43.5 [31, 61]	45.5 [38, 58.3]	45.5 [33, 60.5]	0.284

N, number; PECS, pectoralis nerve block; SD, standard deviation; mg, milligram.

TABLE 4 Logistic regression analysis of overall opioid consumption adjusted by surgery length or surgery type.

Variable	Level	Control ($n = 131$)	PECS block ($n = 45$)	*P*-value
Overall opioid consumption, MME	Mean (SD)	45.0 (2.9)	46.7 (4.0)	0.601

N, number; SD, standard deviation; PECS, pectoralis nerve block; MME, oral morphine milligrams equivalents.

complications at 30 days was very low (5 [3%]), with wound infection as the only complication observed in the PECS groups ($N = 2$), and hematoma ($N = 2$) and wound dehiscence ($N = 1$) in the control group (Table 5).

Discussion

The results obtained in our study showed that the use of PECS as a strategy for postoperative analgesia after breast surgery did not decrease the perioperative opioid consumption when compared with the use of opioid-free MMA alone (acetaminophen/gabapentin/ketorolac). There were no significant differences in opioid consumption between groups during the intraoperative period, the PACU stay or the overall in-hospital perioperative period. In addition, when adjusted, overall opioid consumption by surgery length and type, there were no inter-group substantial differences either.

The results of our study differ slightly from some recently published evidence showing the efficacy of PECS block on reducing perioperative opioid use in subjects undergoing breast surgery. The vast majority of prospective and retrospective studies, systematic reviews, and meta-analysis published in recent years have shown that the combination of general anesthesia and PECS blocks reduces the severity of postoperative pain and perioperative opioid consumption, and positively impact other postoperative outcomes such as PONV and the length of hospital stay when compared to MMA strategies without loco-regional anesthesia techniques (16–19, 21–26, 30, 31, 41–45). Therefore, the addition of PECS blocks to general anesthesia may provide adequate postoperative analgesia and substantially reduce perioperative opioid consumption (17, 18, 24, 27, 30, 42, 43, 46).

A retrospective study by *Morioka et al.* in subjects who underwent breast cancer surgery under anesthesia with either total intravenous anesthesia (TIVA) + PECS or TIVA without PECS, showed a substantial reduction in the use of intraoperative remifentanil in the TIVA + PECS group compared with the group that received TIVA alone (TIVA: 10.9 ± 2.9 μg/kg/h; TIVA + PECS: 7.3 ± 3.3 μg/kg/h; $p < 0.001$) (27). However, the authors found no differences between groups in regard to the requirement of postoperative supplemental analgesia (TIVA: 24.3% [9/36]; TIVA + PECS: 17.1% [6/35]; $p = 0.32$) and the incidence of PONV (TIVA: 16.7% [6/36]; TIVA + PECS: 11.4% [4/35]; $p = 0.39$) (27). *Kim et al.* retrospectively studied the perioperative opioid consumption in 80 subjects who underwent breast conservative surgery plus sentinel lymph node biopsy. Forty subjects ($N = 40$) were allocated in the control group (balanced anesthesia) and 40 in the PECS II group (balanced anesthesia + PECS II) (42). The authors reported a reduced opioid consumption during the first 24 postoperative hours in the PECS II group when compared to the control group (43.8 ± 28.5 g vs. 77.0 ± 41.9 g; $p < 0.001$). However, the intergroup incidence of rescue analgesia was equivalent during the same period (42).

A recent single center, randomized control trial (RCT) compared the efficacy of PECS I block, local anesthetic wound infusion (LA infusion), or the combination of both for pain management after breast cancer surgery during a 24-h postoperative period (18). The results of the study showed that the combination of PECS + LA infusion was more effective than LA infusion alone or PECS alone to control postoperative pain (mean [(SD) 71 (34) vs. 58 (41) vs. 23 (20), respectively; $p = 0.002$]). Moreover, the PECS + LA combination was associated with a decreased opioid consumption in the first 24 h after surgery (18). Similarly, *Altiparmak et al.* studied the efficacy of PECS vs. erector spinae plane (ESP) block in terms of postoperative opioid (tramadol) consumption and pain levels measured by numerical rating scale (NRS). Postoperative consumption of tramadol was significantly lower in the PECS group (132.78 ± 22.44 mg in PECS group vs. 196 ± 27.03 mg in ESP group; $p =$

TABLE 5 Postoperative outcomes.

Variables	Control ($N = 174$)	PECS block ($N = 54$)	Total ($N = 228$)	*P*-value
PONV				
PONV incidence, *N* (%)	30 (17%)	12 (22%)	42 (18%)	0.41
PONV rescue medication, *N* (%)	30 (17%)	12 (22%)	42 (18%)	0.41
PONV rescue, *N* (%)	32 (18.4%)	12 (22%)	44 (19.3%)	0.41
Rescue with Promethazine, *N* (%)	1 (1%)	0 (0%)	1 (0%)	0.577
Rescue with Ondansetron, *N* (%)	28 (16%)	4 (7%)	32 (14%)	0.109
Rescue with Haloperidol, *N* (%)	3 (2%)	8 (15%)	11 (5%)	**<0.001**
Ondansetron dose, mg, Median (IQR)	4 [4, 4]	4 [4, 4]	4 [4, 4]	0.712
Haloperidol dose, mg, median (IQR)	1 [1, 1]	1 [1, 1]	1 [1, 1]	0.999
Postoperative complication (30 days)				
Wound infection, *N* (%)	0	2 (100%)	2 (29%)	0.2
Wound dehiscence, *N* (%)	1 (20%)	0	1 (14%)	NA
Hematoma, *N* (%)	2 (40%)	0	2 (29%)	NA

N, number; %, percentage; PECS, pectoralis nerve block; PONV, postoperative nausea and vomiting; mg, milligram. Bold values indicate statistically significant results.

0.001) as well as NRS scores after 30 min and up to 24 h (43).

A recently published RCT by *Choi et al.* analyzed 39 subjects undergoing breast surgery under TIVA (propofol-remifentanil). Subjects were randomized to receive either TIVA + PECS II block with ropivacaine 0.5% (PECS group; $n = 20$) or TIVA alone (control group; $n = 18$) (17). The authors concluded that not only the total remifentanil infused dose was much lower in the PECS group than in the control group (6.8 ± 2.2 μg/kg/h vs. 10.1± 3.7 μg/kg/h; $P = 0.001$), but also the rescue analgesic requirements in the PACU were lower in the PECS group (17). *Karaca et al.* recently studied the impact of PECS block in 54 subjects undergoing breast augmentation surgery. In this study, PECS block was performed in 27 subjects after general anesthesia induction (group P) while 27 subjects were the control group (group C) (30). Both groups received postoperative analgesia with patient-controlled analgesia (PCA)-fentanyl for up to 24 h after surgery. Fentanyl total doses, incidence of PONV, and PACU and hospital length of stay were analyzed. Authors reported that 24-h fentanyl consumption was significantly reduced in Group P when compared to Group C (378.7 ± 54.0 mg and 115.7 ± 98.1 mg, respectively: $p < 0.001$). Moreover, significant reductions were observed in pain levels (visual analog scale or VAS score), PONV incidence, and hospital LOS in Group P in comparison with Group C (30). A meta-analysis performed by *Zhao et al.* compared the effectiveness of general anesthesia + PECS II block (experimental group) vs. general anesthesia (GA) + sham block (control group) on intra- and postoperative opioid consumption (sufentanil, fentanyl, and remifentanil), incidence of PONV, postoperative pain scores up to 24-h, and requirements of opioids and non-opioids analgesic rescue medications (45). Compared to the GA group, the use of PECS block effectively reduced the intraoperative and postoperative use of opioids, the incidence of PONV, the need for postoperative rescue analgesia, and pain scores within 0–6 h after surgery. Nevertheless, a subgroup analysis showed no significant reduction on perioperative opioid consumption after a PECS II block (45). Lastly, a recent meta-analysis conducted by *Hussain et al.* evaluated the analgesic effectiveness of PECS II vs. control vs. paravertebral block in breast cancer surgery settings (28). The study analyzed the data from 14 RCT that included 887 subjects and concluded that PECS II reduced at least 30 mg of morphine consumption and in-rest pain during the first 24 h following breast cancer surgery when compared with the control group (28). In addition, there were not significant differences in all outcomes between the use of PECS and paravertebral block (28).

Conversely, some authors have reported similar results to our study, in which the use of PECS block did not significantly reduce perioperative opioid use when compared to MMA alone (29, 47, 48). A dual-centered, placebo-controlled RCT performed by *Cros et al.* in 128 subjects to evaluate the efficacy of ultrasound- guided PECS I vs. placebo in managing pain after unilateral cancer breast surgery, showed that there was no significant intergroup differences in intraoperative sufentanil consumption (20.0 [15.0–20.0] μg vs. 20.0 [15.0–25.0] μg, respectively; $p = 0.8536$) (47). Likewise, there were no statistical differences in PACU morphine consumption (1.5 [0.0–6.0] mg vs. 3.0 [0.0–6.0] mg; $p = 0.20$) and up to 24-h postoperatively (47). In a double-blinded, placebo-controlled prospective study conducted by *Lanier et al.* 47 subjects undergoing tissue expander/implant breast reconstruction were randomly allocated to either intraoperative PECS block with bupivacaine 0.25%, or a sham nerve block (control group) with normal saline (29). No statistical differences were reported between both groups in pain level, opioid consumption (8 vs.

17 MME; $p = 0.26$), quality of recovery, and antiemetic rescue medication during PACU stay and during hospitalization (92 vs. 114; $p = 0.31$) (29).

The overall incidence of PONV in our study population was 18%, with a slightly higher incidence in the PECS group than in the control group (22 vs. 17%, respectively; $p = 0.410$). No subjects experienced delayed hospital discharge, remained in the hospital after surgery due to PONV or were admitted after discharge due to delayed PONV (DPONV). The overall and between-group incidence of PONV in this study is lower than the prevalence reported in recent literature for ambulatory surgery (49, 50) and specifically for breast surgery (35, 45, 51, 52). The fact that opioid consumption in our study was comparable between groups most likely did not allow for a significant inter-group difference in PONV. Several clinical studies and meta-analysis showing a significant impact of PECS blocks on opioid consumption have reported a marked reduction in PONV frequency when compared with control groups or with MMA regimens without peripheral nerve block (19, 26, 28, 30, 31, 45, 48).

The prevalence rate of 30-day surgical complications was 3%, with no significant between-groups difference (3 vs. 4%). Hematoma (0.88%) and wound infection (0.88%) were the most common complications observed in that timeframe. In 2007, *El-Tamer et al.,* using the database of The National Surgical Quality Improvement Program Patient Safety in Surgery (NSQIP), reported that the most common 30-day complication after breast cancer surgery was wound infection (4.34%) (53). A later study by *Qin et al.,* also examining the data collected from NSQIP, reported the overall incidence of complications after breast cancer surgery was 5.4% (54). More recently, *Spataro et al.,* conducted a retrospective study from a secondary data repository which included a sample of 513,423 subjects and reported a 1.6% incidence of complications after ambulatory breast augmentation surgery (55).

Recent published evidence have questioned the benefits of using gabapentinoids in postoperative pain management regimens due to the high incidence of adverse effects such as sedation, dizziness, and visual disturbances that impede early mobilization and delay recovery; in addition, opioid-sparing effects of gabapentinoids have resulted clinically insignificant (40, 56–61). In addition, a few meta-analysis have been recently conducted to assess the effect of gabapentinoid in postoperative pain. *Chaparro et al.* conducted a Cochrane systematic review assessing trials that use perioperative gabapentin and ketamine in patients undergoing orthopedic and cardiac surgeries (59). The study suggested that the use of gabapentin did not significantly reduce postoperative pain when compared to placebo at 3 and 6 months and ketamine significantly reduced the incidence of chronic pain after surgery (59). Another meta-analysis conducted by *Clarke et al.* assessed the effect of perioperative use of gabapentinoids across different postoperative timepoints and concluded that its use could reduce the incidence of chronic pain (60). Lastly, another meta-analysis assessed acute and chronic pain in patients receiving preoperative pregabalin or gabapentin undergoing breast cancer surgery (61). The study concluded that gabapentin and pregabalin reduced opioid consumption in PACU, gabapentin reduces postoperative pain during the first 24 h after surgery and neither drug had an effect on reducing chronic postoperative pain (61).

We are aware of some limitations in our study that could increase the risk of bias in our results. First, due to the intrinsic limitation of a retrospective study, the small sample size, and the inability to collect opioid consumption for 24 h, limited our study to investigate an extended postoperative opioid consumption outcome that could provide us a better understanding of the analgesic needs and postoperative acute or chronic pain for this outpatient population. Second, most of study population received preoperative acetaminophen and gabapentin (82%) and intraoperative dexamethasone (90%) as part of the MMA regimen, and a few subjects (11%) received intraoperative ketorolac. Consequently, the doses of MMA regimen were not consistent among subjects because clinicians guided their clinical postoperative pain management according to institutional clinical guidelines, pre-existing medical conditions and/or their own or personalized clinical discretions could also play a role in this variability. Third, an important factor that could have influenced the slightly higher intraoperative opioid requirements in the PECs group is the longer duration of surgical procedures in the PECS block group when compared to the control group. Fourth, a potential human error during data collection and/or data transferring, as well as some inconsistencies among medical records may have occurred. Fifth, the recent implementation (2018) of PECS block use at our institution contributed to the uneven number of subjects analyzed on each group. Sixth, due to the retrospective research methodology of the study, we were not able to collect pain scores after surgery because the data was inconsistent on the number and time of pain scores assessed after surgery. Seventh, the inclusion of different breast procedures, mainly breast reduction and mastectomy/lumpectomy, with various degrees of invasiveness might reflect different trajectories of postoperative pain and opioid consumption might interfered the outcomes of this study. Finally, other factors that were not within the scope of our analysis, such as subjects' comorbidities, concomitant medication and/or pharmacodynamic considerations may had impact our outcomes.

Conclusions

Despite the fact that intraoperative peripheral nerve blocks are commonly used as an adjunct safe approach for pain management, our results suggest that the use of PECS block combined with MMA may not reduce intraoperative and/or

PACU opioid consumption in subjects undergoing outpatient elective breast surgery.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: Available upon request. Requests to access these datasets should be directed to alberto.uribe@osumc.edu.

Ethics statement

The studies involving human participants were reviewed and approved by Office of Responsible Research Practices (ORRP)—The Ohio State University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

Conceptualization: AU, TW, MP, RS, SP, and JH. Data curation and investigation: AU, ME-V, LP, JP, JF-D, and JH. Formal analysis: AU, JF-D, and MP. Methodology and resources: AU and JH. Project administration: AU, ME-V, JF-D, and JH. Supervision: AU, TW, and JH. Validation: AU, TW, ME-V, LP, JP, and JH. Visualization: AU, ME-V, LP, JP, and JH. Writing original draft and writing review and editing: AU, TW, ME-V, LP, JP, JF-D, MP, RS, SP, and JH. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Race, ethnicity, and the use of regional anesthesia in cancer patients undergoing open abdominal surgery: A single-center retrospective cohort study

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Background: Where applicable, regional anesthesia has been shown to be superior to opioid or non-opioid analgesic modalities alone. However, some studies have shown ethnic-based disparities in the use of regional anesthesia in patients undergoing surgical procedures. In this study of patients who had undergone major oncologic surgery, our main objective was to compare the use of regional anesthesia between patients of different ethnicities.

Methods: A retrospective review of adults who had undergone major open abdominal surgical procedures between 2016 and 2021 was performed. Logistic regression models were used to assess the association between baseline patient characteristics and the use of regional anesthesia.

Results: A total of 4,791 patients were included in the analysis. The median age was 60.5 years [interquartile range, 49, 69], the majority were female (65%), and of American Society of Anesthesiologists Physical Status Class (ASA) 3 (94.7%). Regional anesthesia was used in 2,652 patients (55.4%) and was not associated with race or ethnicity ($p = 0.287$). Compared to White patients, the odds of regional anesthesia use in other racial/ethnic groups were: Asian {odds ratio (OR) 0.851 [95% confidence interval (CI), 0.660–1.097]; $p = 0.2125$}, Black/African American [OR 0.807 (95% CI, 0.651–1.001); $p = 0.0508$], Hispanic/Latino [OR 0.957 (95% CI, 0.824–1.154); $p = 0.7676$], Other race [OR 0.957 (95% CI, 0.627–1.461); $p = 0.8376$]. In the multivariable analysis, age [OR 0.995 (95% CI, 0.991–1.000); $p = 0.0309$] and female gender [OR 1.231 (95% CI, 1.090–1.390); $p = 0.0008$] were associated with the use of regional anesthesia.

Conclusion: In this single-institution retrospective study of adults who had undergone major open abdominal surgery, the use of regional anesthesia was not associated with race or ethnicity. In the multivariable analysis, age and female gender were associated with the use of regional anesthesia.

KEYWORDS

regional anesthesia (RA), race, ethnicity, postoperative pain, opioids

Introduction

Racial and ethnic-based disparities in healthcare delivery have been long studied. These disparities are not only associated with higher morbidity and mortality among ethnic minorities from diseases such as diabetes, cardiovascular disease, and cancer, but have also been associated with a lesser likelihood of receiving optimal pain management (1–3).

The inclusion of regional anesthesia in perioperative pain control regimens has been shown to be superior to opioid or non-opioid analgesic modalities alone (4–6). However, some studies have shown ethnic-based disparities in the use of regional anesthesia (1, 7–11). For example, in a retrospective study of 639 patients in an enhanced recovery program, the use of epidural anesthesia or transversus abdominis plane (TAP) blocks was 13% lower in non-White patients than in White patients (1). In another retrospective cohort study of 5,810 adults who had undergone inguinal hernia repair, patients who identified as Black and those of other ethnic minority groups were up to 68% less likely to receive epidural anesthesia compared with their White counterparts (8). A similar observation was made in 81, 345 patients who had undergone mastectomy, where compared to White patients, the odds of receipt of regional anesthesia was up to 21% lower in non-White patients (9). Potential reasons for these disparities have included implicit bias (1, 8, 11), language barriers (10, 11), and cultural preferences (11).

On the other hand, other studies including some with very large cohorts, have not shown an association between race or ethnicity and the receipt of regional anesthesia. For example, in a retrospective propensity matched cohort study of patients in the American College of Surgeons-National Surgical Quality Improvement Program (ACS NSQIP) database, patient race or ethnicity was not associated with the type of anesthesia received for total joint arthroplasty (12). In another a single-center study of 25,664 children undergoing surgery at a tertiary children's hospital, race and ethnicity were not associated with the odds of receiving regional anesthesia (13). These differences in findings suggest ethnic-based disparities in the use of regional anesthesia may vary from institution to institution.

To effectively identify and address any such disparities, studies in different patient populations and at local and institutional levels are required. To the best of our knowledge, racial or ethnic-based differences in the use of regional anesthesia in patients undergoing major abdominal surgery for cancer has not been evaluated. To that end, we conducted a retrospective study of adult patients who had undergone major open abdominal surgery, with the primary objective of comparing the use of regional anesthesia (epidural or truncal blocks) between non-Hispanic White patients and patients of different races and ethnicities. Based on the results of previous studies (1, 8, 9), our hypothesis was that non-Hispanic White patients were more likely to receive regional anesthesia than patients of other racial or ethnic groups. The secondary objectives included racial or ethnic-based comparisons of intraoperative and immediate postoperative opioid administration, and early postoperative pain intensity scores.

Materials and methods

This study was approved by the Institutional Review Board (IRB) of the University of Texas MD Anderson Cancer Center on September 27, 2021 (IRB # 2021-0738).

Patient selection

The institutional data warehouse was used to identify patient admissions for surgical procedures between March 1, 2016, and August 1, 2021. The patient selection process was designed to include only those patients who would have been offered a regional anesthetic preoperatively. Thus, non-abdominal procedures and those performed by surgical services who do not use regional anesthesia were excluded. Additionally, due to the lesser likelihood of use of epidural anesthesia or truncal blocks, patients of American Society of Anesthesiologists Physical Status (ASA PS) 4 and above, and those undergoing emergency and outpatient procedures were excluded. Furthermore, due to the higher likelihood of surgeon-performed local anesthetic block, laparoscopic and robotic assisted procedures were excluded. To avoid over-representation of individual patients, only data from their index admission for open abdominal surgery was evaluated. The patient selection process is illustrated in Figure 1.

Clinical variables of interest

Perioperative variables were extracted from subsections of the institutional data warehouse including the Anesthesia, Pharmacy, Orders, Order Reconciliation, and Oncology Universes.

Patient demographics, a history of anxiety, depression, chronic pain, opioid use within the 3 months prior to surgery (preoperative opioid use), as well as any history of smoking, alcohol or drug abuse were recorded. Baseline coagulation parameters including platelet count, prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT) were also recorded.

The use of epidural anesthesia or truncal blocks which were performed as a part of the initial anesthetic were recorded as "Regional Anesthesia" (Yes/No). The use of rescue blocks, and regional anesthetics which were performed postoperatively was not evaluated for this study. Intraoperative opioid administration, Post Anesthesia Care Unit (PACU) opioid consumption in morphine daily dose equivalents (MEDD),

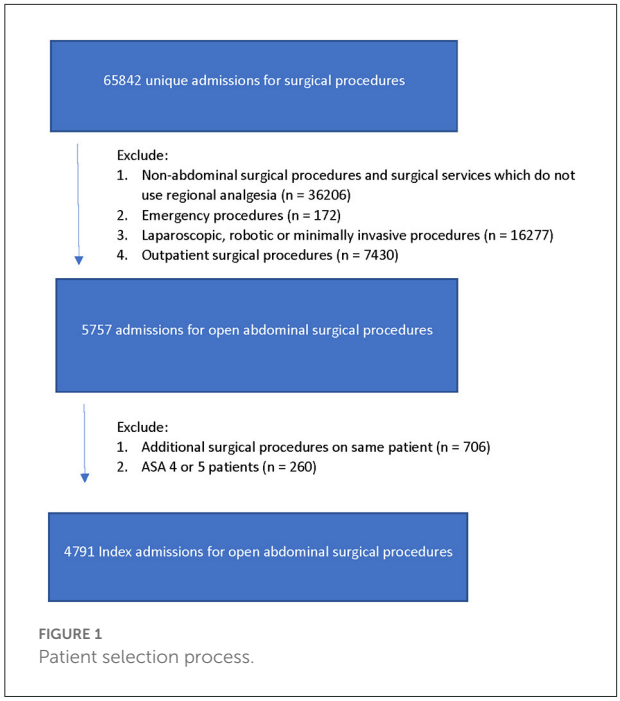

FIGURE 1
Patient selection process.

PACU pain intensity using verbal numeric rating scores (0 = no pain, 10 = worst pain ever), PACU length of stay (hours), and verbal numeric rating pain scores on postoperative day one were also recorded.

Anesthetic and postoperative pain management

At our institution, the decision to use regional anesthesia or not is largely determined by our surgeons' established preferences. The type of regional anesthetic is also largely determined by surgeons' preferences. For the most part, regional anesthesia for open abdominal procedures involves either a thoracic epidural catheter or bilateral transversus abdominis plane (TAP) and quadratus lumborum blocks. Occasionally, paravertebral blocks and erector spinae plane blocks are used. All regional anesthetics which are performed for postoperative management are performed prior to the surgical incision. Other aspects of anesthetic management including intraoperative opioid administration and the use of multimodal analgesic techniques are not standardized. In particular, multimodal analgesic techniques are used to varying degrees by different practitioners.

In the PACU, a standardized order-set with preset dosages and limits for opioid and non-opioid analgesic medications is used. Additional doses are ordered for inadequate pain control. After discharge from the PACU, pain control in patients who did not receive regional anesthesia is managed by the surgical services according to service-based customized order-sets. Patients who received regional anesthesia continue to be managed by the acute pain service until regional anesthesia catheters have been discontinued, or adequate pain control has been established with the use of opioid and non-opioid analgesics. During this period, pain assessment is initially performed every hour for the first 12 h, then every 4 h thereafter. In addition, pain assessments are performed 1 h after any change in medication administration.

Statistical analysis

Patients' demographics, treatment, and clinical outcomes were summarized through descriptive statistics. The Wilcoxon rank sum test or Kruskal-Wallis test was used to compare location parameters of continuous distributions between or among patient groups. The Chi-square test was used to evaluate the association between two categorical variables. A multivariable logistic regression model was fitted to estimate the effects of important covariates on regional anesthesia use and highest or average PACU pain score using 5 as the cutoff point. Statistical software SAS 9.4 (SAS, Cary, NC) and Splus 8.2 (TIBCO Software Inc., Palo Alto, CA) were used for all the analyses.

Results

A total of 4,791 patients were included in the analysis. The median age [Interquartile Range (IQR)] was 60.5 years [IQR, 49, 69], the majority were female (65%), and of ASA class 3 (94.7%).

Information about race and ethnicity was missing for 34 patients. Among those patients with information, 257 (5.4%) were Asian, 373 (7.8%) were Black or African American, 652 (13.7%) were Hispanic or Latino, 3,391 (71.3%) were non-Hispanic White (White), and due the small numbers in their individual groups, 89 (1.9%) were classified together as Other race. Of the patients who were classified together as Other race, 66 (1.4%) self-identified as Other race, 17 (0.4%) as American Indian or Alaska Native, and 6 (0.1%) as Native Hawaiian or Other Pacific Islander.

Baseline characteristics of the study population are shown in Table 1. Compared to patients of other races or ethnicities, the group of White patients were older [median 61 years, interquartile range (IQR) 50, 69] and had the highest proportion of proportion of patients with a diagnosis of anxiety or depression (683/3,391 [20.1%]). Black or African American patients had the highest proportion of female patients (189/368 [51.4%]), and highest values for platelet counts (median 241, IQR [193, 305]), PT (median 13.7, IQR [13.1, 14.4]), and INR (median 1.04, IQR [1.0, 1.1]). The group of Asian patients had the highest median value for aPTT (median 31.1, IQR [29.2,

TABLE 1 Demographic and baseline characteristics of 4,791 adults undergoing open abdominal surgery.

Baseline characteristics	All ($n = 4,791$)	Asian ($n = 257$)	Black or African American ($n = 373$)	Hispanic or Latino ($n = 652$)	Other ($n = 89$)	White ($n = 3,391$)	p-value
Age, years	60.0 [49, 69]	55 [45, 66]	59 [49, 67]	55 [44, 65]	55 [44, 66]	61 [50, 69]	<0.001
Gender, *n* (%)							0.027
Female	2,187 (45.7)	98 (38.1)	189 (51.4)	294 (45.1)	39 (43.8)	1,554 (45.8)	
Male	2,604 (54.3)	159 (61.9)	179 (48.6)	358 (54.9)	50 (56.2)	1,837 (54.2)	
Body mass index	27.6 [24.2, 31.7]	24.0 [21.9, 26.9]	29.4 [25.4, 33.5]	28.5 [24.8, 32.8]	27.3 [24.5, 30.8]	27.6 [24.2, 31.6]	<0.001
ASA, *n* (%)							0.144
1/II	256 (5.3)	18 (7.0)	17 (4.6)	45 (6.9)	7 (7.9)	169 (5)	
III/IV	4,535 (94.7)	239 (93.0)	351 (95.4)	607 (93.1)	82 (92.1)	169 (5)	
Anxiety/depression, *n* (%)							<0.01
Yes	905 (18.9)	17 (6.6)	58 (15.8)	129 (19.8)	14 (15.7)	683 (20.1)	
No	3,886 (81.1)	240 (93.4)	310 (84.2)	523 (80.2)	75 (84.3)	2,708 (79.9)	
Chronic pain, *n* (%)							0.765
Yes	20 (0.4)	1 (0.4)	2 (0.5)	1 (0.2)	0 (0)	16 (0.5)	
No	4,771 (99.6)	256 (99.6)	366 (99.5)	651 (99.8)	89 (100)	3,375 (99.5)	
Preop opioid use, *n* (%)							0.038
Yes	1,231 (25.7)	71 (27.6)	105 (28.5)	176 (27)	33 (37.1)	840 (24.8)	
No	3,560 (74.3)	186 (72.4)	263 (71.5)	476 (73)	56 (62.9)	2,551 (75.2)	
Smoking history, *n* (%)							0.301
Yes	12 (0.3)	0 (0)	2 (0.5)	1 (0.2)	1 (1.1)	8 (0.2)	
No	4,779 (99.7)	257 (100)	366 (99.5)	651 (99.8)	88 (98.9)	3,383 (99.8)	
Alcohol abuse, *n* (%)							0.717
Yes	76 (1.6)	3 (1.2)	5 (1.4)	7 (1.1)	2 (2.2)	58 (1.7)	
No	4,715 (98.4)	254 (98.8)	363 (98.6)	645 (98.9)	87 (97.8)	3,333 (98.3)	
Preop labs,							
Platelet count, K/uL	221 [179, 277]	214 [170, 267]	242 [193, 305]	227 [184, 288]	216 [179, 279]	219 [176, 272]	<0.001
PT, secs	13.4 [12.8, 14]	13.2 [12.7, 13.7]	13.7 [13.1, 14.4]	13.5 [12.9, 14.1]	13.5 [12.9, 14.1]	13.4 [12.8, 14]	<0.001
INR	1.02 [0.96, 1.08]	1.00 [0.95, 1.05]	1.04 [1.00, 1.11]	1.02 [0.97, 1.09]	1.02 [0.96, 1.08]	1.01 [0.96, 1.07]	<0.001
aPTT, secs	29.9 [27.7, 32.7]	31.1 [29.2, 33.8]	30.4 [27.9, 33.7]	30.3 [28.0, 33.0]	29.4 [27.1, 33.2]	29.8 [27.5, 32.4]	<0.001

Data expressed as median [interquartile range] unless otherwise indicated. BMI, Body Mass Index; ASA, American Society of Anesthesiologists Physical Status Score; Preop, Preoperative; PT, Prothrombin Time; INR, International Normalized Ratio; aPTT, activated Partial Thromboplastin Time.

33.8]), and the lowest proportion of patients with a BMI > 25 (108/255 [42.4%]). Preoperative opioid use was highest within the group of patients categorized as "Other race".

Use of regional anesthesia

Regional anesthesia was used in 2,652/4,791 patients (55.4%) and included epidural catheters (1,221/4,791, 25.5%), TAP/quadratus lumborum blocks (1,429/4,791, 29.8%), paravertebral blocks (1/4,791, 0.02%), and erector spinae plane blocks (1/4791, 0.02%). A larger proportion of females than males received regional anesthesia (58.4 vs. 52.8% males, $p = 0.0001$).

Patients who received regional anesthesia were also younger than those who did not receive regional anesthesia (median 59.5 years, IQR [48, 68], vs. 61 years, IQR [49, 69], $p = 0.0029$).

The use of regional anesthesia was not associated with statistically significant differences based on race or ethnicity ($p = 0.287$). The proportions of patients who received regional

TABLE 2 Association between baseline patient characteristics and the use of regional anesthesia.

	Univariable analysis			Multivariable analysis		
Effect	**OR estimate**	**95% CI for OR**	***p*-value**	**OR estimate**	**95% CI for OR**	***p*-value**
Asian vs. White	0.851	0.660, 1.097	0.2125	0.825	0.633, 1.074	0.1528
Black/AA vs. White	0.807	0.651, 1.001	0.0508	0.842	0.672, 1.055	0.1348
Hispanic/Latino vs. White	0.957	0.824, 1.154	0.7676	0.958	0.804, 1.140	0.6274
Other race vs. White	0.957	0.627, 1.461	0.8376	0.988	0.640, 1.524	0.9548
Age	0.995	0.991, 1.000	0.0296	0.995	0.991, 1.000	0.0309
Female vs. Male	1.259	1.122, 1.412	<0.0001	1.231	1.090, 1.390	0.0008
BMI	1.001	0.991, 1.010	0.8935	1.001	0.991, 1.011	0.8073
Platelet count	1.000	0.999, 1.001	0.7789	1.000	0.999, 1.000	0.4664
aPTT	0.995	0.981, 1.009	0.4716			
PT	0.838	0.794, 0.885	<0.0001			
INR	0.335	0.203, 0.553	<0.0001			
Anxiety or depression (Yes vs. No)	1.215	1.049, 1.407	0.0093	1.096	0.940, 1.278	0.2441
Chronic pain (Yes vs. No)	0.804	0.334, 1.936	0.6274			
Preoperative opioids (Yes vs. No)	1.071	0.940, 1.221	0.3006			
Alcohol abuse (Yes vs. No)	1.110	0.702, 1.757	0.6555	1.170	0.729, 1.877	0.5159
Smoking (Yes vs. No)	1.128	0.358, 3.560	0.8366			

AA, African American; BMI, Body Mass Index; aPTT, activated Partial Thromboplastin Time; PT, Prothrombin Time; INR, International Normalized Ratio.

anesthesia within each racial or ethnic group were; Asian (52.1%), Black or African American (50.8%), Hispanic or Latino (55.5%), Other race (55.1%), and White (56.1%). The univariate analysis (Table 2) showed that age {odds ratio (OR) 0.995 [95% confidence interval (CI), 0.991–1.000]; $p = 0.0296$}, female gender [OR 1.259 (95% CI, 1.122–1.412); $p < 0.0001$], ASA class (56.3% of ASA 3 or higher vs. 38.3% of ASA 2; $p < 0.001$), and a history of anxiety or depression [OR 1.215 (95% CI, 1.049–1.407); $p = 0.0093$] were associated with the use of regional anesthesia. Higher values of PT [OR 0.838 (95% CI, 0.794–0.885); $p < 0.0001$], and INR [OR 0.335 (95% CI, 0.203–0.553); $p < 0.0001$] were associated with decreased odds for the receipt of regional anesthesia. The multivariate analysis indicated that only age [OR 0.995 (95% CI, 0.991–1.000); $p = 0.0309$] and female gender [OR 1.231 (95% CI, 1.090–1.390); $p = 0.0008$] were independent predictors of the use of regional anesthesia (Table 2).

Opioid administration in the operating room and post anesthesia care unit

Intraoperative opioid administration was not associated with patient race or ethnicity (Table 3). However, opioid administration in the PACU was associated with race/ethnicity ($p = 0.038$) with the highest administration observed in patients who were categorized as Other race.

Postoperative pain scores

Pain intensity in the PACU was associated with race and ethnicity ($p < 0.001$). The highest and average PACU pain scores were significantly lower in Asian patients, and highest in Black or African American Patients (Table 3). Pain intensity on postoperative day one was also significantly associated with race/ethnicity. Similar to pain intensity in the PACU, the highest and average pain scores on postoperative day one were significantly lower in the group of Asian patients, and highest in the group of Black or African American patients (Table 3).

Regarding highest PACU pain scores ≥ 5, patients who were 60 years of age or older (1,646/2,468 [66.7%]; $p < 0.001$), male patients (1,777/2,599 [68.4%]; $p < 0.001$), Asian patients (154/257 [59.9%]; $p = 0.0001$), those without a history of anxiety or depression (2,713/3,881 [69.9%]; $p < 0.001$), and those who did not use opioids prior to surgery (2,464/3,559 [69.2%]; $p < 0.001$) had significantly lower proportions of patients with a highest PACU pain score of 5 or higher (Table 4). In the multivariable analysis (Table 5), the association between race/ethnicity and a highest PACU pain score ≥ 5 was significant ($p < 0.001$). In this regard, compared to White patients, Asian patients had a significantly lower likelihood of having a highest PACU pain score of 5 or greater [OR 0.581 (95% CI, 0.443–0.762); $p < 0.001$], and Black or African American patients had greater than a 30% likelihood of having a score of 5 or greater [OR 1.384 (95% CI, 1.066–1.797); $p = 0.015$]. Furthermore, patients who used opioids preoperatively [OR 1.372 (95% CI,

TABLE 3 Opioid administration and average pain scores of 4,791 adults undergoing open abdominal surgery for cancer.

	All ($n = 4,791$)	Asian ($n = 257$)	Black or African American ($n = 373$)	Hispanic or Latino ($n = 652$)	Other ($n = 89$)	White ($n = 3,391$)	p-value
Intraoperative opioids, MEDD	35.6 (±27.8)	32.7 (±22.1)	37.3 (±26.7)	35.5 (±28.3)	36.9 (±24.3)	35.6 (±28.3)	0.151
PACU opioids, MEDD	9.3 (±9.0)	8.1 (±8.5)	9.8 (±7.7)	8.9 (±8.6)	10.2 (±9.1)	9.3 (±9.3)	0.038
Highest PACU pain score	5.9 (±2.9)	5.2 (±3.2)	6.5 (±2.9)	5.9 (±2.9)	6.2 (±2.9)	5.9 (±2.9)	<0.001
Average PACU pain score	2.7 (±1.8)	2.3 (±1.7)	3.0 (±1.9)	2.7 (±1.8)	2.7 (±1.9)	2.7 (±1.8)	<0.001
Highest POD # 1 pain score	5.7 (±2.5)	5.2 (±2.3)	6.1 (±2.5)	5.9 (±2.5)	6.0 (±2.6)	5.7 (±2.5)	<0.001
Average POD #1 pain score	2.8 (±1.6)	2.5 (±1.5)	3.0 (±1.7)	2.9 (±1.7)	2.8 (±1.5)	2.8 (±1.6)	0.002

MEDD, Morphine Equivalent Daily Dose; PACU, Post Anesthesia Care Unit; POD, Postoperative Day.

1.178–1.598); $p < 0.001$], and those with a history of anxiety or depression [OR 1.229 (95% CI, 1.034–1.461); $p = 0.019$] had greater odds of having a highest PACU pain score of 5 or greater. Additionally, the likelihood of having a highest PACU pain score ≥ 5 lessened with increasing patient age [OR 0.917 (95% CI, 0.895–0.939); $p < 0.001$].

The proportion of patients with an average PACU pain score of 5 or higher was significantly lower among patients who were 60 years of age or older (205/2,468 [8.3%]; $p < 0.001$), male patients (278/2,599 [10.7%]; $p < 0.027$), Asian patients (18/257 [7%]; $p = 0.0004$), those without a history of anxiety or depression (403/3,881 [10.4%]; $p < 0.001$), and those who did not use opioids prior to surgery (317/3,559 [8.9%]; $p < 0.001$). The multivariable model (Table 5) demonstrated a significant association between race/ethnicity and an average PACU pain score of 5 or higher ($p = 0.0015$). Compared to White patients, Asian patients had a lesser likelihood of having an average pain score of 5 or higher [OR 0.594 (95% CI, 0.359–0.985); $p = 0.044$]. On the other hand, Black or African American patients had a >60% likelihood of having an average PACU pain score of 5 or higher [OR 1.617 (95% CI, 1.203–2.175); $p = 0.002$]. Patient age [OR 0.894 (95% CI, 0.865–0.924); $p < 0.001$], BMI [OR 1.002 (95% CI, 1.008–1.037); $p = 0.003$], preoperative opioid use [OR 2.416 (95% CI, 2.003–2.914); $p < 0.001$], and a history of anxiety and/or depression [OR 1.569 (95% CI, 1.268–1.940); $p < 0.001$] were also independently associated with an average PACU pain score of 5 or higher.

Discussion

In this single-center retrospective study, there were no statistically significant racial or ethnic-based differences in the use of regional anesthesia or in intraoperative opioid administration. However, significant racial and ethnic-based differences were observed in terms of postoperative pain intensity and in the administration of opioids in the PACU. In this regard, the severity of postoperative pain was lowest in the group of Asian patients and highest in Black or African American patients. Postoperative opioid administration was highest in patients who were grouped together as "Other Race".

Similar to our findings, the absence of an association between the use of regional anesthesia and patient race or ethnicity has been reported in other patient populations (12, 13). For example, in a retrospective cohort study by Elsharydah et al. (12), the proportion of African American patients who underwent total hip and knee arthroplasty with regional anesthesia was 2.3% less than in White patients. However, this observed difference was not detectable after propensity score matching. Similarly, in a large single-center study of pediatric patients, the proportion of minority patients who received regional anesthesia for their procedures was 1.4% less than their White counterparts. However, there was no statistically significant difference after multivariable and sensitivity analyses.

One of the major challenges in addressing racial or ethnic-based disparities in healthcare delivery is the difficulty in determining the reasons for its existence or absence. Regarding our study, the decision to use regional anesthesia or not was largely based on individual surgeons' established preferences. On any given day, modifications or changes to this established preference was discussed between the surgeon and the anesthesiologist. We speculate that this added level of discussion may have aided in ameliorating any potential racial or ethnic-based biases in offering regional anesthesia to patients.

In this study, younger age and female gender were independently associated with higher odds of receiving regional anesthesia. The reasons for these significant associations are not discernible from our data. With regard to age, the difference in age between the study groups, although statistically significant, may not be clinically significant. Thus, it is difficult to speculate about possible reasons for this statistical significance. With regard to female patients having higher odds of receiving regional anesthesia, a survey investigating patient perceptions of regional anesthesia revealed that more patients, especially females, would accept regional anesthesia if reassured

TABLE 4 Univariable analysis of the association between highest and average PACU pain scores and the perioperative characteristics of 4,791 adults undergoing open abdominal surgery.

Variable, *n* (%)	Highest pain in PACU < 5	Highest pain in PACU ≥ 5	*p*-value	Average pain in PACU < 5	Average pain in PACU ≥ 5	*p*-value
Age			<0.0001			<0.0001
<60	562 (24.2)	1,756 (75.8)		1,966 (84.8)	352 (15.2)	
≥60	822 (33.3)	1,646 (66.7)		2,263 (91.7)	205 (8.3)	
Gender			<0.0001			0.0268
Female	562 (25.7)	1,625 (74.3)		1,908 (87.2)	279 (12.8)	
Male	822 (31.6)	1,777 (68.4)		2,321 (89.3)	278 (10.7)	
Race/ethnicity			0.0001			0.0004
Asian	103 (40.1)	154 (59.9)		239 (93)	18 (7)	
Black/African American	81 (22.1)	285 (77.9)		300 (82)	66 (18)	
Hispanic or Latino	181 (27.8)	470 (72.2)		577 (88.6)	74 (11.4)	
Other	23 (25.8)	66 (74.2)		78 (87.6)	11 (12.4)	
White	987 (29.1)	2,402 (70.9)		3,004 (88.6)	385 (11.4)	
ASA			0.6738			0.5757
I/II	77 (30.1)	179 (69.9)		229 (89.5)	27 (10.5)	
III	1,307 (28.9)	3,223 (71.1)		4,000 (88.3)	530 (11.7)	
BMI			0.9055			0.0690
>25	953 (28.9)	2,348 (71.1)		1,316 (89.7)	151 (10.3)	
≤25	426 (29)	1,041 (71)		2,901 (87.9)	400 (12.1)	
Anxiety or depression			0.0002			<0.0001
Yes	216 (23.9)	689 (76.1)		751 (83)	154 (17)	
No	1,168 (30.1)	2,713 (69.9)		3,478 (89.6)	403 (10.4)	
Chronic pain			0.1689			0.0619
Yes	3 (15)	17 (85)		15 (75)	5 (25)	
No	1,381 (29)	3,385 (71)		4,214 (88.4)	552 (11.6)	
Preoperative opioids			<0.0001			<0.0001
Yes	289 (23.6)	938 (76.4)		987 (80.4)	240 (19.6)	
No	1,095 (30.8)	2,464 (69.2)		3,242 (91.1)	317 (8.9)	
Alcohol abuse			0.4408			0.1341
Yes	25 (32.9)	51 (67.1)		63 (82.9)	13 (17.1)	
No	1,359(28.9)	3,351 (71.1)		4,166 (88.5)	544 (11.5)	
Smoker			0.7644			0.1484
Yes	3 (25)	9 (75)		9 (75)	3 (25)	
No	1,381 (28.9)	3,393 (71.1)		4,220 (88.4)	554 (11.6)	
Regional anesthesia			0.5377			0.2959
Yes	757 (28.6)	1,894 (71.4)		2,354 (88.8)	297 (11.2)	
No	627 (29.4)	1,508 (70.6)		1,875 (87.8)	260 (12.2)	
Intraoperative opioids, MEDD (mean ± SD)	34 ± 28	36 ± 27	0.0007	34 ± 25	45 ± 41	<0.0001
PACU opioids, MEDD (mean ± SD)	2 ± 5	11 ± 9	<0.0001	8 ± 7	18 ± 12	<0.0001
PACU duration, hrs (mean ± SD)	3 ± 2	4 ± 2	<0.0001	4 ± 2	4 ± 2	0.1813

ASA, American Society of Anesthesiologists Physical Status Class; BMI, Body Mass Index; MEDD, Morphine Equivalent Daily Dose; PACU, Post Anesthesia Care Unit.

appropriately (14). Furthermore, patients were more likely to accept regional anesthesia if they had chosen it in the past. Based on the findings of this survey, it may be possible that prior experience with labor epidurals contributed to a higher rate of acceptance of regional anesthesia among females patients in our study population.

TABLE 5 Multivariable analysis of the association between highest and average PACU pain scores and the perioperative characteristics of 4,791 adults undergoing open abdominal surgery.

	Multivariable analysis for PACU pain scores							
	Highest PACU pain ≥ 5				Average PACU pain ≥ 5			
Effect	OR estimate	95% CI		*p*-value	OR Estimate	95% CI		*p*-value
Age	0.917	0.895	0.939	<0.0001	0.894	0.865	0.924	<0.0001
BMI	0.998	0.987	1.009	0.7621	1.022	1.008	1.037	0.0027
Female vs. male	1.259	1.105	1.435	0.0006	1.098	0.911	1.322	0.3261
Asian vs. White	0.581	0.443	0.762	<0.0001	0.594	0.359	0.985	0.0436
Black/African American vs. White	1.384	1.066	1.797	0.0148	1.617	1.203	2.175	0.0015
Hispanic/Latino vs. White	0.977	0.807	1.183	0.8102	0.849	0.645	1.117	0.2417
Other vs. White	1.067	0.656	1.735	0.7934	0.921	0.478	1.776	0.8064
ASA III vs. I/II	1.146	0.863	1.524	0.3463	1.211	0.787	1.862	0.3836
Preoperative opioids, Yes vs. No	1.372	1.178	1.598	<0.0001	2.416	2.003	2.914	<0.0001
Regional anesthesia, No vs. Yes	1.010	0.888	1.149	0.8786	1.156	0.962	1.389	0.1226
Anxiety/depression Yes vs. No	1.229	1.034	1.461	0.0193	1.569	1.268	1.940	<0.0001

ASA, American Society of Anesthesiologists Physical Status Class; BMI, Body Mass Index.

In our study population, postoperative pain intensity was statistically different based on race and ethnicity. In this regard, Asian patients had the lowest and Black or African American had the highest pain scores in the PACU and on postoperative day one. The results of studies evaluating postoperative and experimental pain in the Asian population have been mixed (15–18). These mixed results may be due to the complex interaction of cultural, social, biologic and genetic factors. The diverse nature of the population on the Asian continent may also contribute to the mixed findings.

On the other hand, several studies have demonstrated that Black patients have a lower threshold to painful stimuli and report more postoperative pain than White patients (16, 17, 19). Some have reported on this disparity even when regional anesthesia has been used (20). This higher burden of pain has been attributed to physiological, social, cultural and provider-level reasons (21).

In our study, higher BMI was independently associated with greater odds of an average PACU score of 5 or higher. Furthermore, BMI was significantly associated with race and ethnicity, with the group of Black or African American patients having the highest median BMI among all racial or ethnic groups. The association between BMI and postoperative pain has been reported by other studies as well (22, 23). Postulated mechanisms for the decreased effectiveness of regional anesthetic techniques in obese patients include an increased rate of failure to accurately identify anatomical landmarks (23, 24), and altered pharmacokinetics of local anesthetics in adipose tissue (22). Other authors have suggested that compared to ultrasound guided transversus abdominis plane block, ultrasound guided erector spinae block may be more feasible and effective in providing intra and postoperative analgesia in patients with high BMI (25).

Other factors which were independently associated with a higher intensity of postoperative pain included younger patient age, female gender, preoperative opioid use, and a history of anxiety or depression. In a recent systematic review and meta-analysis representing 53,362 patients, Yang et al. identified similar factors to be predictive of poor acute postoperative pain control (26). In the current study, despite having significantly higher odds of receiving regional anesthesia, younger patients and female patients had significantly higher pain intensity. This finding suggests that other measures may have been necessary to attain adequate pain control in this group of patients. For example, in women undergoing breast cancer surgery, preoperative interventions such as music therapy and aromatherapy have been shown to be effective in reducing preoperative anxiety, whilst music therapy and acupuncture were shown to be effective in minimizing postoperative pain (27). With regard to preoperative anxiety, preoperative complimentary therapies such as music therapy, aromatherapy and guided imagery have been shown to reduce preoperative anxiety, albeit to varying degrees (27, 28).

With regard to the association between preoperative opioid use and higher postoperative pain intensity, chronic opioid use has been associated with tolerance to opioids and opioid induced hyperalgesia (OIH), both of which could result in higher postoperative pain intensity and increased opioid requirements (29, 30). In our study, the group of patients who were classified as "Other" race had a significantly higher proportion of patients who used opioids preoperatively. Accordingly, postoperative opioid requirements were significantly higher

in this sub-group of patients. The molecular mechanisms of tolerance and OIH may be due to neuroplastic changes in the peripheral and central nervous systems that result in sensitization of pronociceptive pathways, and the N-methyl-D-aspartate (NMDA) receptor system has been shown to play a significant role (31). The inclusion of NMDA receptor modulators such as methadone and ketamine in pain control regimens has been shown to reduce opioid usage and improve pain control in patients who may be tolerant to opioids and in those who are susceptible to OIH (32, 33).

This study has several limitations. Firstly, the retrospective nature of this study meant details of the decision to use or not to use regional anesthesia could not be determined with certainty. Second, several missing values for platelet counts, PT, INR, and aPTT meant they could not be included in the multivariable analysis to determine their effect on the use of regional anesthesia. Lastly, the lack of available studies on ethnic disparities in the use of regional anesthesia during major abdominal surgery meant we could not perform an *a priori* sample-size analysis.

In conclusion, in this single-center retrospective study of adults who had undergone major abdominal surgery for cancer, the use of regional anesthesia was not associated with patient race or ethnicity. However, postoperative pain intensity and PACU opioid consumption were associated with race/ethnicity with the group of Asian patients having significantly lower pain scores, and the group of patients classified together as "Other race" having the highest PACU opioid consumption.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Institutional Review Board (IRB) of the University of Texas MD Anderson Cancer Center (IRB # 2021-0738). Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

PO-A: conceptualization of study, data collection, and writing of manuscript. JC: conceptualization of study, critical review of data, and writing of manuscript. VP and UW: critical review of data and writing of manuscript. LF: statistical analysis. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Moderate sedation by total intravenous remimazolam-alfentanil vs. propofol-alfentanil for third molar extraction: A prospective randomized controlled trial

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Background: Oral dental treatment cause anxiety, fear, and physical stress. This study aimed to investigate the efficacy and safety of moderate sedation by remimazolam with alfentanil vs. propofol with alfentanil in third molar extraction.

Methods: This single-center, randomized, single-blind clinical trial included 100 adults who underwent third molar ambulatory extraction. All patients had continuous infusion of Alfentanil 0.2 μg/kg/min. Group remimazolam with alfentanil (group RA) had an induction dose of 80 μg/kg and maintenance dosage of 5 μg/kg/min. In group propofol with alfentanil (PA group), propofol was infused at an initial concentration of 1.8 μg/mL under target controlled infusion (TCI) mode and a maintenance concentration of 1.5 μg/mL. The incidence rates of adverse effects were recorded and compared. Depth of sedation was assessed using the modified observer alertness/sedation assessment (MOAA/S) and entropy index. Recovery characteristics were recorded and complications observed for next 24 h.

Results: The incident of adverse events 6 (12%) in the group RA was lower than the group PA 25 (50%) [Mean difference 0.136 (95%CI, 0.049–0.377); $P < 0.05$], with no serious adverse events during the sedation procedure. The incidence of injection pain in group RA was significantly lower than that in group PA [4 vs. 26%, mean difference 0.119 (95%CI, 0.025–0.558); $P = 0.004$]. Before starting local anesthesia, the mean arterial pressure, heart rate, and respiratory rate of the PA group were lower than those of the RA group. None of the patients required further treatments for a decreased heart rate, blood pressure, or low SpO_2. The rate of moderate sedation success was 100% in both groups. The MOAA/S score was similar between the groups indicating that the depth of sedation was effective. Group RA had significantly shorter recovery and discharge times than those of group PA.

Conclusions: Remimazolam with alfentanil is a safer and more effective alternative for ambulatory sedation and can reduce recovery and discharge time and the incidence of perioperative adverse events compare with propofol.

Clinical trial registration: http://www.chictr.org.cn/index.aspx, identifier: ChiCTR2200058106.

KEYWORDS

sedation, remimazolam, propofol, alfentanil, third molar

Introduction

Oral dental treatment remains a serious problem in many vulnerable patients (1). While people with varying levels of anxiety may tolerate minor dental treatment, they may be more reluctant to undergo more invasive procedures or simply refuse to see a dentist (2, 3). Dental procedures, especially the extraction of third molars, often cause anxiety, fear, and physical stress to the patient because of the possibility of pain (4). Intravenous sedation has been widely used in dental procedures to minimize these unpleasant conditions (5, 6). Advantages of this sedation method may include reduced patient anxiety (7–9), reduced post-operative pain (10), increased patient and surgeon satisfaction (11) and suppressed gag reflex (12). Propofol is the most commonly used intravenous anesthetic. It has a rapid onset of action and an extremely short half-life, resulting in rapid awakening and recovery of cognitive function. Sedatives alone can provide sedation, anxiolysis, and amnesia, but when combined with opioids, they have the advantage of reducing injection pain and deep tissue traction pain (13). Alfentanil is also used in combination with benzodiazepines, propofol, and reduced doses of sedatives (14). Although propofol is commonly used, there are still defects in its clinical use in dental sedation. This includes possible hypotension and respiratory depression, especially in geriatric patients (15, 16). Injection pain, metabolic acidosis, egg and soy allergy, and propofol infusion syndrome have also been reported (17, 18).

Remimazolam, a full agonist of the benzodiazepine-binding site of the gamma-aminobutyric acid (GABA) receptor (19), is a newer class of benzodiazepines with rapid onset of action and short maintenance and recovery times (20–24). It does not accumulate in tissues; its metabolism is independent of liver and kidney, reducing serious side effects (25, 26). A study using population pharmacokinetic and pharmacodynamic (PK-PD) models to assess remimazolam (0.03 mg/kg) infused over 1 min developed a population kinetic model with a clearance of 66.7 L/h, an apparent volume of distribution at steady state of 37 L, a terminal half-life of 0.92 h, and a mean residence time of 0.57 h (27). Remimazolam was expected to be safe and effective for a wide range of patients undergoing intravenous sedation for dental procedures (28).

Based on the pharmacological characteristics of the regimens, we hypothesized that moderate sedation with total intravenous remimazolam-alfentanil for third molar extraction will have a shorter onset time, more stable hemodynamics, and less respiratory depression compared with propofol-alfentanil.

Materials and methods

Trial design and oversight

This single-center, prospective, single-blind study was conducted from March to April 2022. All study protocols were approved by the Ethics Committee of Chongqing Medical University (CQHS-REC-2022(LSNo.18)), and participants were explained the ethical aspect of the study. Participants also provided signed informed consent before participation following the Declaration of Helsinki Law (IR.SUMS.REC.1397.759). Registration Number is ChiCTR2200058106.

Sites and patients

In the Comfort Dental Center, the Affiliated Hospital of Stomatology, Chongqing Medical University, Chongqing, China, 110 patients between 18 and 60 years old were consecutively recruited into the study, inclusion criteria for study were: body mass index (BMI) of 19–30 kg/m^2, with an American Society of Anesthesiologists (ASA) score of I and II. The tooth extraction was limited to the ipsilateral upper and lower third molars. Ipsilateral upper simple extraction cases and lower surgical cases of impacted third molars in the horizontal position (Winter's classification) in Class II, and position B, according to the Pell and Gregory classifications, were selected after clinical and radiological examination. Exclusion criteria for the study were: patients who were pregnant or lactating; patients with clinically significant cardiovascular, respiratory, and/or hepatic disease; hypersensitivity or intolerance to opioids; chronic use of opioids for pain; those who refused treatment under sedation; those suspected or having a history of alcohol and drug abuse; acute tooth extraction such as pericoronitis of wisdom teeth; those who participated in other clinical activities

within 3 months; and patients who could not use smartphones to fill out and submit questionnaires on the WeChat applet.

Randomization and blinding

Participants were randomly allocated to the remimazolam-alfentanil group (Group RA) or the propofol-alfentanil group (Group PA) using web-based random number generators (https://www.randomizer.org/). Assignments were placed in an opaque envelope table by a statistical advisor who did not participate in this research. The attending anesthesiologist and outcome assessors were blinded to the allocation. To ensure covert allocation, an opaque envelope containing computer-generated random allocation was opened before each sedation procedure, and sedation was performed accordingly by a research assistant anesthesiologist. The drugs used in this study were prepared by a nurse who was not involved in the anesthesia process. Attending anesthesiologists, surgical dentists, resuscitation room nurses, and patients were all blinded to the grouping assignments.

Medicine preparation

The nature of the procedure and study protocol were explained to all patients, and they signed a consent form. After obtaining consent for surgery and research, we randomly divided the 104 patients into two groups: who underwent routine surgical tooth extraction under either remimazolam or propofol moderate sedation.

Remimazolam (remimazolam besylate, 25 mg, SFDA No 10T11021, Yichang Humanwell, Inc., YiChang, HuBei, CHN) (50 mg) diluted with normal saline (total 5 mL) and normal saline (45 mL) were prepared for induction and maintenance syringes in the remimazolam group; propofol (propofol injectable emulsion, 0.1 g:10 ml, SFDA No. 2104062, Sichuan Guorui Pharmaceutical, Inc., LeShan, Sichuan, CHN) was drawn into a 50 ml syringe. Alfentanil (1 mg) was diluted with saline (18 ml) (alfentanil hydrochloride 1 mg:2 ml, SFDA No. 13S03021, Yichang Humanwell, Inc., YiChang, HuBei, CHN).

Surgical procedures and intrasurgical measurements

Two surgical dentists were recruited for the trial. They are experts in the field of oral surgery with more than 10 years of experience and perform at least 500 third molar extraction operations every year. None of the patients underwent preoperative sedation. Each patient was asked to consume only liquids and light, soft meals for 2 h prior to sedation. Before entering the outpatient operating room the patient's anxiety level was measured using the modified dental anxiety scale (MDAS) (29). The MDAS score was recorded by the attending anesthesiologist. A 22G catheter was inserted in the non-dominant forearm vein. After entering the outpatient operating room, the patient was placed supine on a dental chair for 10 min while using a multifunction monitor. Non-invasive continuous monitoring of the mean arterial pressure (MAP), heart rate (HR), electrocardiogram (ECG), respiratory rate (RR), and peripheral oxygen saturation (SpO_2) was performed using anelectrocardiogram monitor (B650; GE Healthcare, Helsinki, Finland). During the sedation procedure, the anesthesiologist monitored the vital signs every 5 min. Entropy electrodes were placed on the forehead of each patient, and entropy was also monitored. The entropy of an EEG signal is derived as two quantitative values, namely, state entropy (SE), from frequencies in the range of 0.8–32 Hz, and response entropy (RE), from frequencies in the range of 0.8–47 Hz (30). SE and RE were recorded by a dedicated researcher. Data were recorded by the researcher, and the depth of sedation was assessed by an anesthesiologist using the modified observer alertness/sedation assessment (MOAA/S) (31). The anesthesiologists were unaware of entropy; therefore, they were only able to measure the depth of sedation using clinical MOAA/S. We defined MOAA/S 3 as moderate sedation, and MOAA/S 5 as baseline sedation and recovery from sedation. Baseline data were recorded 2 min before sedation, with the patient lying still and breathing spontaneously. SpO_2, MAP, HR, RR measurements, MOAA/S scores, and entropy were recorded when entering the room (baseline), at the start of local anesthesia (T1), at the start of the operation (T2), 15 min after the start of the operation (T3), and at the end of the operation (T4). Immediately after surgery, the surgeon was asked to rate their satisfaction with the sedatives, the placement of local anesthetic, and the procedure using a standard 10 cm visual analog scale (VAS), with 0 cm for "very satisfied" and 10 cm for "very unsatisfactory". Surgeons were verbally instructed to rate and record their satisfaction with this intravenous sedation technique.

Sedation protocol

Both groups of patients were intravenously administered with a multi-channel infusion workstation (HP-30pro; Medcaptain MEDICAL Technology Co., Ltd.; ShenZhen, CHN). The schemes and study doses used for sedation of the two groups are shown in Table 1. All the patients received 0.2 μg/kg/min of alfentanil during the moderate sedation and alfentanil was administered 2 min before moderate sedation as pre-analgesia medication. In group PA, propofol were given by TCI mode (Schneider pharmacokinetic model, maximal flow rate < 700 mL/h) set at an initial effect-site concentration (Ce) of 1.8 μg/mL. The anesthesiologist used the MOAA/S scale to assess the achievement of MOAA/S 3. If MOAA/S > 3 after 5 min of induction, Ce was increased by 0.2 μg/mL every min until MOAA/S $= 3$ was reached. After completing local anesthesia, the propofol TCI group (group PA) was maintained at a concentration (Ce) of 1.5 μg/mL. The

remimazolam group (group RA) was induced slowly (>60 s) by a bolus remimazolam dose of 80 μg/kg with the same rate limitation (<700 mL/h) followed by a maintenance dose of 5 μg/kg/min as previously reported (32). Five min after the completion of intravenous induction; if MOAA/S > 3, a bolus remimazolam (2.5 mg) was immediately administered as an intravenous bolus until MOAA/S = 3 was reached. If the patient reported injection pain during intravenous induction, 40 mg of lidocaine was immediately administered as an intravenous bolus. The anesthesiologist recorded the sedation induction time after reaching MOAA/S = 3. Routing local anesthesia were performed by dentist with 4% articaine hydrochloride and epinephrine tartrate injection (1.7 ml:68 mg, Produits Dentaires Pierre Rolland; SFDA No. H20140732), with the maximum dosage not exceeding 5 mg/kg. Surgery was started 5 min after local anesthetic infiltration was complete. MOAA/S remained between three and four in both groups. Both anesthetics were discontinued after the last suture was completed.

Participants were immediately transferred to the post-anesthesia care unit (PACU) after procedure. While the patient was in the PACU, vital signs (HR, MAP, and SpO_2) were continuously monitored every 5 min. The MOAA/S score was determined every minute with the patient undisturbed until a MOAA/S score of five was reached, and the recovery time was recorded by a recovery room nurse. Time to discharge from the hospital was determined using Chung's post-anesthetic discharge scoring system (33). Chung's post-anesthetic discharge scoring system was repeated every 5 min thereafter until the patient was >9. Post-operative adverse events that occurred during recovery period were recorded and managed instantly. Intravenous ondansetron (4 mg) was administered as required for post-operative nausea and vomiting (PONV) events. Appropriate post-operative instructions were provided, intravenous catheters and infusions were stopped, and follow-up preparations were made. Upon reaching the required discharge score, the patients were asked to fill out a satisfaction questionnaire about moderate sedation techniques. The following points were used to measure patient satisfaction with the sedatives using a Likert 5-point scale: (1) indicating "very much"; (2) satisfied; (3) neutral; (4) dissatisfied; and (5) very dissatisfied. Both groups received the same medications, namely amoxicillin 1 g (1 tablet every 12 h) and NSAID pain relievers (NSAID) and theirsutures were removed 7 days post-operatively.

The next day, patients were asked to completed a short questionnaire from a WeChat applet to collect information about potential adverse events for tele-consultant during COVID-19 pandemic. They were asked if they had experienced any post-operative adverse reactions within the past 24 h. For example, PONV was defined as any additional complaints regarding moderate sedation.

Outcomes measures

Primary outcome

The primary outcomes of this study were various adverse events, such as injection pain, low SpO_2, bradycardia, and hypotension (see Table 1 for definitions). These events can be treated with intravenous atropine or mask assistant ventilation. Adverse events, including injection pain, bradycardia (<50 beats/min), hypotension (systolic blood pressure >30% or <90 mmHg from baseline, diastolic blood pressure < 50 mmHg), or low SpO_2 (SpO_2 < 95%), were recorded and counted.

Secondary outcome

Patient vital sign data fluctuations, including mean arterial pressure (MAP), HR, SpO_2, RR, MOAA/S, SE, and RE were recorded at all timepoints. The Surgeon Satisfaction Survey was recorded immediately after the surgery was completed, and in the recovery room, the duration of arousal and PACU staying were recorded by anesthesiologists blinded to the group assignments. Sedation depth measurements were acquired every 5 min using the MOAA/s scores of by assistant nurses. The results of the patient satisfaction survey were recorded before charging.

Exploratory outcomes

The WeChat applet (Pic 1) was used to collect information about potential adverse events related to alfentanil. These symptoms included nausea, emesis, pain, bleeding, and pruritus.

Statistical analysis

All statistical analyses were performed using the IBM SPSS Statistics software, version 26 (IBM Corp., Armonk, NY, USA). Continuous variables are reported as mean and standard deviation (SD). The normality test statistical software in SPSS was used for data analysis to determine whether the data fit a normal distribution. Normally distributed continuous variables were expressed as mean ± standard deviation and analyzed using Student's *t*-test. The Mann–Whitney *U*-test was used for non-normally distributed continuous variables. Hemodynamic and respiratory parameters were compared using a repeated-measures analysis of variance. Categorical data are presented as frequencies and percentages. Statistical differences between the groups were tested using the chi-square test or Fisher's exact test. Statistical significance was set at $P < 0.05$.

Results

Patients

From March 2022 to April 2022, 110 patients were enrolled in the study and randomly assigned to treatment

TABLE 1 Sedation protocol in the two groups.

Group	Analgesic dose	Initial dose	Maintain dose	Top-up dose
RA	Alfentanil 0.2 μg/kg/min continuous infusion from 2 minutes before the start of sedation until the end of the procedure	A bolus remimazolam dose of 80 μg/kg inject slowly (>60 s)	5 μg/kg/min continuous infusion	2.5 mg
PA		An initial concentration (Ce) of 1.8 μg/mL	Maintenance concentration (Ce) of 1.5 μg/mL	Ce 0.2 μg/mL

Schemes used during sedation; alfentanil was combined with either remimazolam or propofol.

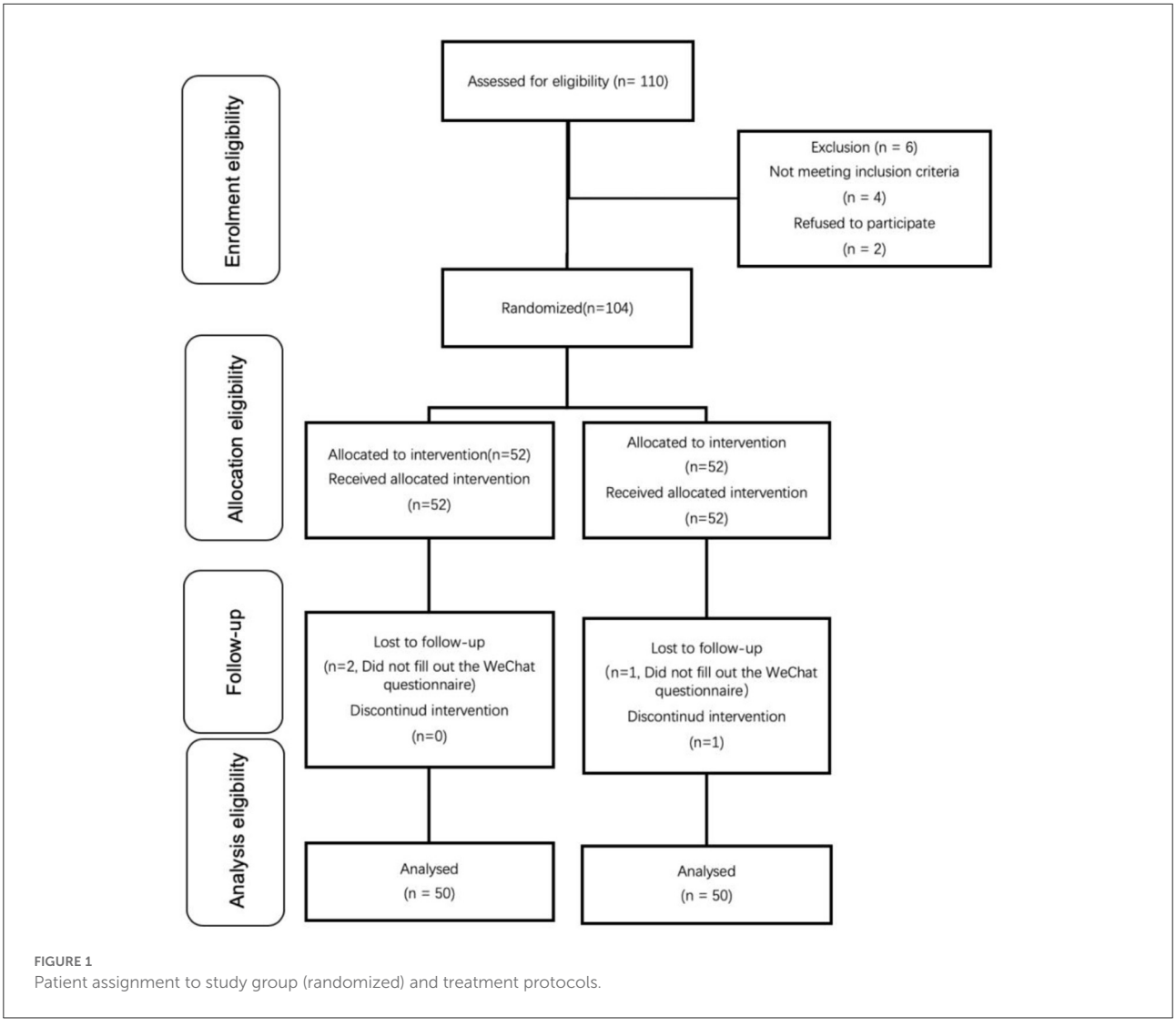

FIGURE 1
Patient assignment to study group (randomized) and treatment protocols.

groups. Of these, six were not randomized and four were lost to follow-up, leaving 100 patients available for analysis (Figure 1). The baseline characteristics of the patients enrolled in the study are presented in Table 2. Their age, sex, weight, height, and time of surgery were no statistical difference between the groups after randomization.

A pilot study of outpatient third molar extraction using target-controlled infusion of propofol in combination with alfentanil reported that their incidence of various intraoperative

TABLE 2 Baseline demographic and clinical characteristics.

	Group RA ($n = 50$)	Group PA ($n = 50$)	*P*-value	[Mean (95% CI)]
Age (years)	30.5 (21.59)	29.0 (21.58)	0.19	2.000 (−1.000, 5.000)
Weight (kg)	55.73 ± 8.92	57.18 ± 7.01	0.39	−1.450 (−4.774, 1.874)
Height (cm)	163.46 ± 6.65	163.58 ± 7.00	0.93	−0.120 (−2.832, 2.592)
Male: female	12/38	14/36	0.65	0.812 (0.332, 1.989)
MDAS	13.80 ± 5.12	12.58 ± 4.25	0.11	1.220 (−0.647, 3.087)
Duration of surgery (min)	28.12 ± 4.48	29.28 ± 4.02	0.18	−0.160 (−2.850, 0.592)

Results are presented as mean ± standard deviation and age values are median (range), and there were no significant differences between the treatment groups ($p > 0.05$); 95% CI:95% confidence interval.
MDAS, modified dental anxiety scale.

TABLE 3 The definition and incidence of adverse events.

Treatment-emergent adverse event	Definitions	No. (%)		*P*-value	[Mean (95% CI)]
		Group RA ($n = 50$)	Group PA ($n = 50$)		
Injection pain	Patient self-reported pain in arm when initiating drug intravenous sedation	2 (4%)	13 (26%)	0.004*	0.119 (0.025, 0.558)
Low SpO_2	Intraoperative $SpO_2 < 95\%$	0	2 (4%)	0.50	1.042 (0.984, 1.102)
Bradycardia	Intraoperative HR < 55 bpm	0	2 (4%)	0.50	1.042 (0.984, 1.102)
Hypotension	Intraoperative SBP < 9 0 mmHg	1 (2%)	8 (16%)	0.03*	0.107 (0.013, 0.892)
Nausea	Nausea in the hospital	1 (2%)	0	1	0.980 (0.980, 1.020)
Vomiting	Vomiting in the hospital	0	0	-	-
Hiccup	Hiccup in the hospital	2 (4%)	0	0.495	0.960 (0.907, 1.016)
Total		6 (12%)	25 (50%)	<0.05*	0.136 (0.049, 0.377)

Values are presented as numbers (%).
*Statistically significant differences ($p < 0.05$, the chi-square test or Fisher's exact test) for quantitative variables.
HR, heart rate; SBP, systolic blood pressure.

adverse events was 25%. The results of our small pilot trial showed that the incidence of clinical adverse events was significantly reduced to 5% when remimazolam was used in combination with alfentanil. Using an α error rate for the control of false positives of 0.05 and power to detect a difference if one exists (to control the false negative rate) of 80%, 49 patients per group were needed for this study (PASS 15.0, NCSS, USA). Anticipating dropouts and missing data, we planned to enroll 55 patients in each group (34).

Primary outcome

Adverse events

The proportion of patients experiencing adverse events in group RA 6 (12%) was lower than in group PA 25 (50%) [mean difference 0.136 (95% CI, 0.049–0.377); $P < 0.05$], with no serious adverse events occurring during the sedation procedure in either group. The incidence of injection pain in group RA was significantly lower than that in group PA [4 vs. 26%, mean difference 0.119 (95%CI, 0.025–0.558); $P = 0.004$]. The incidence of other adverse events, including low SpO_2, bradycardia, nausea, and vomiting, was not significantly different between the two groups ($p > 0.05$). In our study, two patients developed hiccups while receiving remimazolam sedation (Table 3). The hiccup symptoms disappeared 10 min and 12 min after drug withdrawal, respectively.

Secondary outcomes

MOAA/S score and entropy index

In this study, the rate of moderate sedation success was 100% in both groups. The MOAA/S, SE, and RE scores were similar during surgery, indicating that the depth of sedation was effective (Figure 2).

Cardiorespiratory alterations

Figure 3 shows the trends of average blood pressure, heart rate, SpO_2, and respiratory rate before and after medication. Before receiving the study drugs, patients in both groupshad similar MAP, HR, SpO_2, and RR values (baseline) in the two groups ($P > 0.05$). Five min after injection of the study drug, the MAP, HR, and respiratory rate of group PA at time T1 were reduced compared to those of group RA [8.580, (95%CI, 5.729–11.431); $P < 0.05$, 9.840, (95%CI, 6.595–13.085); $P < 0.05$, 1.480 (95%CI, 0.853–2.107); $P < 0.05$, respectively]. There was no significant difference in the MAP, HR, and respiratory rate of the two groups at the T2-4 time points ($P > 0.05$). During the induction of sedation, two patients had bradycardia (HR < 55 bpm) and nine had hypotension (SBP < 90 mmHg), but these conditions improved rapidly when local anesthesia began. There was no significant difference in the mean SpO_2 values between the two groups. Although two patients in Group PA had low SpO_2 (SpO_2 < 95%) during moderate sedation, this condition quickly recovered when the patient was tapped on the shoulder to wake up and was told to take a deep breath. None of the patients required treatment for a decreased heart rate, blood pressure, or low SpO_2.

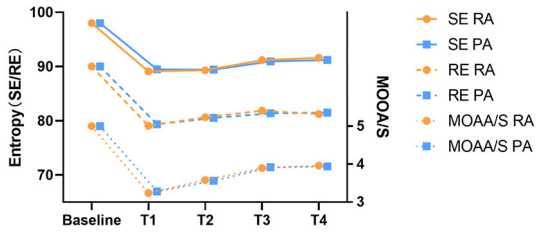

FIGURE 2
The depth of Sedation alterations during the moderate sedation.Baseline, before administration of remimazolam/propofol; T1, at the start of the local anesthesia; T2, at the start of the operation; T3, 15 min after the start of the operation; T4, end of the operation. MOAA/S, the Modified observer alertness/sedation assessment.

PACU stay

The recovery time to MOAA/S 5 of group RA was (5.48 min ± 1.57), which was significantly shorter than that of group PA (7.44 min ± 1.82) [−1.960 (95%CI, −2.634 to −1.286); $P < 0.01$]. Similarly, the time to discharge in group PA (21.66 min ± 4.50) was significantly longer than that in group RA (17.28 min ± 3.20) [−4.380 (95%CI, −2.850 to 0.592) $P < 0.01$] (Table 4).

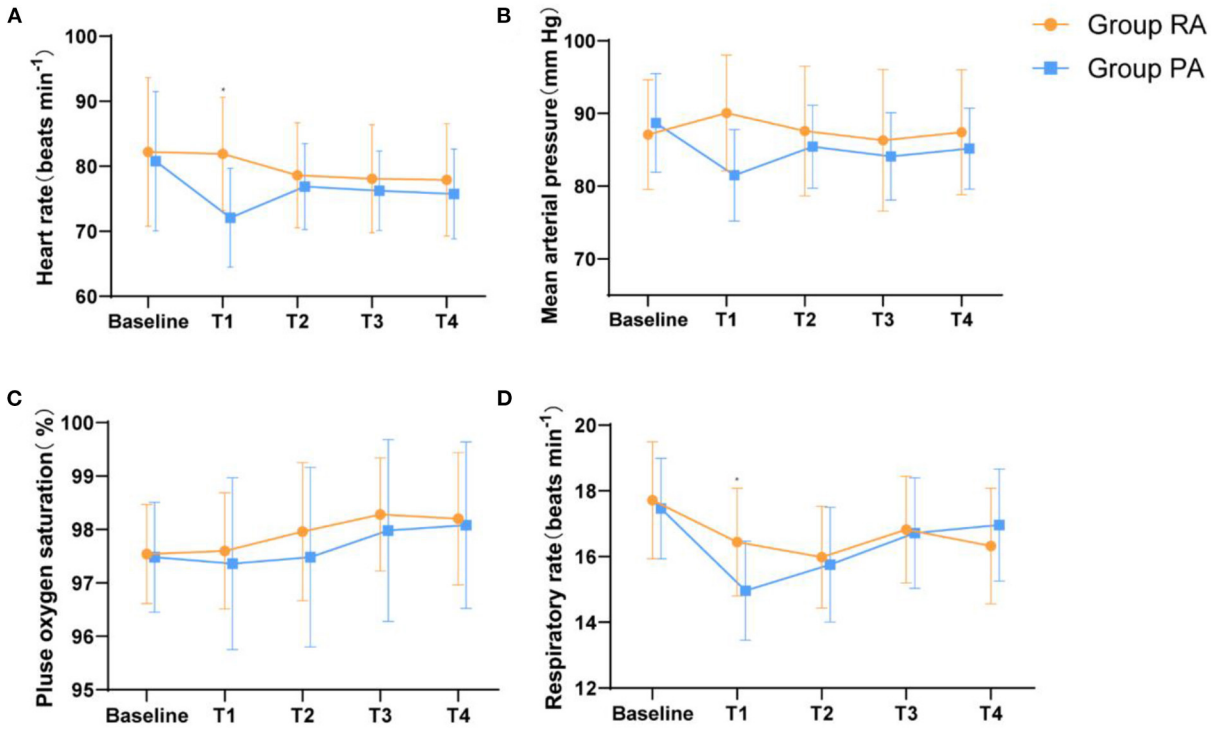

FIGURE 3
Haemodynamic and respiratory parameters changes during the moderate sedation. **(A)** HR, **(B)** MAP, **(C)** RR, and **(D)** SpO_2.Baseline, before administration of remimazolam/propofol; T1, at the start of the local anesthesia; T2, at the start of the operation; T3, 15 min after the start of the operation; T4, end of the operation. Data are expressed as mean (SD). *$P < 0.05$ compared with Group PA.

TABLE 4 Comparison of time for recovery and time to discharge between the two groups.

	Group RA ($n = 50$)	Group PA ($n = 50$)	*P*-value	[Mean (95% CI)]
Recovery time to MOAA/S 5 (min)	5.48 ± 1.57	7.44 ± 1.82	<0.05*	−1.960 (−2.634, −1.286)
Time to discharge (min)	17.28 ± 3.20	21.66 ± 4.50	<0.05*	−4.380 (−5.931, −2.828)

Results are presented as mean ± standard deviation. p-values obtained by the Student's t-test.
*Statistically significant differences between groups. 95% CI: 95% confidence interval.

TABLE 5 Comparison of the sedation satisfaction survey between the two groups.

	Group RA ($n = 50$)	Group PA ($n = 50$)	*P*-value	[Mean (95% CI)]
VAS score of surgeon satisfaction	1.48 ± 1.01	1.58 ± 1.75	0.73	−0.100 (−0.734, 0.495)
Patient satisfaction (5-pt Likert scale, 1 = very satisfied)	1.12 ± 0.33	1.20 ± 0.40	0.28	−0.080 (−0.226, 0.661)

Results are presented as mean ± standard deviation and there were no significant differences between the treatment groups ($p > 0.05$); 95% CI: 95% confidence interval.
VAS, visual analog scale.

Satisfaction survey

The results of the satisfaction questionnaires completed by the patients using 5-point Likert scales and the VAS scores of the surgeon are shown in Table 4. Although the mean total patient satisfaction scores were higher in the remimazolam group (1.12 ± 0.33) than in the propofol group (1.20 ± 0.40), the difference was not statistically significant [−0.080 (95%CI, −0.226 to 0.661), $P = 0.28$]. There was also no significant difference between the two groups in the surgeon satisfaction scores for the VAS scores [0.460, (95%CI, −0.324 to 1.243), $P = 0.25$] (Table 5).

Exploratory outcomes

There was no significant difference in the incidence of PONV between the two groups. Four patients in group RA and two patients in groupPA experienced nausea [8 vs. 4%, 2.087 (95%CI, 0.365–11.948); $P = 0.68$]. Two patients in group RA and 0 patients in group RA experienced vomiting [4 vs. 0%, 0.321 vs. 0.960 (95%CI, 0.907–1.016); $P = 0.50$]. No other clinically relevant adverse events were observed (Table 6).

Discussion

This study aimed to evaluate the efficacy and safety of moderate sedation by remimazolam with alfentanil vs. propofol with alfentanil in ambulatory third molar extraction. Our trial had two important findings. First, remimazolam has a low incidence of adverse reactions related to sedation. Second, remimazolam had a rapid onset of action and prompt recovery of cognitive function. Therefore, our results proved remimazolam besylate continuous pump injection consider to be a safe moderate sedation method for third molar extraction in dental clinics. The results of this study confirmed our hypothesis that adverse events were less frequent and that the onset and recovery were rapid. Throughout the course of the study we observed no serious adverse events or adverse reactions that required withdrawal from the trial in either group. The incidence of adverse events in group RA (6/50, 12%) was significantly lower than that in group PA (25/50, 50%) ($p < 0.05$). Injection pain and hypotension were the most common adverse events (Table 2; $p < 0.05$). In a previous trial in China, 384 eligible patients who underwent colonoscopy were randomized to the remimazolam and propofol groups. In this study the remimazolam group had lower incidences of hypotension [46 (23.71%) vs. 97 (51.05%)] and respiratory depression [6 (3.09%) vs. 32 (16.84%)] compared to that of the propofol group (35). Another prospective, double-blind, randomized, multicenter study reported on the efficacy of remimazolam compared with placebo and open-label midazolam at 30 sites in the United States in patients undergoing bronchoscopy and serious adverse events occurred in 5.6% of patients in the remimazolam group vs. 6.8% in the placebo group (26). Zhang et al. reported that in a single-center, randomized, controlled trial, the incidence of pain on injection was lower in the remimazolam group [1 (2.4%) vs. 33 (80.5%) than of the propofol group] (36). Our experiments further confirmed these results. Injection pain is one of the most common adverse reactions of propofol in clinical practice. Although alfentanil with propofol was previously reported to reduce the incidence of injection pain (37), our results showed that the incidence of injection pain in group PA was significantly higher than that in group RA ($P < 0.05$). These findings show that remimazolam has the same sedative effect as propofol and can effectively avoid the adverse reactions of injection pain and improve the comfort of patients. During the initial 5-min induction dose, the propofol group had a significantly decreased heart rate and MAP at 5 min

TABLE 6 Post-operative adverse effects were collected from the smartphone WeChat applet.

Sedation-related adverse events for 24 h	No. (%)			
	Group RA ($n = 50$)	Group PA ($n = 50$)	*P*-value	[Mean (95% CI)]
Nausea	4 (8%)	2 (4%)	0.68	2.087 (0.365, 11.948)
Vomiting	2 (4%)	0	0.50	0.960 (0.907, 1.016)
Intestinal bloating	0	0	-	-
Constipation	0	0	-	-
Pruritus	0	0	-	-
Headache	0	0	-	-
Others	0	0	-	-

Data were analyzed using chi-square test or the fisher exact test. 95% CI: 95% confidence interval.

of dosing which increased steadily after the initiation of local anesthesia injection. Two of the patients had heart rates below 55 during the induction period, which was associated with a basal heart rate of <60, but their heart rates increased to above 60 after receiving local anesthesia. In this study, two patients in the PA group developed low SpO_2, while no patients in the RA group developed low SpO_2. After tapping the patient's shoulder and asking the patient to breathe deeply, the oxygen saturation rose to more than 95%. However, there was no statistical difference between the two groups. In a previous study (22) in volunteers administered remimazolam, respiration was maintained, only two episodes of desaturation were noted, which were both managed with simple measures.

In this study, propofol infusion under TCI mode in Group PA, The prespecified target propofol concentration (1.8 μg/mL) in this study was chosen because Oei-Lim et al. previously reported that patients undergoing minor dental procedures were sedated but responsive to verbal stimuli at the target site at concentrations of ∼1–1.5 μg/mL in the absence of opioids. The alfentanil doses used in this study were determined based on previous studies (38, 39). An infusion rate of 0.2 μg/kg/min was chosen because Avramov and White (38) reported excellent intraoperative sedation, analgesia, and amnesia with continuous infusion of propofol (25–50 μg/kg/min) with a low incidence of side effects with available rate infusion of alfentanil (0.2–0.4 μg/kg/min). However, ultra-short-acting sedatives such as remimazolam require multiple refills in most procedures. To avoid this situation, group RA was induced by a bolus of remimazolam, followed by a continuous infusion, as previously reported (32) we believe that continuous infusion of remimazolam during dental procedures will help achieve good and smooth sedation.

Similar to the bispectral index (BIS), the entropy index is a commonly used monitoring method for sedation depth in surgery, and it has been confirmed to have a good correlation with the MOAA/S score (40–43). However, BIS is more of an anesthesia depth monitoring index designed for propofol, so we used the entropy index to more accurately compare the sedative effects of propofol and benzodiazepines (44). SE and RE have been shown to correlate strongly with OAA/S ($r^2 = 0.58$ and 0.61, respectively) during propofol-induced loss of consciousness followed by an episode of wakefulness (43). Balci et al. (40) showed that entropy corresponded to the level of sedation, so we used entropy to monitor the hypnotic level induced by our sedative agents. There was no statistical difference in entropy (SE and RE) between the two groups throughout the sedation period. Furthermore, patient and surgeon satisfaction with the two sedation combinations in our study was similar. In addition, there was no statistically significant difference in patient satisfaction between the two groups.

In the recovery room, we did not observe differences in patient response to recovery time measured using entropy. We also found that the time (minutes) to reach MOOA/S 5 was significantly shorter in group RA (5.5 min) than in group PA (7.4 min) according to the MOOA/S sedation score. The time to reach the discharge score was also significantly shorter in group RA (17.3 min) than that in group PA (21.7 min) ($P < 0.05$). The surgery in this study was a day-case surgery, and all sedation was performed on outpatient settings. The time from the end of surgery to when our patients were ready to be discharged from the hospital was significantly shorter in the remimazolam group, reducing their overall length of hospital stay. Previous U.S. phase I pharmacokinetic trials demonstrated that remimazolam had an onset time of 1–3 min and a steady-state half-life of 7–8 min after a 2-h simulated infusion similar to propofol (22). Mertens et al. reported a 17% higher blood concentration from continuous infusion of propofol in combination with alfentanil (45). They hypothesized that alfentanil reduces propofol clearance, distribution clearance, and the peripheral volume of distribution.

Sedative hypnotic drugs and opioids are known to increase the risk of PONV, which can negatively impact patient comfort, increase post-operative morbidity, and prolong the need for monitoring post-operative care, all of which delay patient outcomes. These adverse effects can be avoided through the use of rapidly metabolized opioids during oral outpatient sedation (e.g., alfentanil and propofol do not increase nausea and vomiting) (46). The incidence of nausea and vomiting during the recovery period and post-operatively was similar in our remimazolam and propofol groups. We observed symptoms of hiccups during the sedation procedure in two patients in the remimazolam group, which disappeared within 10 and 12 min of stopping the drug without medication treatment. Several previous studies have reported hiccups as an adverse event during remimazolam infusion, with a low incidence (47, 48). Chen et al. reported that hiccups occurred "frequently" in patients who received remimazolam 0.4 mg/kg in 1 min followed by infusion in 1.5 mg/kg/h (49). This may be related to the bolus rate of remimazolam administered during sedation induction. Although remimazol-induced hiccups, they are self-limiting and these adverse events should be focused on patients undergoing dental treatment who are at risk of regurgitation and aspiration.

This study had two minor limitations. This was a single-center survey with a relatively small sample size, which limited the statistical analysis of our two groups of patients. Second, this study only provided descriptive statistics and simple statistical analysis of entropy and sedation depth, and further correlation analysis of entropy index and sedation depth may improve our understanding of the findings.

In conclusion, in patients undergoing third molar extraction, moderate sedation by a bolus remimazolam dose of 80 μg/kg and followed by a maintenance dose of 5 μg/kg/min with 0.2 μg/kg/min of alfentanil continuous infusion had similar sedative efficacy, patient satisfaction, fewer adverse effects, and faster onset and recovery times compared with propofol with alfentanil.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Ethics Committee of Chongqing Medical University. The patients/participants provided their written informed consent to participate in this study.

Author contributions

Study design, conduct, analysis, and manuscript preparation: CY, JZ, NZ, and JW. Patient recruitment, conduct of the study, and interpretation of data: JW, LF, CZ, SHZ, BZ, and KL. Study design and finalizing the manuscript: CY, JZ, and NZ. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Postoperative analgesia efficacy of erector spinae plane block in adult abdominal surgery: A systematic review and meta-analysis of randomized trials

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Objectives: Erector spinae plane block (ESPB) has been used for many thoracic and abdominal surgeries. However, evidence of its analgesic efficacy following abdominal surgery, compared with that of thoracic analgesia, is insufficient. Our study explored the analgesic effect of ESPB after abdominal surgery.

Methods: We searched PubMed, Embase, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov. Primary outcomes were pain scores at 6, 12 and 24 h and 24-h opioid consumption. Secondary outcomes included time to first rescue analgesia, length of hospital stay, and incidence of postoperative nausea and vomiting (PONV). We calculated standardized mean differences (SMDs) with 95% confidence intervals (CIs) for primary outcomes and mean differences (MDs) and risk ratios (RRs) with 95% CIs for secondary outcomes.

Results: We systematically included 1,502 cases in 24 trials. Compared with placebo, ESPB significantly reduced pain scores at 6 h (SMD −1.25; 95% CI −1.79 to −0.71), 12 h (SMD −0.85; 95% CI −1.33 to −0.37) and 24 h (SMD −0.84; 95% CI −1.30 to −0.37) and 24-h opioid consumption (SMD −0.62; 95% CI −1.19 to −0.06) post-surgery. ESPB prolonged the time to first rescue analgesia and decreased the incidence of PONV. Compared with transversus abdominal plane block (TAPB), ESPB significantly reduced pain scores at 6, 12, and 24 h and 24-h opioid consumption and prolonged the time to first rescue analgesia postsurgically. Furthermore, subgroup analysis showed that ESPB significantly reduced pain scores at various time points and opioid consumption within 24 h after laparoscopic cholecystectomy, percutaneous nephrolithotomy and bariatric surgery.

Conclusion: Compared with placebo, ESPB improves the postoperative analgesic efficacy after abdominal surgery. Furthermore, our meta-analysis confirmed that ESPB provides more beneficial analgesic efficacy than TAPB.

Systematic review registration: [https://www.crd.york.ac.uk/PROSPEROFILES/301491_STRATEGY_20220104.pdf], identifier [CRD42022301491].

KEYWORDS

erector spinae plane block, abdominal surgery, nerve block, opioid consumption, anesthesia

Introduction

Abdominal surgery is one of the most common surgical procedures clinically, and postoperative pain is a foreseeable problem. Although epidural analgesia yields good analgesic effects in major open abdominal surgery (1–4), its application is limited by the use of coagulants (5), which have unforeseeable effects on blood coagulation and compromise the safety of neuraxial techniques (6). In recent years, clinical guidelines have proven that nerve block has a better benefit/risk ratio (RR) than central neuraxial blocks and have recommended that nerve block should be performed to relieve pain after primary thoracoabdominal surgeries (7, 8). However, transversus abdominal plane block (TAPB) has several drawbacks as the nerve block is currently mainly used for abdominal surgery. For example, the needle tip may pierce the transversus abdominis (and peritoneum), injuring the internal organs and peritoneum while inducing TAPB (9).

Erector spinae plane block (ESPB) was first reported in 2016 by Forero et al. (10) and has gained much attention due to its safety and ease of application. In this technique, the local anesthetic (LA) is injected into the fascia between the erector spinae and the transverse process and diffuses in this fascia, which can block the nearby spinal nerve. ESPB not only affects the dorsal and ventral rami of spinal nerves and causes temporary loss of sensation in the corresponding body surface sensory areas innervated by them but also affects the rami communicants that transmit sympathetic fibers. It has been proven that ESPB provides both somatic and visceral sensory blocks of the abdomen (10, 11), which makes it an ideal nerve block for abdominal surgery.

There has been an increasing amount of new evidence regarding ESPB's effectiveness in preventing pain during abdominal surgery. However, thus far, most meta-analyses have focused mainly on validating the effects of ESPB in thoracic or breast surgery and comparing them with thoracic paravertebral blocks, there is a lack of studies exploring their effectiveness in abdominal surgery or comparing them with other trunk blocks such as TAPB. The current meta-analyses (12–15) only included a small number of studies involving abdominal surgery and Daghmouri et al. (16) only researched the effect of ESPB in laparoscopic cholecystectomy (LC).

Therefore, our systematic review and meta-analysis aimed to determine the analgesic effect of ESPB after abdominal surgery. We identified randomized controlled trials (RCTs) comparing ESPB with either placebo or TAPB.

Methods

This systematic review and meta-analysis were performed and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (17). Our meta-analysis was registered prospectively with PROSPERO (CRD42022301491).

Search strategy

Literature searches were performed using PubMed, Embase, the Cochrane Central Register of Controlled Trials, and the ClinicalTrials.gov register from 2016 until 24 September 2021 for English RCTs meeting the listed inclusion criteria, as ESPB is a new regional nerve block first introduced in 2016. The search used the MeSH keywords "Paraspinal Muscles," "Cardiac Surgical Procedures," "Nerve Block," and "Anesthesia, Local." The detailed search strategy is provided in **Supplementary Appendix A**.

Study selection criteria

The two authors (GZ and LL) independently screened the search results and included trials that met the following criteria: (i) adult patients (age ≥18 years) treated with abdominal surgery, including LC, percutaneous nephrolithotomy (PCNL) and bariatric surgery (BS), etc., under general anesthesia; (ii) interventions: treatment with a single-injection ESPB with LA

before or after surgery; and (iii) controls: placebo (no block and sham block) and TAPB. (iv) One or more of the following outcomes were assessed: postoperative pain scores at 6, 12 and 24 h, 24-h postoperative cumulative opioid consumption (mg), the incidence of postoperative nausea and vomiting (PONV) within 24 h postoperatively; length of hospital stay (days); time to first rescue analgesia (hours). (v) Only studies published in English were included. (vi) Only studies that were RCTs were included.

In our meta-analysis, trials were excluded that met the following criteria: (i) studies which did not provide available data (ii) studies which were withdrawn;

Data extraction

Two investigators (GZ and LL) independently reviewed the full manuscripts of eligible studies and conducted data extraction using a standardized form. Extracted data included the author names, publication year; sample size; type of surgery; unilateral or bilateral; comparator(s); LA type, concentration, and volume; timing of block (before or after surgery); guidance of ESPB (ultrasound-guided or fluoroscopy-guided); postoperative outcomes including postoperative pain scores, 24-h cumulative opioid consumption, time to first rescue analgesia, length of hospital stay, and incidence of PONV. Any discrepancies regarding the extraction of data were resolved by an additional investigator (XW). When the pain score data were absent, they were replaced by the pain score data during movement, and if they were still absent, the pain score data were replaced by the pain score data at rest. If patients in the intervention and control groups received the same nerve block, this nerve block was not considered in this analysis.

To facilitate meta-analysis, medians, interquartile ranges (IQRs), and range values were approximated into standardized mean differences (SMDs) and mean differences (MDs) with their corresponding SDs. If data values were represented in a graphical format, numerical data were extracted from graphs by Web Plot Digitizer (18). The risk of bias assessment was independently assessed by two investigators, with any disagreements judged by a third investigator (XW), according to the Cochrane Collaboration tool for assessing the risk of bias (19). Studies were assessed on randomization, allocation concealment, participant and personnel blinding, outcome assessment blinding, incomplete data and selective reporting; each category of the study was assigned "low risk," "high risk," or "unclear risk."

Outcome measurement

Our primary outcomes were postoperative pain scores at 6, 12, and 24 h, as well as 24-h cumulative opioid consumption. Pain scores were measured by a visual or numerical scale (0–10 scale, where 0 = no pain and 10 = worst pain imaginable). Any visual analog scale (VAS) scores reported on a 0–100 scale were converted to a 0–10 scale for analysis. All reported perioperative opioid consumption was converted to intravenous morphine equivalents (20). Our secondary outcomes were the time to first rescue analgesia measured by hours after surgery, days of hospital stay after surgery, and incidence of PONV within 24 h postoperatively.

Data analysis

All meta-analyses were conducted using Review Manager V5.4.1. (Cochrane Collaboration, Copenhagen) and Stata 16.0 software. For continuous data of primary outcomes, including postoperative pain scores and 24-h cumulative opioid consumption, SMDs with a 95% confidence interval (95% CI) were calculated, but for continuous data of secondary outcomes, including length of hospital stay and time to first rescue analgesia, MDs with 95% CIs were calculated. Dichotomous data are presented by using RRs with 95% CIs.

If $I^2 > 50\%$, differences would be regard as significant (21). The random-effects model was used for all outcomes, and forest plots were used to represent and evaluate treatment effects. Subgroups were created to explore and resolve potential heterogeneity within the intervention and control groups based on the type of surgery, the timing of the block (before surgery or after surgery), and ESPB techniques (bilateral or unilateral). Subgroup analysis was performed if the number of studies included was not less than two. For outcomes with the data of ten or more studies, Egger's regression (DerSimonian–Laird approach) was used to assess potential publication bias of the small-study effect. Moreover, a sensitivity analysis was performed by removing each study in turn to evaluate the stability of pooled estimate. Sensitivity analyses were performed for those studies with a high degree of heterogeneity ($I^2 \geq 50\%$ or $P < 0.1$). Finally, pooled analyses were visualized with forest plots and tables and $P < 0.05$ was considered statistically significant.

Results

A total of 1,409 studies were identified by our search criteria, and 375 duplicates were removed. Of the 1,034 remaining studies screened, 24 studies (22–45) were included in this review (**Figure 1**), with a total of 1,502 patients (701 who received ESPB, 801 who did not). The risk of bias assessment is summarized in **Figure 2**. The main sources of bias from the included studies were the lack of a description of participant and personnel blinding.

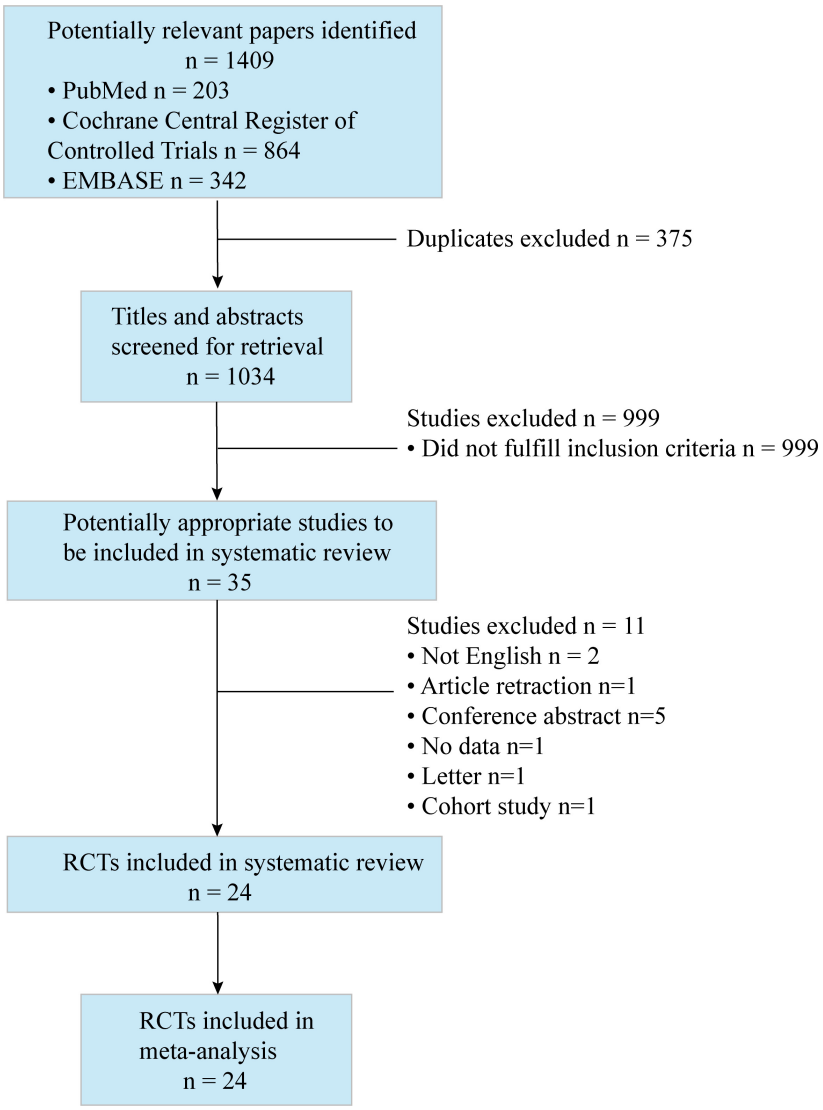

FIGURE 1
Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram. The diagram shows the process and the reason for excluding studies.

The characteristics of the included studies are summarized in **Table 1**. There were twenty RCTs (22–25, 27–32, 34, 36–39, 41–45) that compared ESPB with placebo, six studies (23, 26, 33, 35, 39, 40) that compared ESPB with TAPB. Abdominal surgeries were performed under general anesthesia in all studies: in nine studies (25, 26, 28, 33, 37, 40, 42–44) for LC, in four studies (27, 31, 34, 41) for PCNL, in three studies (23, 38, 45) for BS, in two studies (30, 36) for laparoscopic hepatectomy (LH), in two studies (32, 35) for total abdominal hysterectomy, in one study (22, 24) for hernia repair, in one study (22) for open nephrectomy, in one study (29) for open radical prostatectomy and in one study (39) for emergency laparotomy. Moreover, in the majority (20 of the 24) of the studies (22–27, 29–34, 36–40, 42, 43, 45), ESPB was performed before the surgery. Bilateral ESPB was conducted in 18 of the 24 studies (23, 24, 26, 28–30, 32, 33, 35–40, 42–45), while unilateral ESPB was used in the remaining studies (6 of the 24) (22, 25, 27, 31, 34, 41).

Postoperative pain scores

Compared with the placebo group, there was a significant reduction in postoperative pain scores in the ESPB group at various time points (**Table 2**): fifteen studies (23–25, 27–29, 31, 32, 36–38, 41, 43–46) reported significantly lower pain scores at 6 h (−1.25 cm; 95% CI −1.79 to −0.71; $P < 0.00001$; $I^2 = 93\%$) (**Figure 3A**). However, 16 studies (23–25, 27–29,

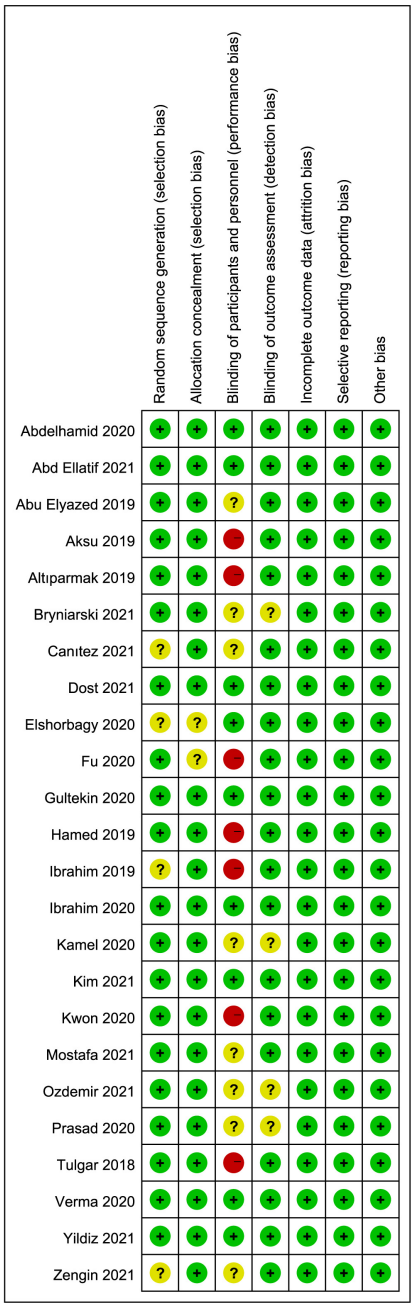

FIGURE 2
Risk of bias summary: review authors' judgments about each risk of bias item for each included study. Green circle, low risk; red circle, high risk; yellow circle, unclear risk of bias.

31, 32, 34, 36–38, 41, 43–45) reported significantly lower pain scores at 12 h (−0.85 cm; 95% CI −1.33 to −0.37; P = 0.0005; I^2 = 91%) (**Figure 3B**) and 24 h (−0.84 cm; 95% CI −1.30 to −0.37; P = 0.0004; I^2 = 91%) (**Figure 3C**). In our meta-analysis, compared with TAPB, ESPB significantly reduced pain scores at time points after abdominal surgery (**Table 2**): three trials (23, 35, 40) reported significantly lower pain scores at 6 h (−0.71 cm; 95% CI −1.18 to −0.24; P = 0.003; I^2 = 51%) (**Figure 4A**) after abdominal surgery and four studies (23, 26, 35, 40) revealed significantly lower postoperative pain scores at 12 h (−1.00 cm; 95% CI −1.54 to −0.46 P = 0.0003; I^2 = 65%) (**Figure 4B**) and 24 h (−0.84 cm; 95% CI −1.37 to −0.30; P = 0.002; I^2 = 73%) (**Figure 4C**). Moreover, we conducted subgroup analyses to determine the postoperative analgesia conferred by ESPB compared with placebo in different types of surgery. The subgroup analysis of primary outcomes was performed as follows.

In the subgroup analysis of LC, five trials (25, 28, 37, 43, 44) reported that, compared with placebo, ESPB significantly reduced pain scores at 6 h (−1.42 cm; 95% CI −2.23 to −0.60; P = 0.0006; I^2 = 91%) and 24 h (−0.98 cm; 95% CI −1.74 to −0.21; P = 0.01; I^2 = 89%) (**Table 3**). Interestingly, five trials (25, 28, 37, 43, 44) showed that no significant difference was detected in postoperative pain scores at 12 h (−0.62 cm; 95% CI −1.39 to 0.15; P = 0.11; I^2 = 90%) between the groups (**Table 3**).

In the subgroup analysis of PCNL, three studies (27, 31, 41) reported that, compared with placebo, ESPB provided comparable pain scores at 6 h (−0.42 cm; 95% CI −1.10 to 0.25; P = 0.22; I^2 = 81%) and significantly lower postoperative pain scores at 24 h (−0.44 cm; 95% CI −0.73 to −0.15; P = 0.003; I^2 = 0%) (**Table 3**). Meanwhile, four studies (27, 31, 34, 41) reported a significant reduction in postoperative pain scores at 12 h (−0.49 cm; 95% CI −0.97 to −0.02; P = 0.04; I^2 = 70%) (**Table 3**) in the ESPB group after PCNL, compared with placebo.

In the subgroup analysis of BS, three trials (23, 38, 45) revealed that, compared with placebo, ESPB significantly reduced pain scores at 6 h (−3.22 cm; 95% CI −5.95 to −0.48; P = 0.02; I^2 = 97%) (**Table 3**). However, no significant difference was found in postoperative pain scores at 12 h (−3.77 cm; 95% CI −9.77 to 2.23; P = 0.22; I^2 = 99%) and 24 h (−2.08 cm; 95% CI −4.59 to 0.42; P = 0.10; I^2 = 97%) after BS between the groups (**Table 3**).

In the subgroup analysis of LH, two studies (30, 36) found no significant difference in postoperative pain scores at 24 h (−1.59 cm; 95% CI −4.46 to 1.27; P = 0.28; I^2 = 98%) between ESPB and placebo groups (**Table 3**). However, subgroup analysis was not performed due to the limited number of studies involving pain scores at 6 and 12 h after LH.

Postoperative 24-h cumulative opioid consumption

The 24-h cumulative opioid consumption after abdominal surgery was investigated in 16 studies (22–25, 27–29, 31, 32, 34, 36–39, 41, 42), with a significant reduction (−1.44 mg; 95% CI −2.01 to −0.87; P < 0.00001; I^2 = 93%) in the ESPB group compared with the placebo group (**Table 2** and **Figure 5A**).

TABLE 1 Overview of included studies' characteristics: ESPB vs. placebo and ESPB vs. TAPB.

Study	Sample	Type of surgery	ESPB group		Control group		Block timing	Guide	Outcome
			Intervention	Local analgesia drug	Control	Local analgesia drug			
Abdelhamid et al. (23)	66	Bariatric surgery	Bilateral ESPB (n = 22)	30 ml 0.25% bupivacaine (each side)	Bilateral STAPB (n = 22) No block (n = 22)	30 ml 0.25% bupivacaine (each side)	Before surgery	Ultrasound-guided	Pain scores; opioid consumption within 24 postoperative hours; time to first rescue analgesia; incidence of PONV
Abd Ellatif and Abdelnaby (22)	75	Open nephrectomy	Unilateral ESPB (n = 25)	0.3–0.4 ml/kg 0.25% bupivacaine with a maximum volume of 30 ml	No block (n = 25)	0.3–0.4 ml/kg 0.25% bupivacaine with a maximum volume of 30 ml	Before surgery	Ultrasound-guided	Opioid consumption within 24 postoperative hours; the first time to rescue analgesia; length of hospital stay
Abu Elyazed et al. (24)	60	Open epigastric hernia repair	Bilateral ESPB (n = 30)	20 ml 0.25% bupivacaine (each side)	Sham block (n = 30)	/	Before surgery	Ultrasound-guided	Pain scores; opioid consumption within 24 postoperative hours; time to first rescue analgesia; incidence of PONV;
Aksu et al. (25)	46	Laparoscopic cholecystectomy	Unilateral ESPB (n = 23)	20 ml 0.25% bupivacaine	No block (n = 23)	/	Before surgery	Ultrasound-guided	Pain scores; opioid consumption within 24 postoperative hours; incidence of PONV
Altıparmak et al. (26)	68	Laparoscopic cholecystectomy	Bilateral ESPB (n = 34)	20 ml 0.375% bupivacaine (each side)	OSTAPB (n = 34)	20 ml of 0.375% bupivacaine (each side)	Before surgery	Ultrasound-guided	Pain scores; opioid consumption within 24 postoperative hours; incidence of PONV
Bryniarski et al. (27)	68	Percutaneous nephrolithotomy	Unilateral ESPB (n = 34)	20 ml 0.5% bupivacaine	No block (n = 34)	/	Before surgery	Ultrasound-guided	Pain scores; opioid consumption within 24 postoperative hours; incidence of PONV
Canıtez et al. (28)	82	Laparoscopic cholecystectomy	Bilateral ESPB (n = 41)	20 ml consisting of 7.5 ml 0.5% bupivacaine + 2.5 ml 2% lidocaine + 10 ml 0.9% saline (each side)	No block (n = 41)	/	After surgery	Ultrasound-guided	Pain scores; opioid consumption within 24 postoperative hours; incidence of PONV
Dost et al. (29)	50	Open radical prostatectomy	Bilateral ESPB (n = 25)	10 ml 1% lidocaine + 10 ml 0.5% bupivacaine (each side)	Sham block (n = 25)	/	Before surgery	Ultrasound-guided	Pain scores; opioid consumption within 24 postoperative hours
NCT03989570 (39)	93	Emergency laparotomies	Bilateral ESPB + sham TAPB (n = 31)	ESPB with 40 ml 0.25% bupivacaine/TAPB with 40 ml 0.9% saline	Bilateral TAPB/sham ESPB (n = 31) No block (n = 31)	TAPB with 40 ml 0.25% bupivacaine/ESPB with 40 ml 0.9% saline	Before surgery	Ultrasound-guided	Opioid consumption within 24 postoperative hours; time to the first rescue analgesia
Fu et al. (30)	60	Laparoscopic hepatectomy	Bilateral ESPB (n = 30)	20 ml 0.5% ropivacaine (each side)	No block (n = 30)	/	Before surgery	Ultrasound-guided	Pain scores; length of hospital stay

(Continued)

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TABLE 1 (Continued)

Study	Sample	Type of surgery	ESPB group		Control group		Block timing	Guide	Outcome
			Intervention	Local analgesia drug	Control	Local analgesia drug			
Gultekin et al. (31)	60	Percutaneous nephrolithotomy	Unilateral ESPB (n = 30)	20 ml 0.5% bupivacaine	No block (n = 30)	/	Before surgery	Ultrasound-guided	Pain scores; opioid consumption within 24 postoperative hours; length of hospital stay; time to the first rescue analgesia
Hamed et al. (32)	60	Total abdominal hysterectomy	Bilateral ESPB (n = 30)	20 ml 0.5% bupivacaine (each side)	Sham block (n = 30)	/	Before surgery	Ultrasound-guided	Pain scores; opioid consumption within 24 postoperative hours; length of hospital stay
Ibrahim and Elnabtity (34)	50	Percutaneous nephrolithotomy	Unilateral ESPB (n = 25)	30 ml 0.25% bupivacaine	Sham block (n = 25)	/	Before surgery	Ultrasound-guided	Pain scores; opioid consumption within 24 postoperative hours; time to the first rescue analgesia; incidence of PONV
Ibrahim (33)	63	Laparoscopic cholecystectomy	Bilateral ESPB (n = 21)	20 ml 0.25% bupivacaine hydrochloride (each side)	OSTAP (n = 21)	20 ml 0.25% bupivacaine hydrochloride (each side)/ 40 ml 0.25% bupivacaine + sham block	Before surgery	Ultrasound-guided	Opioid consumption within 24 postoperative hours; time to the first rescue analgesia; incidence of PONV
Kamel et al. (35)	48	Total abdominal hysterectomy	Bilateral ESPB (n = 24)	20 ml bupivacaine 0.375% + 5 μg/ml adrenaline (each side)	Bilateral TAPB (n = 24)	20 ml of bupivacaine 0.375% + 5 μg/ml adrenaline (each side)	After surgery	Ultrasound-guided	Pain scores; opioid consumption within 24 postoperative hours; time to the first rescue analgesia; incidence of PONV
Kim et al. (36)	70	Laparoscopic hepatectomy	Bilateral ESPB (n = 35)	40 ml 0.5% ropivacaine	No block (n = 35)	/	Before surgery	Ultrasound-guided	Pain scores; opioid consumption within 24 postoperative hours; time to the first rescue analgesia; incidence of PONV
Kwon et al. (37)	53	Laparoscopic cholecystectomy	Bilateral ESPB (n = 26)	ESPB with 20 ml 0.20% ropivacaine (each side)	No block (n = 27)	15 ml 0.20% ropivacaine (each side)	Before surgery	Ultrasound-guided	Pain scores; opioid consumption within 24 postoperative hours; incidence of PONV
Mostafa et al. (38)	60	Bariatric surgery	Bilateral ESPB (n = 30)	20 ml 0.25% bupivacaine (each side)	Sham block (n = 30)	/	Before surgery	Ultrasound-guided	Pain scores; opioid consumption within 24 postoperative hours; time to the first rescue analgesia; incidence of PONV
Ozdemir et al. (40)	64	Laparoscopic cholecystectomy	Bilateral ESPB (n = 32)	10 ml 0.25% bupivacaine + 10 ml 2% prilocaine (each side)	Bilateral STAPB (n = 32)	10 ml 0.25% bupivacaine + 10 ml 2% prilocaine (each side)	Before surgery	Ultrasound-guided	Pain scores; opioid consumption within 24 postoperative hours; length of hospital stay

(Continued)

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TABLE 1 (Continued)

Study	Sample	Type of surgery	ESPB group		Control group		Block timing	Guide	Outcome
			Intervention	Local analgesia drug	Control	Local analgesia drug			
Prasad et al. (41)	61	Percutaneous nephrolithotomy	Unilateral ESPB (n = 31)	20 ml 0.375% ropivacaine	No block (n = 30)	/	After surgery	Fluoroscopy-guided	Pain scores; opioid consumption within 24 postoperative hours; time to the first rescue analgesia; incidence of PONV
Tulgar et al. (42)	30	Laparoscopic cholecystectomy	Bilateral ESPB (n = 15)	20 ml 0.375% bupivacaine (each side)	No block (n = 15)	/	Before surgery	Ultrasound-guided	Opioid consumption within 24 postoperative hours
Verma et al. (43)	84	Laparoscopic cholecystectomy	Bilateral ESPB (n = 42)	20 ml 0.375% ropivacaine (each side)	Sham block (n = 42)	/	Before surgery	Ultrasound-guided	Pain scores
Yildiz et al. (44)	68	Laparoscopic cholecystectomy	Bilateral ESPB (n = 34)	10 ml 0.5% bupivacaine + 5 ml 2% lidocaine + 5 ml isotonic saline (each side)	No block (n = 34)	/	After surgery	Ultrasound-guided	Pain scores; incidence of PONV
Zengin et al. (45)	63	Bariatric surgery	Bilateral ESPB (n = 31)	20 ml 0.5% bupivacaine + 5 ml 0.2% lidocaine (each side)	No block (n = 32)	/	Before surgery	Ultrasound-guided	Pain scores

PONV, postoperative of nausea and vomiting; ESPB, erector spinae plane block; STAPB, subcostal transversus abdominis plane block; OSTAPB, oblique subcostal transversus abdominis plane block; TAPB, transversus abdominis plane block; PONV, postoperative nausea and vomiting.

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TABLE 2 Outcomes data for comparison of ESPB group versus placebo/TAPB group.

Comparison	Outcome	Participants	Trials	Relative effect (95% CI)	I^2 (%)	*P*-values
ESPB vs. placebo	6-h pain scores	929	15	SMD −1.25 (−1.79, −0.71)	93	$P < 0.00001$
ESPB vs. placebo	12-h pain scores	979	16	SMD −0.85 (−1.33, −0.37)	91	$P = 0.0005$
ESPB vs. placebo	24-h pain scores	989	16	SMD −0.84 (−1.30, −0.37)	91	$P = 0.0004$
ESPB vs. placebo	24-h opioids	906	16	SMD −1.44 (−2.01, −0.87)	93	$P < 0.00001$
ESPB vs. placebo	Length of hospital stay	230	4	MD −0.31 (−0.69, 0.07)	81	$P = 0.11$
ESPB vs. placebo	Time to first rescue analgesia	494	9	MD 6.97 (4.92, 9.02)	100	$P < 0.00001$
ESPB vs. placebo	Incidence of PONV	662	11	RR 0.67 (0.46, 0.97)	20	$P = 0.04$
ESPB vs. TAPB	6-h pain scores	156	3	SMD −0.71 (−1.18, −0.24)	51	$P = 0.003$
ESPB vs. TAPB	12-h pain scores	224	4	SMD −1.00 (−1.54, −0.46)	65	$P = 0.0003$
ESPB vs. TAPB	24-h pain scores	224	4	SMD −0.84 (−1.37, −0.30)	73	$P = 0.002$
ESPB vs. TAPB	24-h opioids	308	6	SMD −1.85 (−2.54, −1.15)	81	$P < 0.00001$
ESPB vs. TAPB	Length of hospital stay	64	1	MD −0.13 (−0.18, −0.08)	/	$P < 0.00001$
ESPB vs. TAPB	Time to first rescue analgesia	240	5	MD 5.57 (0.03, 11.11)	99	$P = 0.05$
ESPB vs. TAPB	Incidence of PONV	182	4	RR 0.68 (0.26, 1.77)	0	$P = 0.43$

Outcomes data for comparison of ESPB group vs. placebo/TAPB group. ESPB, erector spinae plane block; TAPB, transversus abdominal plane block; PONV, postoperative nausea and vomiting; CI, confidence interval; MD, mean difference; SMD, standardized mean difference; RR, risk ratio.

The 24-h cumulative opioid consumption after abdominal surgery was investigated by six studies (23, 26, 33, 35, 39, 40), with a significant reduction in opioid intake (−1.85 mg; 95% CI −2.54 to −1.15; $I^2 = 81\%$; $P < 0.00001$) in the ESPB group compared with TAPB group (Table 2 and Figure 5B).

In the subgroup analysis of LC, four studies (25, 28, 37, 42) reported that, compared with placebo, ESPB significantly reduced the 24-h cumulative opioid consumption (−1.19 mg; 95% CI −1.81 to −0.56; $P = 0.0002$; $I^2 = 76\%$) after LC (Table 3).

In the subgroup analysis of PCNL, compared with placebo group, four studies (27, 31, 34, 41) reported that ESPB significantly reduced 24-h cumulative opioid consumption (−0.62 mg; 95% CI −1.19 to −0.06; $P = 0.03$; $I^2 = 71\%$) (Table 3).

In the subgroup analysis of BS, two studies (23, 38) revealed that, compared with placebo group, ESPB significantly reduced 24-h cumulative opioid consumption (−2.57 mg; 95% CI −3.10 to −2.04; $P < 0.00001$; $I^2 = 0\%$) (Table 3). However, due to the limitation of the number of studies involving 24-h cumulative opioid consumption after LH, subgroup analysis was not performed (Table 3).

Secondary outcome measures

Time to first rescue analgesia

The time to first rescue analgesia after abdominal surgery was reported in nine trials (22–24, 31, 34, 36, 38, 39, 41), and compared with the placebo group, ESPB significantly prolonged the time to first rescue analgesia (6.97 h; 95% CI 4.92 to 9.02; $P < 0.0001$; $I^2 = 100\%$) (Table 2). Five studies (23, 33, 35, 39, 40) including 240 patients undergoing abdominal surgery reported that, compared with the TAPB group, ESPB significantly extended the time to first rescue analgesia (5.57 h; 95% CI 0.03 to 11.11; $P = 0.05$; $I^2 = 99\%$) (Table 2).

Length of hospital stay

Four trials (22, 30–32) compared the length of hospital stay of 230 patients undergoing abdominal surgery between the ESPB group and placebo group. However, the length of hospital stay was not significantly different (−0.31 days; 95% CI −0.69 to 0.07; $P = 0.11$; $I^2 = 81\%$) between the groups (Table 2). In one study by Ozdemir et al., which compared ESPB with TAPB for LC, there was a significantly shorter hospital stay in the ESPB group (40) (Table 2).

Incidence of postoperative nausea and vomiting

Eleven trials (23–25, 27, 28, 34, 36–38, 41, 44) reported the impact of ESPB on the incidence of PONV in 662 patients undergoing abdominal surgery. ESPB significantly reduced the incidence of PONV (RR 0.67; 95% CI 0.46 to 0.97; $P = 0.04$; $I^2 = 20\%$) compared with that in the placebo group (Table 2 and Figure 6A). In addition, four studies (23, 26, 33, 35) analyzed the incidence of PONV in patients receiving ESPB vs. TAPB. However, there was no significant difference in the incidence of PONV (RR 0.68; 95% CI 0.26 to 1.77; $P = 0.43$; $I^2 = 0\%$) between the groups (Table 2 and Figure 6B).

Subgroup analysis of block techniques and timing of block

Subgroup analyses of block techniques (unilateral or bilateral ESPB) and the timing of block (before or after surgery) are presented in Table 4. Our meta-analysis revealed

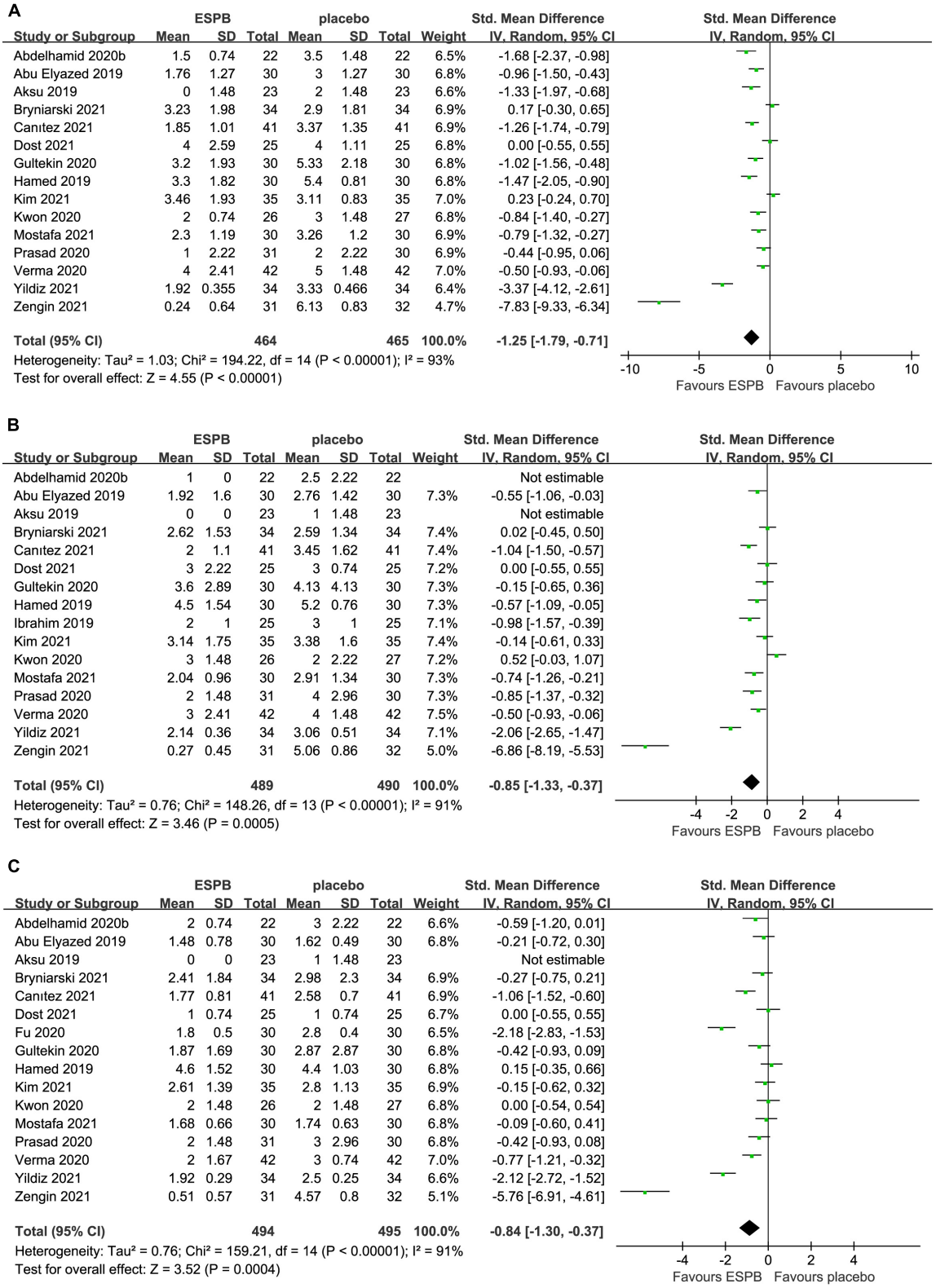

FIGURE 3
Forest plot of pain scores for the ESPB vs. placebo in the first 24 h after surgery. **(A)** Pain scores at 6 h after surgery. **(B)** Pain scores at 12 h after surgery. **(C)** Pain scores at 24 h after surgery.

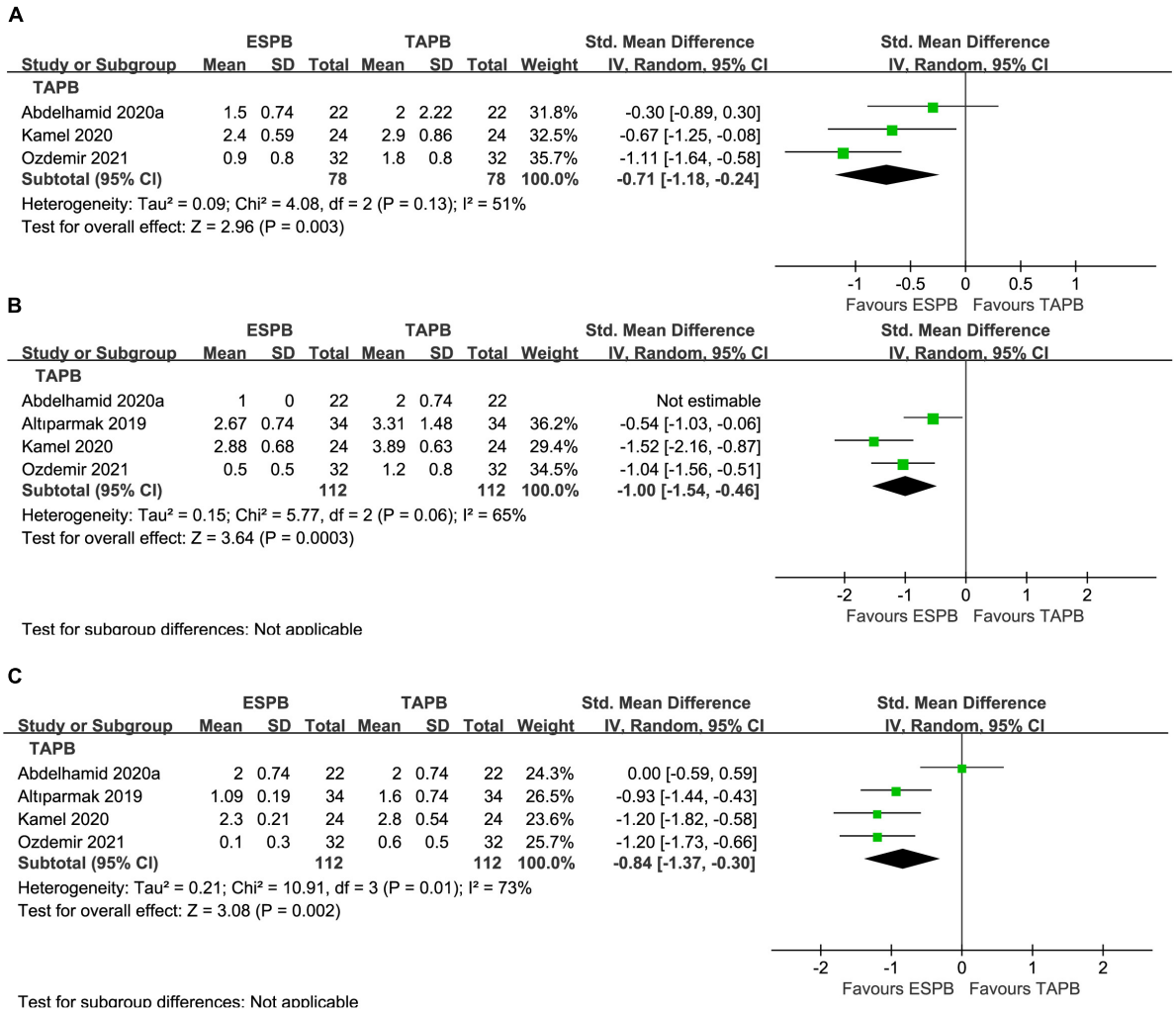

FIGURE 4
Forest plot of pain scores for the ESPB vs. TAPB in the first 24 h after surgery. **(A)** Pain scores at 6 h after surgery. **(B)** Pain scores at 12 h after surgery. **(C)** Pain scores at 24 h after surgery.

that performing ESPB after surgery significantly prolonged the time to first request for analgesia after abdominal surgery compared with that in the before-surgery subgroup ($P = 0.002$, DerSimonian–Laird approach). However, for other outcomes, the block technique and the timing of the block showed no statistical subgroup differences ($P > 0.05$).

Publication bias and sensitivity analysis

Egger's test showed that the *P*-value for postoperative pain scores at 6, 12, and 24 h and for 24-h cumulative opioid consumption was less than 0.0001, which was less than 0.05 (Table 5). Therefore, some publication bias existed in the primary outcome and may have influenced the final result, but publication bias did not exist for the incidence of PONV.

According to the sensitivity analysis, most of overall outcomes did not change after the exclusion of a single study except postoperative pain scores at 6 h and time to first rescue analgesia between ESPB and TAPB (Supplementary Figures 2, 4).

Discussion

This systematic review and meta-analysis showed the postoperative analgesic efficacy of ESPB in adults undergoing abdominal surgery under general anesthesia. When compared with placebo (e.g., no block and sham block), ESPB provided better postoperative analgesia at various time points and reduced opioid consumption within 24 h after surgery. Furthermore, ESPB was associated with a longer time to first

TABLE 3 Subgroup analysis of type of surgery.

Subgroup	Outcome	Trials	Participants	Relative effect (95% CI)	I^2 (%)	*P*-values
ESPB vs. placebo for LC	6-h pain scores	5	333	SMD −1.42 (−2.23, −0.60)	91	$P = 0.0006$
ESPB vs. placebo for LC	12-h pain scores	5	333	SMD −0.62 (−1.39, 0.15)	90	$P = 0.11$
ESPB vs. placebo for LC	24-h pain scores	5	333	SMD −0.98 (−1.74, −0.21)	89	$P = 0.01$
ESPB vs. placebo for LC	24-h opioids	4	211	SMD −1.19 (−1.81, −0.56)	76	$P = 0.0002$
ESPB vs. placebo for PCNL	6-h pain scores	3	189	SMD −0.42 (−1.10, 0.25)	81	$P = 0.22$
ESPB vs. placebo for PCNL	12-h pain scores	4	239	SMD −0.49 (−0.97, −0.02)	70	$P = 0.04$
ESPB vs. placebo for PCNL	24-h pain scores	3	189	SMD −0.44 (−0.73, −0.15)	0	$P = 0.003$
ESPB vs. placebo for PCNL	24-h opioids	4	239	SMD −0.62 (−1.19, −0.06)	71	$P = 0.03$
ESPB vs. placebo for BS	6-h pain scores	3	167	SMD −3.22 (−5.95, −0.48)	97	$P = 0.02$
ESPB vs. placebo for BS	12-h pain scores	3	167	SMD −3.77 (−9.77, 2.23)	99	$P = 0.22$
ESPB vs. placebo for BS	24-h pain scores	3	167	SMD −2.08 (−4.59, 0.42)	97	$P = 0.10$
ESPB vs. placebo for BS	24-h opioids	2	104	SMD −2.57 (−3.10, −2.04)	0	$P < 0.00001$
ESPB vs. placebo for LH	24-h pain scores	2	130	SMD −1.59 (−4.46, 1.27)	98	$P = 0.28$
ESPB vs. placebo for LH	24-h opioids	1	70	SMD −0.13 (−0.60, 0.34)	/	$P = 0.59$

ESPB, erector spinae plane block; LC, laparoscopic cholecystectomy; PCNL, percutaneous nephrolithotomy; BS, bariatric surgery; LH, laparoscopic hepatectomy; CI, confidence interval; SMD, standardized mean difference.

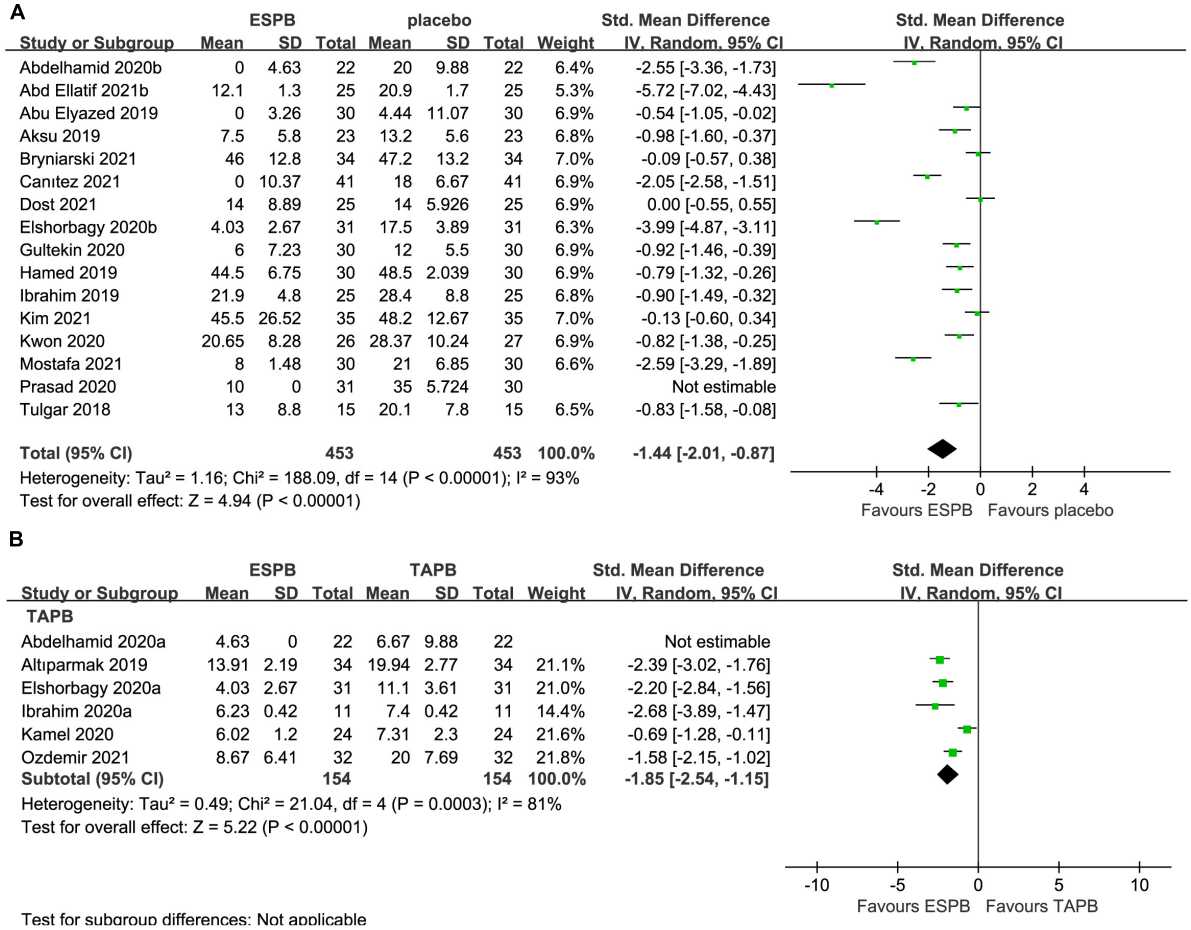

FIGURE 5
Forest plot for the comparison of intravenous morphine equivalents (mg) in the first 24 h after surgery. **(A)** Twenty-four hours cumulative opioid consumption for the ESPB vs. placebo studies. **(B)** Twenty-four hours cumulative opioid consumption for the ESPB vs. TAPB studies.

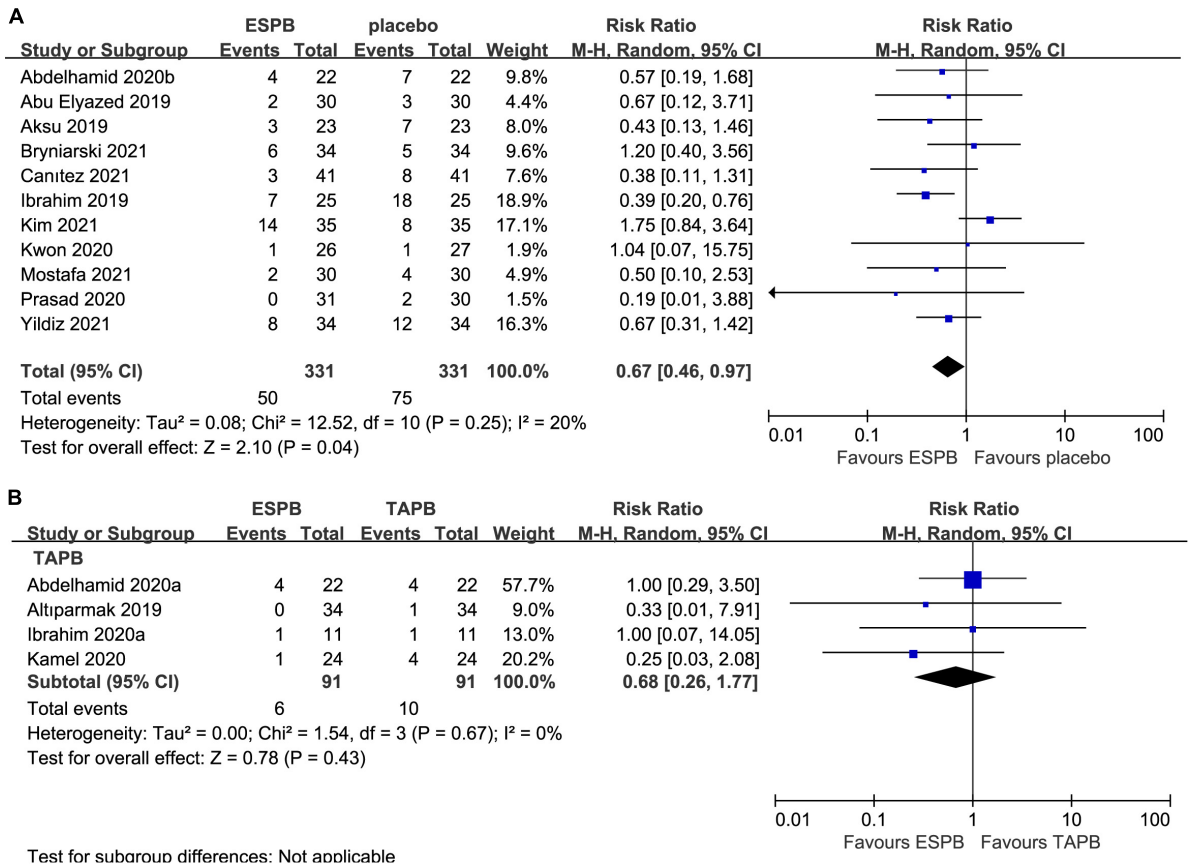

FIGURE 6
Forest plot for the comparison of the incidence of postoperative PONV. **(A)** Postoperative incidence of PONV for the ESPB vs. placebo studies. **(B)** Postoperative incidence of PONV for the ESPB vs. TAPB studies.

rescue analgesia and a lower incidence of PONV postoperatively after abdominal surgery. However, it was not beneficial in shortening the length of hospital stay.

Compared with TAPB, ESPB also provided significantly lower pain scores at the various time points and lower opioid consumption within 24 h after surgery. Meanwhile, ESPB significantly prolonged the time to first rescue analgesia after abdominal surgery. However, we found no significant differences in the incidence of PONV between the groups.

Moreover, we tried to perform a subgroup analysis to explore the effect of ESPB on different types of surgery. Our meta-analysis showed that ESPB seems to be most beneficial in terms of reduction not only in pain scores but also in opioid consumption for patients undergoing LC, PCNL, and BS. Based on our meta-analysis, the best indication for performing ESPB for postoperative analgesia is LC (e.g., reduced postoperative pain at 6 and 24 h and 24-h cumulative opioid consumption) and PCNL (e.g., reduced pain at 12 and 24 h and 24-h cumulative opioid consumption). Similarly, ESPB could be recommended for BS (e.g., reduced pain at 6 h and 24-h postoperative cumulative opioid consumption). However, due to a limited number of studies, there is no effective recommendation for the effect of ESPB in reducing pain or opioid consumption in other types of surgery, such as LH, hernia repair, open nephrectomy, open radical prostatectomy or emergency laparotomy.

Due to the high heterogeneity of the outcomes, we also tried to perform subgroup analyses of the timing of block (before/after the surgery) and ESPB technique (unilateral/bilateral). The time to first rescue analgesia was significantly prolonged by ESPB in both the before-surgery and after-surgery subgroups, and the effect on the after-surgery subgroup was significantly more powerful than that in the before-surgery subgroup. However, the heterogeneity was still high (I^2 = 100%) for both subgroups, and the number of studies for the after-surgery subgroup was limited (only one). Consequently, the results need to be confirmed by more research.

A cadaver study (10) reported the use of ESPB to inject LA into the fascia between the erector spinae and the transverse process; the LA was able to pass through the fascia to infiltrate and paralyze the spinal nerves. ESPB can act on dorsal and

TABLE 4 Subgroup analysis of timing of block (before/after surgery) and ESPB techniques (unilateral/bilateral).

Comparison	Outcome	Subgroup	Participants	Trials	Relative effect (95% CI)	I^2 (%)	*P*-values	*P* for interaction
ESPB vs. placebo	6-h pain scores	Before surgery	718	12	SMD −1.15 (−1.73, −0.56)	92	$P = 0.0001$	0.474
ESPB vs. placebo	6-h pain scores	After surgery	211	3	SMD −1.66 (−3.12, −0.21)	95	$P = 0.02$	
ESPB vs. placebo	12-h pain scores	Before surgery	768	13	SMD −0.73 (−1.27, −0.18)	91	$P = 0.010$	0.297
ESPB vs. placebo	12-h pain scores	After surgery	211	3	SMD −1.30 (−1.98, −0.61)	80	$P = 0.0002$	
ESPB vs. placebo	24-h pain scores	Before surgery	778	13	SMD −0.75 (−1.28, −0.22)	91	$P = 0.006$	0.461
ESPB vs. placebo	24-h pain scores	After surgery	211	3	SMD −1.19 (−2.09, −0.29)	89	$P = 0.010$	
ESPB vs. placebo	24-h opioids	Before surgery	763	14	SMD −1.39 (−1.99, −0.80)	92	$P < 0.00001$	0.58
ESPB vs. placebo	24-h opioids	After surgery	143	2	SMD −2.05 (−2.58, −1.51)	93	$P < 0.00001$	
ESPB vs. placebo	Time to first rescue analgesia	Before surgery	456	8	MD 5.90 (4.04, 7.77)	100	$P < 0.00001$	0.002
ESPB vs. placebo	Time to first rescue analgesia	After surgery	38	1	MD 14.46 (13.78, 15.14)	100	$P < 0.00001$	
ESPB vs. placebo	Incidence of PONV	Before surgery	211	8	RR 0.72 (0.44, 1.19)	0	$P = 0.20$	0.46
ESPB vs. placebo	Incidence of PONV	After surgery	451	3	RR 0.54 (0.29, 1.03)	36	$P = 0.06$	
ESPB vs. placebo	6-h pain scores	Bilateral	694	11	SMD −1.51 (−2.23, −0.80)	94	$P < 0.0001$	0.184
ESPB vs. placebo	6-h pain scores	Unilateral	235	4	SMD −0.63 (−1.28, 0.01)	83	$P = 0.06$	
ESPB vs. placebo	12-h pain scores	Bilateral	694	11	SMD −1.04 (−1.70, −0.38)	93	$P = 0.002$	0.348
ESPB vs. placebo	12-h pain scores	Unilateral	285	5	SMD −0.47 (−0.96, 0.02)	71	$P = 0.06$	
ESPB vs. placebo	24-h pain scores	Bilateral	754	12	SMD −0.98 (−1.57, −0.39)	93	$P = 0.001$	0.33
ESPB vs. placebo	24-h pain scores	Unilateral	235	4	SMD −0.37 (−0.65, −0.08)	0	$P = 0.01$	
ESPB vs. placebo	24-h opioids	Bilateral	617	11	SMD −1.35 (−1.98, −0.72)	92	$P < 0.0001$	0.626
ESPB vs. placebo	24-h opioids	Unilateral	289	5	SMD −1.76 (−3.21, −0.32)	95	$P = 0.02$	
ESPB vs. placebo	Length of hospital stay	Bilateral	120	2	MD −1.18 (−3.52, 1.16)	90	$P = 0.32$	0.357
ESPB vs. placebo	Length of hospital stay	Unilateral	110	2	MD −0.22 (−0.76, 0.32)	61	$P = 0.43$	
ESPB vs. placebo	Time to first rescue analgesia	Bilateral	296	5	MD 8.79 (0.82, 16.76)	99	$P = 0.03$	0.305
ESPB vs. placebo	Time to first rescue analgesia	Unilateral	198	4	MD 5.01 (0.47, 9.55)	100	$P = 0.03$	
ESPB vs. placebo	Incidence of PONV	Bilateral	437	7	RR 0.80 (0.51, 1.25)	12	$P = 0.33$	0.231
ESPB vs. placebo	Incidence of PONV	Unilateral	225	4	RR 0.51 (0.28, 0.92)	14	$P = 0.02$	

ESPB, erector spinae plane block; PONV, postoperative nausea and vomiting; MD, mean difference; SMD, standardized mean difference; RR, risk ratio.

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TABLE 5 Egger's test for outcomes.

Outcomes	Egger's test *P*-value
Pain scores at 6 h	0.0000
Pain scores at 12 h	0.0000
Pain scores at 24 h	0.0000
24-h cumulative opioids consumption	0.0000
Incidence of PONV	0.5110

PONV, postoperative of nausea and vomiting.

ventral branches of the spinal nerves and rami communicants that transmit sympathetic fibers. Due to the erector spinae and erector spinae plane extending down to the lumbar spine, ESPB can provide analgesia for abdominal surgery if the injection is performed at the lower levels of the thoracic spine. Recently, few cadaveric and radiological studies have described the LA diffusion range of ESPB. The results showed that ESPB seemed to work by spreading the LA to the epidural and paravertebral space. In this way, ESPB would be able to implement somatic and visceral analgesic effects such as epidural anesthesia (47–50). Moreover, the transverse process of the spine can now act as a puncture needle support point and anatomic landmark on ultrasound, which means ESPB is easy to perform (22, 26, 51).

A previous meta-analysis (16) that included 5 RCTs with 250 patients undergoing LC concluded that, compared with placebo, ESPB significantly decreased postoperative pain scores and 24-h cumulative opioid consumption as well as significantly prolonged the time to first rescue analgesia. In our analysis, we obtained similar results. We believe these findings suggest that ESPB plays an important role in postoperative analgesia for LC. Moreover, similar to our meta-analysis, a few previous meta-analyses (12–15) demonstrated that the ESPB group had significantly lower pain scores, lower 24-h cumulative opioid consumption, longer time to first rescue analgesia and lower incidence of PONV among patients undergoing surgery. However, these meta-analyses analyzed various surgeries, and as they only contained a small number of trials of abdominal surgery, they could not demonstrate the analgesic effect of ESPB in abdominal surgery. Our meta-analysis included 24 RCTs and performed a meta-analysis to compare ESPB with placebo or TAPB for postoperative analgesia in abdominal surgery patients based on a larger sample size. Moreover, the quality of trials in these meta-analyses should also be considered, as two of them (12, 15) included trials (52) that have been retracted.

This meta-analysis showed the beneficial effect and ease of application of postoperative analgesia compared with placebo and our sensitivity analysis also showed strong ability of the pooled analysis (**Supplementary Figures 1**, **3**–**5**). ESPB has been applied in various kinds of surgeries, including lumbar spine surgery (53), LC (16), breast cancer surgery (54), and other thoracic and abdominal surgeries, and no side effects or complications related to this block have been reported. Our present meta-analysis provides novel evidence that ESPB is an effective nerve block for analgesia after abdominal surgeries.

In comparison with that of TAPB, the injection point of ESPB is remote from the peritoneum and abdominal wall and poses a lower risk of abdominal organ damage and peritoneal breach (9, 10). While ESPB provides somatic and visceral sensory block of the abdomen (10, 11), TAPB only supplies analgesia to the anterolateral abdominal wall (55). Therefore, ESPB may provide more effective analgesia after abdominal surgery. Due to the combination of its efficacy and lower risk of complications, ESPB has been regarded as an alternative to TAPB for postoperative analgesia in certain surgical operations. In addition, our review revealed that, compared with TAPB, ESPB is associated with a longer time to first rescue analgesia and a comparable incidence of PONV after abdominal surgery. However, perhaps due to the influence of different surgical types, different postoperative analgesia regimens and differences in clinician habits, time to first rescue analgesia can vary. For example, Ozdemir et al. (40) reported a longer time to first rescue analgesia in the TAPB group, while other studies report longer time in the ESPB group. It was worth mentioning that sensitivity analysis of postoperative pain scores at 6 h and time to first rescue analgesia found that the outcomes were not stable (**Supplementary Figures 2**, **4**). Moreover, since not many studies have reported on these two outcomes, subgroup analysis was not performed to explore the effect of timing of block (before/after the surgery) and ESPB technique, so the veracity of both outcomes deserve further research. Even so, our meta-analysis still provides new evidence that ESPB may be a promising alternative to TAPB after abdominal surgery. However, the differences in analgesic effects and other postoperative anesthetic outcomes of both nerve blocks still require direct comparison in future large-volume and well-designed RCTs.

However, some limitations of our meta-analysis should be mentioned. First, the main drawback of our meta-analysis is that high heterogeneity was observed between studies. The sources of high heterogeneity also included differences in the types and doses of LAs, differences in multimodal analgesia, performer differences and patient differences (age, sex, etc.), etc. Second, Egger's tests of primary outcomes revealed a high risk of small-study effects, which also reduced the reliability of our meta-analysis. Third, our meta-analysis only included studies involving abdominal surgeries instead of all kinds of surgical procedures. Therefore, the effect of postoperative analgesia may be exaggerated due to selection bias. Fourth, our meta-analysis only focused on the comparison of the ESPB group with the placebo or TAPB group. We did not compare the postoperative analgesic effect of ESPB with that of other postoperative analgesic methods (such as intrathecal morphine, quadratus lumborum block, or local infiltration). Therefore, more studies

in this area are needed in the future. Fifth, the sample sizes of the studies included in this review were all relatively small. The largest sample size of the experimental group was only 42 patients. In the future, large-volume studies are needed in this area. Finally, relatively few studies have focused on the same surgery. Subgroup analyses by type of surgery were only applied to LC, PCNL, BS, and LH, with 6, 4, 3, and 2 RCTs, respectively.

Conclusion

In summary, ESPB is a novel, beneficial nerve block for adult patients undergoing abdominal surgery. Moreover, our meta-analysis confirms that ESPB provides more beneficial postoperative analgesic efficacy than TAPB. Therefore, our research recommends ESPB as a supplement to the multimodal analgesic regimen for abdominal surgery and a valid alternative to TAPB. Future, large-volume, well-designed RCTs with extensive follow-up are needed to confirm and update the findings in this area.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Author contributions

YG and XW were responsible for the conception and design of the study, and drafting and revising the manuscript. YG, LL, and XW conducted the literature retrieval, screening, and quality evaluation. YG, YC, and JZ analyzed the data and explained the results. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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Artificial intelligence in ultrasound-guided regional anesthesia: A scoping review

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Background: Regional anesthesia is increasingly used in acute postoperative pain management. Ultrasound has been used to facilitate the performance of the regional block, increase the percentage of successfully performed procedures and reduce the complication rate. Artificial intelligence (AI) has been studied in many medical disciplines with achieving high success, especially in radiology. The purpose of this review was to review the evidence on the application of artificial intelligence for optimization and interpretation of the sonographic image, and visualization of needle advancement and injection of local anesthetic.

Methods: To conduct this scoping review, we followed the PRISMA-S guidelines. We included studies if they met the following criteria: (1) Application of Artificial intelligence-assisted in ultrasound-guided regional anesthesia; (2) Any human subject (of any age), object (manikin), or animal; (3) Study design: prospective, retrospective, RCTs; (4) Any method of regional anesthesia (epidural, spinal anesthesia, peripheral nerves); (5) Any anatomical localization of regional anesthesia (any nerve or plexus) (6) Any methods of artificial intelligence; (7) Settings: Any healthcare settings (Medical centers, hospitals, clinics, laboratories.

Results: The systematic searches identified 78 citations. After the removal of the duplicates, 19 full-text articles were assessed; and 15 studies were eligible for inclusion in the review.

Conclusions: AI solutions might be useful in anatomical landmark identification, reducing or even avoiding possible complications. AI-guided solutions can improve the optimization and interpretation of the sonographic image, visualization of needle advancement, and injection of local anesthetic. AI-guided solutions might improve the training process in UGRA. Although significant progress has been made in the application of AI-guided UGRA, randomized control trials are still missing.

KEYWORDS

artificial intelligence, ultrasound, regional anesthesia, ultrasound-guided regional anesthesia, training, machine learning, peripheral nerve block, sono-anatomy

Background

Regional anesthesia (RA) is increasingly used in pain management for various surgical procedures. Ultrasound (US) has been used to facilitate the performance of the regional block, increase the percentage of successfully performed procedures and reduce the complication rate. US rapidly gained popularity among practitioners due to its portability, absence of radiation, and the ability to track the performance of the procedure in a real-time fashion (1). Other benefits of US in regional anesthesia include direct visualization of nerves, blood vessels, muscles, bones, tendons, faster sensory onset time, visualization of the local anesthetic spread during injection, timely recognition of maldistribution of local anesthetics, possible prevention of complications (e.g., inadvertent intravascular injection, intraneuronal injection of local anesthetic), longer duration of the block, possible avoidance of painful muscular contractions during nerve stimulation in cases of fractures), possible improvement of quality of block (2–7).

However, the application of ultrasound-guided regional anesthesia is associated with several technical challenges, which are especially prevalent in trainees and not experienced clinicians. The performance of a block can be complicated by the loss of the reflective signal between the needle and probe, which decreases the needle visibility, especially if a deep block is performed or a patient is overweight. Moreover, bone or hyperechoic soft tissue along the needle trajectory may worsen needle visibility. Therefore, clear needle localization is challenging, especially if deep blocks are performed.

Artificial intelligence (AI) has been studied in many medical disciplines with achieving high success, especially in radiology (8). Since sonographic visualization is commonly used in regional anesthesia, AI solutions might be useful for practitioners in anatomical landmark identification and reducing or avoiding possible complications such as injury to the nerve, artery, vein, and puncture of the peritoneum, pleura, internal organs, as well as local anesthetic systemic toxicity. AI-guided solutions can improve the optimization and interpretation of the sonographic image, and visualization of needle advancement and injection of local anesthetic (3–7).

The purpose of this scoping review (SR) was to synthesize and analyze the evidence on the application of artificial intelligence for optimization and interpretation of the sonographic image, and visualization of needle advancement and injection of local anesthetic.

Methods

Protocol

To conduct this SR, we followed the PRISMA guidelines during the design, implementation, and reporting of this review.

We followed the PICO items:

P (patient population): 1. Age 18 years of age and older;

I (intervention): Artificial intelligence-assisted in ultrasound-guided regional anesthesia.

C (comparator): standard methods.

Participants/population: Patients undergoing surgery under regional anesthesia.

Goals of the SR

1. To review and assess the value and performance of AI-assisted UGRA in different anatomical regions and nerves;
2. Machine learning models and algorithms;
3. To assess the benefits of automatic target detection;
4. To assess risks, failures and limitations of the AI-assisted UGRA.

Inclusion criteria

1) Application of Artificial intelligence-assisted in ultrasound-guided regional anesthesia;
2) Any human subject (of any age), object (manikin), or animal.
3) Study design: prospective, retrospective, RCTs;
4) Any method of regional anesthesia (epidural, spinal anesthesia, peripheral nerves);
5) Any anatomical localization of regional anesthesia (any nerve or plexus).
6) Any methods of artificial intelligence;
7) Settings: Any healthcare settings (Medical centers, hospitals, clinics, laboratories).

Exclusion criteria

1) Not enough data reported;
2) Out of inclusion criteria;
3) Application of AI other than anatomic landmark identification and guidance in UGRA (e.g., for AI-based prediction of the need for nerve blocks, AI for robotic nerve blocks, prediction of response of regional anesthesia.

Literature search

Search strategy

Studies were identified by electronic search in PubMed, Google Scholar, Embase, using the following search terms "Artificial intelligence," "Deep learning," "Ultrasound," "Ultrasound-guided," "Needle identification," "Needle tracking," "Regional anesthesia," "Peripheral nerve block." Additionally, we performed a manual search of the articles using the

references from the published studies. Publications in English, German and Russian languages were considered.

Data collection and extraction

The data were extracted into a standardized form. Two authors independently screened the titles and abstracts for eligibility. The following data were extracted: citation, author, year, gender, study goals, sample size, types of surgery, nerve block, the algorithm of AI, comparator, the purpose of AI, benefits, risks and limitations of the study, model performance data and conclusions.

Results

The systematic searches identified 78 citations. After the removal of the duplicates, 19 full-text articles were assessed; and 15 studies were eligible for inclusion in the review (Supplementary Figure 1). The studies were conducted on healthy subjects, parturients in labor or scheduled for cesarean delivery, bovine/porcine lumbosacral, and bovine/porcine lumbosacral spine phantoms.

Characteristics of study goals

The included studies aimed to assess the value of AI by the following methods:

- Studying nerve structure and ultrasound image tracking (9);
- Assessing deep-learning performance for nerve tracking in ultrasound images (10);
- Studying the accuracy of real-time (AI) -based anatomical identification (11);
- Assessment of CNN-based framework for needle detection in curvilinear 2D US (12);
- Evaluation of success rate of spinal anesthesia of AI-assisted methods (13);
- Using AI for precise needle target localization (14);
- Identification of musculocutaneous, median, ulnar, and radial nerve) and blood vessels (15);
- Assessment of the utility of ScanNav to identify structures, teaching and learning UGRA, and increase operator confidence (16);
- Assessment of UGRA expert perception of risks of the use of ScanNav (risk of block failure, unwanted needle trauma (eg, arteries, nerves, and pleura/peritoneum (16);
- Identification of the difference in accuracy between deep learning (DL)-powered ultrasound guidance and regular ultrasound images; the use of artificial intelligence to optimize regional anesthesia puncture path; to identify the effectiveness of ultrasound-guided imaging "scapular nerve block" surgical pain of the fracture (17).

Anatomical region and the nerves

It was found that AI-assisted UGRA has the potential to facilitate the identification of anatomical structures and assist non-experts in locating the correct ultrasound anatomy to perform the intervention. The previous reports highlighted the apparent deficiencies in anatomical knowledge among junior anesthesiologists (18). These deficiencies may be supported by the assistance of ultrasound image interpretation. Therefore, such assistive AI approaches could improve the probability of successful interventions and reduce their risks (18).

Thus, artificial intelligence-assisted ultrasound-guided target identification was used for the identification of the following anatomical structures (nerves): musculocutaneous, median, ulnar, and radial nerves, "interscalene-supraclavicular" and "infraclavicular brachial plexus," "axillary level brachial plexus," "erector spinae plane," rectus sheath, "suprainguinal fascia iliaca," adductor canal, "popliteal sciatic nerve," "transverses abdominis plane," anesthesia in the lower vertebrae regions (sacrum, intervertebral gaps, and vertebral bones), sciatic nerves, femoral nerve, subarachnoid and epidural spaces, facet blocks, navigation of blood vessels during UGRA (9–15, 18–21) (Table 1).

Machine learning models and algorithms

The goal of the included studies was to accurately identify the target region (i.e., nerve block) on the ultrasound images in real-time (4). Therefore, some machine-learning methods have been proposed (Table 1) and their key techniques can be divided into (1) anatomic region segmentation, (2) target detection (i.e., feature extraction), and 3) tracking algorithm (9–15, 18–21).

The U-net is a popular DNN framework to find the region of interest by its fast and precise segmentation performance (Table 2).

The feature extraction methods were divided into typical hand-crafted features and CNN approaches. In general, the hand-crafted feature is more suitable for the smaller size dataset, while the CNN has the strength for more complex classification problems with an automatic feature extraction in the end-to-end framework. The SIFT, LBP, AMBP, HOG, and bag-of-features are well-known hand-craft features and have shown promising results in the US images (9, 21, 24).

The deep-learning models are less optimized with the time complexity, and they predict the given sequential input image independently. Therefore, the model performance is highly sensitive to nerve disappearance due to artifact noise, illumination, or occlusion. Tracking algorithms are one solution

TABLE 1 Study and cohort information.

Author, country, year	Study goal	Study population (diagnosis)	Sample size Gender (males %)	Region of body studied
Bowness et al., 2021 (18)	Assess the AI anatomy identification	Healthy population	244	Interscalene-supraclavicular level brachial plexus block Rectus sheath block Axillary level brachial plexus Erector spinae plane block Suprainguinal fascia iliaca block Adductor canal block Popliteal level sciatic nerve block
Alkhatib et al., 2018, France (9)	To study nerve structure and ultrasound images tracking	–	10 6 (60%) males 4 (40%) females	Median nerve identification
Alkhatib et al., 2019, France (10)	To study the deep-learning performance for nerve tracking in ultrasound images	-	42	Median & sciatic nerves
Gungor et al., 2021 (11)	To study the accuracy of real-time (AI) -based anatomical identification	Healthy population	40 20 (50%) males 20 (50%) females	Block regions: Supraclavicular, infraclavicular, and transversus abdominis plane (TAP)
Hetherington et al., 2017 (19)	Detect the lower vertebral level	–	20	Anesthesia in the lower vertebrae regions (sacrum, intervertebral gaps, and vertebral bones)
Huang et al., 2019 China (20)	femoral nerve on ultrasound images	–	–	Femoral nerve
Mwikirize et al., 2018 (12)	CNN-based framework for needle detection in curvilinear 2D US	bovine/porcine lumbosacral spine phantom	–	
Oh et al., 2019, Singapore (13)	Success rate of spinal anesthesia	Obstetric women	100	Spinal anesthesia
Pesteie et al., 2017 (14)	Precise needle target localization	–	33	–
Smistad et al., 2018, Norway (15)	Identification of musculocutaneous, median, ulnar, and radial nerve) and blood vessels	Healthy volunteers	49	Axillary nerve block: four nerves (musculocutaneous, median, ulnar, and radial nerve) and blood vessels
Tran et al., 2010, Canada (21)	Features of the lumbar anatomy	Parturients in labor or scheduled for cesarean delivery	20	Epidural anesthesia
Bowness et al., 2022 (16)	Assessment of the utility of ScanNav to identify structures, teaching and learning UGRA and increase operator confidence. Assessment of UGRA expert perception of risks of the use of ScanNav (risk of block failure, unwanted needle trauma (eg, arteries, nerves, and pleura/peritoneum	Healthy volunteers	2	Nine peripheral nerve block regions The upper limb (the "interscalene-," "upper trunk-," "supraclavicular-," "axillary-level brachial plexus" regions; "Erector spinae plane block," "rectus sheath plane block regions"; the "suprainguinal level fascia iliaca plane," "adductor canal and popliteal-level sciatic nerve blocks."
Bowness et al., 2022 (22)	Expert-level AI model performance evaluation	Healthy adult subjects	40	**Upper-extremity blocks:** "upper trunk of the brachial plexus," "interscalene-level brachial plexus," "supraclavicular-level brachial plexus," "axillary-level brachial plexus"

(Continued)

TABLE 1 (Continued)

Author, country, year	Study goal	Study population (diagnosis)	Sample size Gender (males %)	Region of body studied
				Thoraco-abdominal blocks: erector spinae plane, rectus sheath block. Lower-extremity blocks: "suprainguinal fascia iliaca," "adductor canal and distal femoral triangle," "popliteal-level sciatic nerve blocks."
Yang et al., 2022 (23)	Development a deep learning algorithm to locate the "interscalene brachial plexus" based on ultrasound images to aid anaesthesiologists.	Patients	1076 (dataset −11 392 images	Interscalene brachial plexus
Liu et al., 2021 (17)	To identify difference in accuracy between deep learning-powered ultrasound guidance and regular ultrasound images; the use of artificial intelligence to optimize regional anesthesia puncture path; to identify the effectiveness of ultrasound-guided imaging "scapular nerve block" surgical pain of the fracture	Patients	100	"Scapular nerve block"

for not losing the target object (i.e., nerve) from the initially represented features in the ROI. Previous studies have shown an efficient tracking performance with the conventional MI algorithms, such as Kalman/particle filter (25), mean shift (26), kanade-Lucas-Tomasi (KLT), etc (8). The DNN-based tracking approaches have recently been proposed in the CV domain, however, it is rarely used in sonographic image. Alkhatiba et al. (10) firstly investigated the performance of 13 DNN models, (e.g., ECO, SANet, SiameFC, CFNet) and compared their performance with the hand-crafted feature (AMBP-PF). The study indicates that the CNN models have outperformed the traditional MI algorithms in terms of accuracy and stability, and reported some important findings for enhancing the performance by (1) using a deeper layer, (2) reducing the redundancies, (3) incorporating particle filter (or RNN) in the network.

In many cases, DNN approaches have been implemented along with data augmentation, knowledge transfer, and visualization to overcome the limitations, i.e., small-size datasets, parameter optimization, and low interpretability, respectively. Positional augmentations (scaling, affine transformation, etc.) are common techniques; Pesteie et al. (14) proposed Walsh-Hadamard transform to train a deep network with a set of distinctive directional features from the spatial domain. Mwikirize et al. (12) employed transfer learning, where the network weights are initialized by non-medical images, then fine-tuned with US images.

Overall performance of detection rate were between 88 and 95% and 0.638–0.722 in terms of the precision rates, and IoU evaluation, respectively (19, 20), and tracking performance was above 85% (10).

Benefits of automatic target detection

The main benefits included an automatic detection and tracking of nerve structure, overall good performance, assistance in successful recognition of specific anatomical structures, confirming the correct placement of the needle, ultrasound view to anesthetists and standardization of clinical procedure, a real-time interpretation of anatomic structures for immediate decision-making during blocks, provides automatized nerve block using the remote control system, successful detection of vertebral regions at the real-time speed (9–15, 18–21, 26, 27). It was reported that artificial intelligence can provide assistance for both novice trainees and experienced clinicians unfamiliar with ultrasound techniques. The ultrasound-guided approach does not increase as the automated ultrasound-guided neuraxial technique takes less than a minute. The automated approach was reported to result in a high rate of first attempt success rate that could reduce the complications from multiple entry attempts (19, 25–28). In another study, DL-assisted ultrasound-guided imaging for scapular nerve block in scapular fracture surgery was

TABLE 2 Artificial intelligence method and its purpose.

Study citation, first author	Machine learning model	Purpose of ML	Benefits	Risks and limitations
Bowness et al. (18)	ScanNav Anatomy Peripheral Nerve Block system (Intelligent Ultrasound Ltd [IUL], Cardiff, UK) - deep convolutional neural networks based on the U-Net architecture	To identify anatomical regions	Identifying the specific anatomical structures, correct ultrasound view to anesthetists and standardization of clinical procedure	Model-related: Recognizes only anatomical structures on images
Alkhatib et al. (9)	Adaptive Median Binary Pattern approach Joint Adaptive Median Binary Pattern approach Three tracking algorithms: particles filter, Mean Shift and Kanade-Lucas-Tomasi (KLT) techniques	To imrove tracking procedure	Automatic detection and tracking of nerve structure, ROIs	Model-related: Nerve appearance might be similar to surroundings Difficulties in real-time tracking Risk of error after many iterations
Alkhatib et al. (10)	Deep learning methods: C-COT, ECO, CNT, MDNet SANet, SiameFC, CFNet, DCFNet, MCPF, HDT, HCFT CREST, DLT, PF-AMBP	Median and the sciatic nerves	Good performance Overcoming noise difficulties No need for pre-filtering images	Model-related: Nerve appearance might be similar to surroundings Failure of retracing the nerve
Gungor et al. (11)	Nerveblox, Smart Alfa Teknoloji San	Identify anatomical structures	A real-time interpretation of anatomic structures	Model-related: Low accuracy in pediatric/geriatric patients
Hetherington et al. (19)	SLIDE (Spine Level IDEntification) System based on deep convolutional neural network	transverse spinal ultrasound planes classification	Successful detection of vertebral regions at real-time speed	Model-related: Failure in identifying the difference between gap and bone images Real-time speed considerations
Huang et al. (20)	Deep learning model: U-Net	identify femoral nerve	Fast training and forecasting of the method Real-time segmentation	Study-related: Small sample size Limited number of images No data augmentation
Mwikirize et al. (12)	Deep learning (DL) based on convolution neural networks (CNNs)	Evaluate the new method	2D US data; deep convolution neural network usage detection data and intensity invariant feature maps	Model-related: Cannot systematically find the needle Relying on an expert sonographer
Oh et al. (13)	to detect the inter-spinous images	Localize L3/4	Confirm the sonographic images and structures. Time saving method Less possible complications	Study-related: Lack of a comparator arm Highly specific algorithm. The system is validated by current study population Absence of complex spinal anatomy, obesity, pediatric and geriatric patients. The risk of misinterpretation of fusion or reduced interspinous distance
Pesteie et al. (14)	CNN-based machine learning technique	Evaluate the convolutional network architecture	Few outliers in detecting the needles Performance is better compared with others	Model-related: Not running in real time

(Continued)

TABLE 2 (Continued)

Study citation, first author	Machine learning model	Purpose of ML	Benefits	Risks and limitations
Smistad et al. (15)	Deep convolutional neural network – U-Net	Identify musculocutaneous, median, ulnar, and radial nerves and blood vessels	Accurate detection of blood vessels, median and ulnar nerves Real-time identification Direct comparison of 4 methods	Study-related: Small sample size Low precision and recall values Poor identification of musculocutaneous, radial nerves
Tran et al. (21)	MATLAB algorithm	Detect the LF depth	Helps to find the epidural space and measure the skin-to-LF depth An implementation in a wide range of ultrasound machines.	Model-related: Insignificant errors and failures to detect the LF mean Poor image quality might result in unsatisfactory outcomes
Bowness et al. (16)	ML/DL	Identification of the anatomical structures	Potential to support non-experts in training /clinical practice, as well as experts in teaching UGRA. It may promote the uptake and spread of UGRA.	Model-related: Experts reported an increase in risk
Bowness et al. (22)	DL (based on U-Net architecture)	Identification of the anatomical structures; highlighting anatomical structures of interest	High TP/TN and low FP/FN rates in key anatomical structure identification	Model-related: UGRA itself has not reduced the incidence of nerve injury; Study-related: remote expert were not present when the subjects were scanned.
Yang et al. (23)	DL		The developed model located the "interscalene brachial plexus" more accurately compared to nonexperts.	
Liu et al. (17)	DL, SegNet Model	to optimize regional anesthesia puncture path;	DL ultrasound guided imaging for scapular nerve block in scapular fracture surgery was more efficient, significantly shortened the time of performing nerve block and reduced complications compared to traditional method.	

ML, machine learning; PPV, positive predictive value; NPV, Negative predictive value; AUC-area under the curve; FP-false-positive; FN-false-negative.

more efficient, significantly shortened the time of performing nerve block, and reduced complication rate compared to the traditional method (17).

Risks, failures, and limitations of the AI-assisted UGRA

Although the application of automated solutions has several benefits, the risks, failures, and limitations were also reported. Thus, the most important limitation was detection and tracking failure (if the nerve appearance is similar to surrounding areas), risk of the nerve disappearance and identical appearance with the surrounding areas- losing the nerve, issues with real-time tracking error after numerous iterations risk of failing to re-track lost nerve (9–15, 18–21). Another limitation of this technology is the failure of distinguishing osseous images. Although real-time allows proper scanning of block regions, it does not always result in the detection of the whole needle, which can occur at a steep insertion angle. The evidence on the application of AI-assisted technologies in regional anesthesia is still in its initial stage. Thus, limited evidence on accuracy in many patient populations, such as in pediatric/geriatric patients is currently available. Overreliance on an expert sonographer to detect the ground-truth tip localization is a limitation especially if the tip is completely invisible. The algorithm is highly specific only if all landmarks are detected. AI algorithms are not designed or validated in the case of complex spinal anatomy, geriatric

patients, obesity patients, and pediatric patients. The risk of image misinterpretation could be high in case of abnormal anatomy (e.g., fusion or reduced interspinous distance).

The following risks were assessed and reported in the studies:

- increased risk of block failure;
- risk of needle trauma to structures (eg, arteries, nerves, pleura, peritoneum);

The assessed complications included:

- nerve injury and "postoperative neurological manifestations";
- "local anesthetic systemic toxicity";
- pleural injury (pneumothorax);
- peritoneal injury.

Discussion

Artificial intelligence-assisted medical image interpretation is one particularly popular research direction in healthcare artificial intelligence (18). Artificial intelligence has been used for the detection of the optimal needle insertion site, estimation of the trajectory of the needle insertion, and facilitating automatic tip localization. Tracking is one of the most widely used tasks in computer vision with such applications as video medical imaging, compression, and robotics.

Several artificial intelligence models have been reported to improve the quality of monographic anatomical target detection. Thus, a multiple model data association tracker has been used to track the left ventricle in the cardiac examination (8).

AI was reported to be helpful in 99.7% of the cases. Identification of specific anatomical structures by ultrasound and confirming the correct view are essential components of ultrasound-guided regional anesthesia (18).

A recent study reported a statistically significant difference between the performances of blocks in different regions. Thus, the rectus sheath and interscalene supraclavicular level brachial plexus regions yielded the lowest results, whereas the adductor canal block and axillary brachial plexus yielded the highest results (18). It is noteworthy to note that two of the three lowest-ranked blocks were plane blocks and anatomical regions that did not have major vascular landmarks in close proximity. Conversely, the highest-ranked anatomic regions have bones and vessels.

The results demonstrate the potential for the clinical utility of AI in UGRA and especially for non-experts users (18). It is challenging to develop the AI algorithms to identify all anatomical features using ultrasound *de novo* due to the diversity, complexity, and operator dependence, such as inter-and intra-individual variation (25). Therefore, automated image interpretation technologies can be trained to identify a wide variety of structures using machine learning (25). This technology could be used to improve the interpretation of ultrasound anatomy by improving target identification such as peripheral nerves and fascial planes, and the mapping of optimal insertion site by detecting the relevant landmarks and guidance structures (such as muscles and bones). The safety profile can be improved by highlighting anatomical structures such as blood vessels) to reduce or even avoid unwanted injury (26).

Although AI-assisted techniques appear to be promising, only a few applications are currently introduced in clinical practice, therefore, the potential for its utilization is yet to be proven (28). Understanding the sonographic anatomy and image interpretation represents critical importance in UGRA. Robust AI-assisted technologies could help clinicians to improve performance and training in ultrasound-guided nerve blocks (26).

AI-assisted technologies can change the practice of UGRA and its education. Anesthesia practitioners should contribute to the transformation of UGRA (28).

Although training can be performed in non-clinical settings, such as educational courses, clinical practice training takes a fundamental role.

AI-assisted UGRA is a novel medical device, with which many clinicians might not be familiar. Therefore, its initial use may be associated with lower confidence, which will improve with time of training and practice.

Generally, the included studies reported a low perception of increased risk associated with using AI assistance, although complications may be clinically important (eg, nerve injury/LAST). Possible causes of error are related to technological performance, e.g., improper highlighting, which may result misinterpretation of the ultrasound images. Block failure and undesirable trauma to critical structures may be more likely if the practitioner is misleadingly reassured by the color on the screen. Other risks may be related to the usage of the device, e.g., highlighting resulting in distraction or focusing on one object and neglecting another structure.

AI-assisted technology therefore should be used as a source of additional information (image augmentation system) rather than a decision-maker. Furthermore, correct anatomical structure identification can be useful for anesthesiologists, although it does not ensure safe UGRA nor guide needle placement. Therefore, it is the performer's responsibility to take into consideration hazards (26, 28).

Challenges in using AI regional anesthesia

Tracking anatomical targets in ultrasound-guided procedures can be challenging due to Illumination changes, occlusion, noise, and deformation of the target, which can result in tracking failure. Moreover, the object motion may exhibit abrupt changes; the images may be corrupted by a multiplicative noise leading to false alarms, misdetection; some detected features may not belong to the object. It is important to

highlight that the wrongly detected features should be neglected by the tracker because they may mislead medical professional and jeopardize the performance of the procedure (8). Finally, the object shape might change during the tracking (8).

Barriers to the development of AI-guided UGRA

AI especially CNNs has been improving success in image recognition for many years, since the development of LeNet-5 (29). One of the major reasons for this success is the development of new algorithms, the availability of large data sets, and improvements in hardware (30). The major limitation of training deep CNNs is the requirement of a large number of images; therefore, it is challenging to achieve good results with training deep CNNs using small data sets (24). The challenge, however, can be overcome with transfer learning that can be used for training CNNs on relatively small data sets (24, 27). Transfer learning uses knowledge learned from one area and applies in another area. Transfer learning can solve classification tasks in a new domain using pre-trained CNNs (27). It can be especially useful in medical image classification. To perform image classification, trained CNNs extract features *via* ascending layers of the network (27). CNNs that have been trained on a large number of images have optimized parameters for image recognition, and, therefore, that knowledge can be transferred to use for other tasks. Moreover, only a few products, especially those assessing images in a real-time manner have received regulatory approval.

Limitations of the current study

The main limitations of this study are that the studies included in this review are small sample size, therefore, the results should be replicated in studies with a larger number of participants with different anatomical abnormalities and comorbidities. Other limitations were an insufficient number of images with a large field of vision and deep depth, no data augmentation limiting image segmentation properties of the studied method. Some studies did not have a comparator arm.

Additional limitation was the "trustworthiness" of clinicians who are under-confident in their anatomical and sonographic expertise, and may over-rely on AI assistance. Therefore, it is important to appreciate that the AI may mistakenly identify the incorrect anatomical location, and a robust understanding of the sonographic anatomy is required even when AI-assisted technologies are used for such procedures (18). Regional anesthesia educators with suitable expertise must be central to training in UGRA and "AI-assisted devices" should not replace expert educators. Trainees should still practice standard methods of sonographic scanning, probe angulation, rotation pressure, and tilt to enhance image acquisition (26).

The next limitation is that the highest were scores demonstrated as regions with major vascular structures and nerves, rather than fascial planes used as a target. Therefore, it is important to find out whether it is due to the operator's input to the system or it is due to the algorithm. This may help to identify what anatomical landmarks and structures are the most beneficial for AI-assisted UGRA (18).

Additionally, the performance of AI-assisted UGRA could be evaluated by diverse criteria such as accuracy, consistency, time complexity, the robustness of noise, and sometimes the visualization results should be qualitatively evaluated by the human. However, current CNN studies have not fully investigated in terms of the model generalization toward a large-size dataset with sufficient evaluation assessments.

Future development

Ultrasound has become an integral part of regional anesthesia and significantly contributed to its development. Nevertheless, it is challenging to develop excellent skills to interpret ultrasound images and achieve the necessary level of proficiency to perform regional anesthesia safely and reduce the rate of block failure, especially for beginners. Moreover, there is a degree of subjectivity in interpreting ultrasound images, which leads to heterogeneous interpretation even among experienced users. Therefore, the application of AI in UGRA might maximize the benefits of ultrasound guidance, improve efficacy and safety and reduce the failure rate.

Computer vision is one of the most promising areas of application of AI in medicine. Deep learning may hold the highest potential to advance image interpretation in UGRA but a high amount of images would be required for its training, followed by validation prior to its implementation into clinical practice. Therefore, a close collaboration of clinicians and engineers is crucial. Clinicians should play a more active role in these collaborations, since they are instrumental in image acquisition, conducting clinical trials, advising, and overall moving this field forward.

Conclusion

Since sonographic visualization is commonly used in regional anesthesia, AI solutions might be useful in anatomical landmark identification, reducing or even avoiding possible complications (such as injury to the anatomical structures and local anesthetic systemic toxicity. AI-guided solutions can improve the optimization and interpretation of the sonographic image, visualization of needle advancement, and injection of local anesthetic. AI-guided solutions might improve the training process in UGRA. Although significant progress has been made in the application of AI-guided UGRA, randomized control trials are still missing. More high-quality studies are warranted

to generate evidence application of AI-guided UGRA in different patient populations, such as pediatric, and geriatric patients, and in different anatomical regions, nerve blocks, and surgeries. This SR could potentially be used as a basis for future clinical trials and systematic reviews and enable future researchers to identify the directions for applications of AI in regional anesthesia. This review can also enable researchers to avoid the limitations of previous studies, which will be suitable for future systematic reviews and meta-analyses.

Author contributions

DV: conceptualization, design and methodology, writing initial draft, and editing. MD and SS: data extraction. M-HL: editing and writing. All authors approved the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.994805/full#supplementary-material

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Efficacy and adverse effects of peripheral nerve blocks and local infiltration anesthesia after arthroscopic shoulder surgery: A Bayesian network meta-analysis

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Study objective: To quantitatively assess and compare the efficacy and adverse effects of six different peripheral nerve block techniques after arthroscopic shoulder surgery (ASS).

Design: Bayesian network meta-analysis.

Methods: The PubMed, Embase, Web of Science, the Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure database, Chinese Scientific Journal database, Wan Fang databases were searched to retrieve randomized clinical trials comparing interscalene brachial plexus block, continuous interscalene brachial plexus block, supraclavicular brachial plexus block, suprascapular nerve block, combined suprascapular and axillary nerve block and local infiltration analgesia on postoperative pain, opioid consumption, and adverse effects (defined as Horner's syndrome, dyspnea, hoarseness, vomiting, and nausea) after ASS under general anesthesia (GA). Two reviewers independently screened the literature, extracted data, and evaluated the risk of bias in the included studies.

Results: A total of 1,348 articles were retrieved initially and 36 randomized clinical trials involving 3,124 patients were included in the final analysis. The network meta-analysis showed that interscalene brachial plexus block was superior in reducing pain and opioid consumption compared to the five other interventions. However, adverse effects were reduced using

suprascapular nerve block and combined suprascapular and axillary nerve block compared to interscalene brachial plexus block.

Conclusion: Interscalene brachial plexus block was superior in reducing pain and opioid consumption compared to other peripheral nerve blocks but had a higher frequency of adverse events.

KEYWORDS

arthroscopic shoulder surgery, pain management, nerve block, complications, Bayesian network meta-analysis

Introduction

Arthroscopic shoulder surgery (ASS) is a commonly used procedure for shoulder surgery with minimal invasiveness, a wide field of vision, and rapid functional recovery (1, 2). Despite the popularity of the surgery, the severe postoperative pain becomes a complication after ASS (up to 45%) that prolongs the patient's recovery period and seriously affect the quality of life (3). Thus, finding a safe and effective postoperative pain regimen is crucial.

Currently, general anesthesia (GA) is combined with a regional nerve block in ASS, which reduces postoperative requirements of analgesia (4). Interscalene brachial plexus block (ISB) is one of the most reliable and commonly performed regional techniques, which has been universally considered a standard technique in postoperative pain management for ASS (5, 6). However, it often associated with a risk of complications, including epidural or subarachnoid injection, Horner's syndrome, dyspnea, hoarseness, intravascular injection, muscle or vascular injury, pneumothorax (7). Some peripheral nerve blocks involving ISB, continuous interscalene nerve block (CISB), supraclavicular nerve block (SCB), suprascapular nerve block (SSNB), suprascapular nerve block combined with axillary nerve block (SSAX) and local infiltration anesthesia (LIA) are also recommended to provide postoperative analgesia for ASS. The ranking of them in terms of efficacy and safety is still unknown, and an excellent method to investigate this is the network meta-analysis provided that certain assumptions are fulfilled.

Methods

This systematic review is reported according to the PRISMA declaration for Network Meta-analysis and the Cochrane Handbook for the Systematic Review of Interventions (8, 9). The study evaluated existing available data retrospectively, hence neither ethical approval nor patient consent is required.

Search strategy

A systematic literature search was designed and conducted separately by two authors to identify relevant randomized controlled trials (RCTs) on PubMed, Embase, Web of Science, the Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure database, Chinese Scientific Journal database, Wan Fang Database, from the date of database inception to 1st June 2022. There were no restrictions on publication year, region, or language. We used Medical Subject Headings (MeSH) Emtree terms, subject headings, and free-text terms in our search strategy, mainly include: "arthroscopic shoulder surgery" "arthroscopy," "shoulder," "nerve block," "regional anesthesia," "regional block," "local block," "interscalene nerve block," "suprascapular nerve block," "supraclavicular nerve block," "suprascapular and axillary nerve blocks," "pain," and "analgesia." We performed a further examination if the paper was presented in a non-English format due to certain restrictions in language.

Additionally, we conducted a battery of recursive searches and manual retrieval for major international conferences, which were presented only with an abstract that met our eligibility criteria. All above screening records will be managed using EndNote X9 (Thomson ISI Research Soft, Philadelphia, PA, USA). The established search strategies for each database were displayed in the "Search Strategies" supplement.

Eligibility criteria and exclusion criteria and data extraction

Inclusion criteria and exclusion criteria were determined as the priority according to PICO principle. Any study that compared the efficacy of anesthesia techniques as postoperative analgesia was thought suitable for our NMA. The inclusion and exclusion criteria were as follows. *Participants:* patients who underwent ASS under GA. *Interventions:* nerve block or regional anesthesia was administered in the operating room combined with GA. *Comparators:* interventions themselves or patients received GA alone. *Outcomes*: the primary outcome was pain

scores (VAS or NRS) in the PACU or within 1 h, 2 or 4 h, 6 or 8 h, 24 h after surgery and opioids consumption in 24 h after surgery; the secondary outcomes were the incidence of adverse events. *Study design:* Only RCTs were included in this review. Exclusion criteria: contraindications to nerve block or local anesthetics, coagulopathy, neuropathy, and chronic opioid use.

Two authors (ZL and J-HW) independently identified the relevant articles. Both titles and abstracts were initially searched according to the established eligible criteria. Duplicate articles were also removed simultaneously. In addition, studies published only in abstract form without any available data were discarded. If there is disagreement, an independent reviewer (P-CS) will serve as the expert referee to ensure consensus was reached on all items. Studies were summarized into seven groups, CISB, ISB, SSNB, SCB, SSAX, LIA, control group (CG).

Outcome measures and quality assessment

Two authors extracted relevant data from the included articles independently as follows: first author(s), year of publication, patient characteristics, sample size, type of block used, pain scores, opioids consumption, incidence of complications (Horner syndrome, dyspnea, hoarseness, vomiting, and nausea). We extracted the mean and standard deviation (SD) of pain scores and opioids consumption as continuous outcomes. As for the dichotomous data, the incidence of side effects and complications were extracted from the articles.

Two independent authors (ZL and J-HW) appraised and classified the risk of bias by using Cochrane's risk of bias (ROB) tool. Seven assessment items were classified as low, high, or unclear rank, which included random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and "other issues" under the guidance of the guidelines of Cochran's Handbook for Systematic Reviews of Interventions (8). The assessment of ROB was performed in Review Manager (Version 5.3). Additionally, the Grade approach was used to access the quality of evidence for each association (10).

Data analysis

Firstly, a network plot was generated for all direct comparisons to simulate a fully connected network, and a comparison-adjusted network funnel plot for funnel plot asymmetry was applied to assess the publication bias. Both analyses were performed in STATA software, version 14.0 (Stata Corp., College Station, TX). Before performing data analyzing, we assessed the transitivity and consistency assumption carefully, which underlies NMA and concerns the validity of making indirect comparisons. The baseline characteristics of participants are described using summary characteristics for the following analysis (11–13). Based on the Bayesian network meta-analysis, a non-informative prior distribution was used to compare the six interventions (14). All the outcomes were analyzed using random-effects models *via* the Markov chain Monte Carlo (MCMC) method, which established three distinct chains with sufficient iteration (15–17). For continuous variable, we used the mean difference (MD) to pool the effect size, as well as their 95% confidence intervals. As for the incidence of side effects and complications, dichotomous data were summarized using the odds ratio (OR) and 95% confidence interval (CI) (18, 19). The surface under the cumulative ranking curve (SUCRA) was calculated to rank probability of each intervention (20). A higher SUCRA value represents the likelihood that the intervention is on the top rank or is highly effective; a SUCRA value of 0 indicates the lowest efficacy compared to other prevention (19). Convergence of iterations was assessed for each parameters using the Brooks-Gelman-Rubin method and visual analysis of trace plots. The network consistency was evaluated with the node-splitting approach, where *P*-values of less than 0.05 indicated the probability of inconsistency of the entire network frame. If necessary, another sensitivity analysis was conducted for studies (8, 16, 21, 22). The above of the Bayesian network analysis was performed using the OpenBUGS (ver. 3.2.3 rev 1012, Members of OpenBUGS Project Management Group) software.

Results

Baseline characteristics and quality of the included studies

A total of 1,348 studies were identified initially by the electronic database searches and 45 discovered by manual searching as a supplement, and 935 articles were discarded due to duplication. After screening on the titles and abstracts, 241 articles were removed, and the 217 articles that met the criteria were remained to go through a further full-text examination. 181 articles were excluded for the following reasons: 104 did not represent a relevant data, 62 did not represent a relevant outcome, 15 were not randomized controlled trials. Finally, 36 RCTs were deemed eligible for the analysis with a unanimous agreement achieved between the review authors. The outline of literature search and selection procedures are shown in **Figure 1**. All searched reference lists were imported and managed in EndNote X9 software (Clarivate Analytics, London, United Kingdom). The basic characteristics of included studies were summarized in **Table 1**.

Thirty-six studies included in the review were published between 2004 and 2021, enrolling a total of 3,124 patients

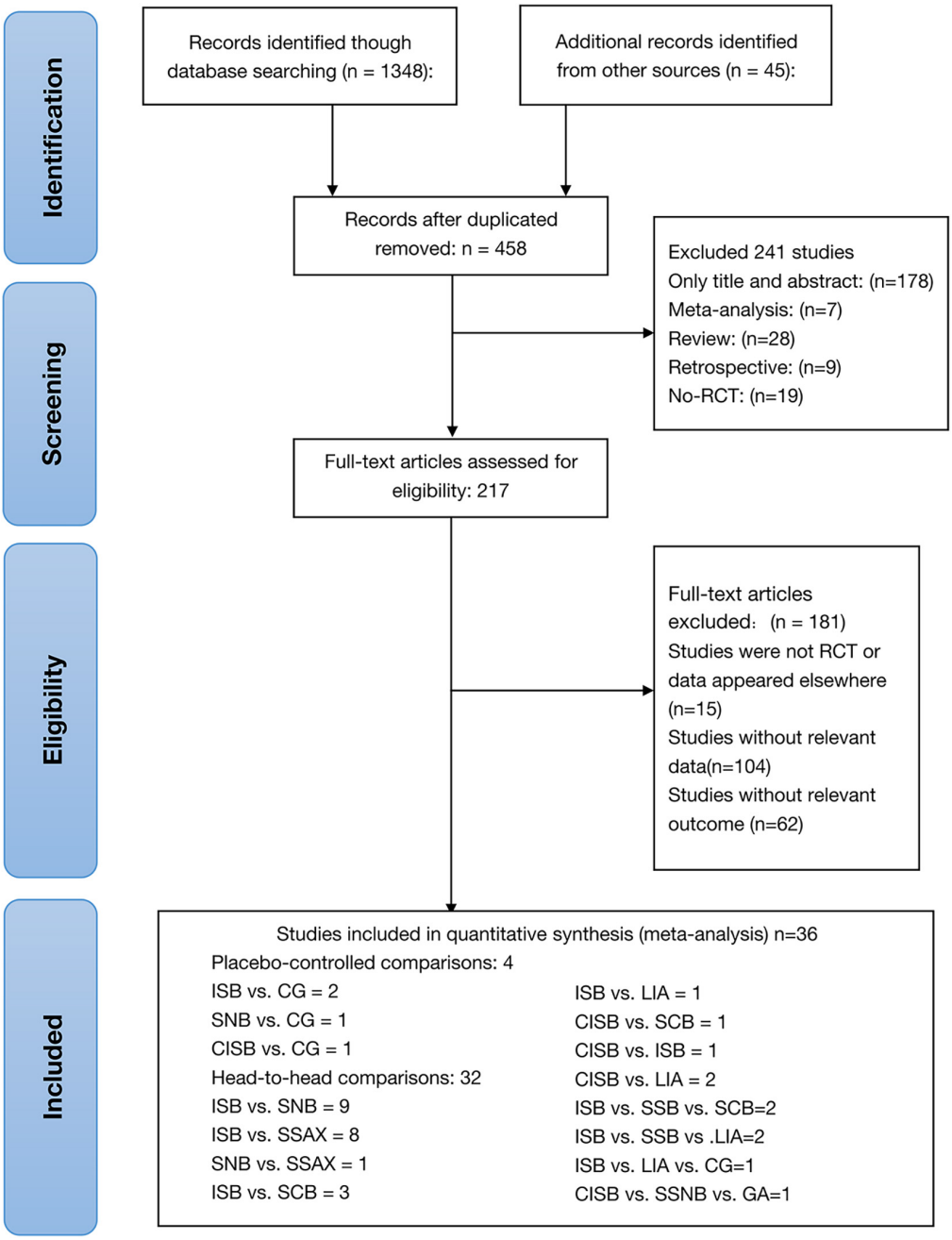

FIGURE 1
Literature review flowchart; RCT, Randomized controlled; CG, Control group.

undergoing ASS for arthroscopic rotator cuff, subacromial decompression and other forms of shoulder surgery (3, 7, 23–56). The RCTs had a parallel (n = 4) or crossover (n = 32) design between six interventions. The sample size was largest for the ISB group (n = 1,174; 29 studies), followed by the SSNB group (n = 693; 17 studies), the CISB group (n = 415; 7 studies), SSAX group (n = 330; 10 studies), and control group (n = 289; 9 studies), the SCB group (n = 267; 6 studies), and LIA group (n = 149; 5 studies). A network plot was generated to visualize all direct comparisons (**Figure 2**).

The overall quality of included studies showed low variations. All the 36 included trials were randomly assigned and had a low risk of bias (ROB) in "Random sequence generation." Five studies had a low ROB for the selective reporting item. Seven RCTs had a high or unclear ROB due to attrition. 25 used allocation concealment and 16 described the blinding

TABLE 1 Characteristics of included studies.

ID	Study	Total	Age	Gender (M/F)	ASA	Primary anesthesia	Pain outcome	Ultrasound used	Amount and type of anesthetic agent	Intervention	Outcome	Complication
1	Auyong et al. (24)	189	54 ± 13 vs. 0.53 ± 14 vs. 55 ± 14	38/25 vs. 39/24 vs. 42/21	I-III	GA	NRS	Y	All: 15 mL of 0.5% ropivacaine	ISB/SSB/SCB	PACU/24 h/O	[1][2][3][4]
2	Desroches et al. (30)	53	56.5 ± 9 vs. 60.8 ± 8.7	16/9 vs. 17/11	I-III	GA	VAS	Y	ISB: 20 mL of 0.75% of ropivacaine SSB: 10 mL of 0.75% of ropivacaine	ISB/SSB	PACU/24 h	/
3	Dhir et al. (31)	59	51.3 ± 14.2 vs. 46.5 14.5	26/4 vs. 22/7	I-III	GA	NRS	N	ISB: 20 mL of 0.5% ropivacaine SSAX: 15 mL of 0.5% ropivacaine + 15 mL of 0.5% ropivacaine	ISB/SSAX	PACU/6–8 h/24 h/O	[4]
4	Kumara et al. (3)	60	60–18 years	not mention	I-II	GA	VAS	N	ISB:20 mL of 0.5% bupivacaine SSB:15 mL of 0.5% bupivacaine	ISB/SSB	PACU/6–8 h//2–4 h/24 h	/
5	Neuts et al. (44)	98	50 ± 10 vs. 0.51 ± 10	28/22 vs. 18/30	I-III	GA	VAS	Y	ISB:20 mL of 0.75% ropivacaine SSB:10 mL of 0.75% ropivacaine + 10 mL of 0.75% ropivacaine	ISB/SSAX	PACU/6–8 h//2–4 h/24 h	[4]
6	Ovesen et al. (45)	91	48.95 vs. 48.70 vs. 54.77 vs. 48.79	11/11 vs. 7/11 vs. 7/15 vs. 10/14	not mention	GA	VAS	N	ISB: 30 mL of 0.75% ropivacaine SSB: 20 mL of 0.5% bupivacaine LIA:10 mL 0.5% bupivacaine and 5 ml morphine (0.4 mg/mL)	ISB/SSB/LIA/CG	PACU/2–4 h/24 h/O	[4]
7	Singelyn et al. (50)	120	52 ± 14 vs. 54 ± 15 vs. 50 ± 14 vs. 53 ± 17	15/15 vs. 12/14 vs. 11/19 vs. 12/18	I-III	GA	VAS	N	SSB: 10 mL of 0.25% bupivacaine LIA: 20 mL of 0.25% bupivacaine ISB: 20 mL of 0.25% bupivacaine	ISB/SSB/LIA/CG	PACU/2–4 h/24 h/O	[4]
8	Yao et al. (56)	80	51.1 ± 9.29 vs. 53.03 ± 8.09	17/23 vs. 19/21	I-II	GA	VAS	Y	ISB: 20 mL of 0.5% ropivacaine SSAX: 10 mL of 0.5% ropivacaine + 10 mL of 0.5% ropivacaine	ISB/SSAX	PACU/6–8 h/24 h	[1][2][3][4]
9	Qianqian (42)	40	52.35 ± 11.90 vs. 49.55 ± 13.54 vs. 0.48.63 ± 12.68	13/20 vs. 9/20 vs. 11/20	I-II	GA	VAS	Y	ISB: 20 mL of 0.25% ropivacaine SSAX: 15 mL of 0.25% ropivacaine + 5 mL of 0.25% ropivacaine	ISB/SSAX	PACU/6–8 h//2–4 h/24 h/O	[4]
10	Pani et al. (47)	72	37.70 ± 13.65 vs. 37.06 ± 12.52	29/8 vs. 29/6	I-III	GA	VAS	Y	ISB: 10 mL of 0.75% ropivacaine SSAX: 10 mL of 0.75% ropivacaine + 10 mL of 0.75% ropivacaine	ISB/SSAX	PACU/6–8 h//2–4 h/24 h	[1][2][3][4]
11	Saini et al. (48)	70	26.97 ± 7.67 vs. 27.29 ± 6.41	31/4 vs. 0.30/5	I-II	GA	VAS	Y	ISB: 10 mL of 0.5% ropivacaine SSAX: 10 mL of 0.5% ropivacaine + 10 mL of 0.5% ropivacaine	ISB/SSAX	PACU/6–8 h//2–4 h/24 h	[2]
12	Waleed (51)	60	27.37 ± 5.87 vs. 28.57 ± 6.12	19/11 vs. 20/10	I-II	GA	VAS	Y	ISB: 20 mL of levobupivacaine 0.25% SSAX: 10 mL of levobupivacaine 0.25% + 10 mL of levobupivacaine 0.25%	ISB/SSAX	PACU/6–8 h//2–4 h/24 h/O	[1][2][3][4]
13	Aksu et al. (23)	60	45.1 ± 5.87 vs. 44.2 ± 15.9 vs. 43.4 ± 13.5	13/7 vs. 12/8 vs. 13/7	I-II	GA	VAS	Y	ISB: 20 mL 0.25% bupivacaine LIA: 20 mL 0.25% bupivacaine	ISB/LIA/CG	PACU/6–8 h//2–4 h/24 h/O	/

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TABLE 1 (Continued)

ID	Study	Total	Age	Gender (M/F)	ASA	Primary anesthesia	Pain outcome	Ultrasound used	Amount and type of anesthetic agent	Intervention	Outcome	Complication
14	Beaudet et al. (25)	60	48 ± 11 vs. 51 ± 10	8/22 vs. 16/14	I-III	GA	NRS	N	CISB: 0.25 mL/kg of 2% lidocaine + 0.25 mL/kg of 0.5% bupivacaine LIA: 0.25 mL/kg of 2% lidocaine	CISB/LIA	PACU/24 h	/
15	Contreras-Domínguez et al. (28)	47	37 ± 7 vs. 43 ± 5	14/9 vs. 15/9	I-II	GA	VAS	N	CISB: 25 mL of 0.2% ropivacaine + 2 mg of morphine + 7 mL/h of 0.0625% bupivacaine + 1 microg/mL of sufentanil IA: 25 mL of 0.2% ropivacaine	CISB/LIA	PACU/6–8 h//2–4 h/24 h	/
16	Ikemoto et al. (35)	30	54 (39–65) vs. 57 (45–69) vs. 57 (47–76)	10/5 vs. 11/4 vs. 11/4	/	GA	VAS	N	ISB: 2 mg/kg of 0.5% ropivacaine SSB: 2 mg/kg of 0.5% ropivacaine	ISB/SSB	PACU/6–8 h/24 h	/
17	Wiegel et al. (53)	329	53 ± 13 vs. 55 ± 13	98/66 vs. 106/59	I-III	GA	VAS	Y	ISB: 20 mL 0.75% of ropivacaine SSB: 10 mL 0.75% of ropivacaine	ISB/SSB	PACU/2–4 h/24 h	[1][2][3]
18	Janssen et al. (36)	82	51 ± 10 vs. 53 ± 9	19/23 vs. 18/23	I-II	GA	VAS	N	ISB: 40 mL of 1% mepivacaine	ISB/CG	PACU/24 h	[4]
19	Abdallah et al. (7)	136	40 ± 15 vs. 46 ± 15	53/16 vs. 46/21	I-III	GA	NRS	Y	ISB: 15 mL of 0.5% ropivacaine SSB: 15 mL of 0.5% ropivacaine	ISB/SSB	PACU/6–8 h/24 h/O	/
20	Jiang et al. (37)	47	56.4 ± 13.3 vs. 55.0 ± 10.7	9/15 vs. 8/15	I-II	GA	VAS	Y	ISB: 20 mL of 0.375% ropivacaine SSB: 20 mL of 0.375% ropivacaine	ISB/SSB	PACU/6–8 h/24 h/O	/
21	Shi et al. (49)	60	55.83 ± 11.6 vs. 55.26 ± 11.75	19/11 vs. 17/13	I-II	GA	VAS	Y	SSB: 15 mL of 0.5% ropivacaine	SSB/CG	PACU/6–8 h//2–4 h/24 h	/
22	Yao et al. (55)	95	54.1 ± 9.2 vs. 53.6 ± 8.6	30/18 vs. 28/19	I-II	GA	VAS	Y	ISB: 20 mL of 0.5% ropivacaine SSB: 15 mL of 0.5% ropivacaine	ISB/SSB	PACU/6-8h//2-4h/24h/O	[1][2][3][4]
23	Janssen et al. (36)	42	54.0 ± 8.0 vs. 55.8 ± 8.0	14/7 vs. 14/7	/	GA	VAS	Y	SSB: 10 mL of 0.75% ropivacaine SSAX: 10 mL of 0.75% ropivacaine + 10 mL of 0.75% ropivacaine	SSB/SSAX	PACU/6–8 h//2–4 h/24 h	/
24	Cabaton et al. (26)	103	57 (51–65) vs. 58 (54–65)	32/20 vs. 27/24	I-II	GA	VAS	Y	ISB: 20 mL of 0.5% levobupivacaine SCB: 20 mL of 0.5% levobupivacaine	ISB/SCB	PACU/24 h/O	/
25	Karaman et al. (38)	60	52 ± 20 vs. 55.8 ± 8.0	20/11 vs. 14/15	I-II	GA	VAS	Y	ISB: 20 mL of 0.25% bupivacaine SCB: 20 mL of 0.25% bupivacaine	ISB/SCB	5 min/6–8 h/24 h	[1][2][3]
26	Koltka et al. (41)	50	48.8 ± 11.2 vs. 52.2 ± 9.8	17/8 vs. 16/9	I-II	GA	VAS	Y	ISB: 30 mL of 0.5% bupivacaine SCB: 30 mL of 0.5% bupivacaine	ISB/SCB	PACU/6–8 h//2–4 h/24 h/O	[1][3][4]
27	Wiesmann et al. (54)	114	53 ± 13 vs. 52.7 ± 13	34/22 vs. 34/24	I-II	GA	NRS	Y	ALL: 10 mL of ropivacaine 0.2% + a patient controlled analgesia (PCA) bolus of 4 ml/h 0.2% ropivacaine	CISB/SCB	PACU/24 h	[1][2][3]
28	Wang and Lin (52)	120	53 ± 12 vs. 52 ± 14 vs. 54 ± 14	24/16 vs. 25/15 vs. 27/13	I-III	GA	VAS	Y	ISB: 15 ml of 0.375% ropivacaine SSB: 15 ml of 0.375% ropivacaine	ISB/SSB/SCB	PACU/24 h/O	[1][2][3][4]

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TABLE 1 (Continued)

ID	Study	Total	Age	Gender (M/F)	ASA	Primary anesthesia	Pain outcome	Ultrasound used	Amount and type of anesthetic agent	Intervention	Outcome	Complication
29	Faiz et al. (32)	80	48.80 ± 7.48 vs. 49.70 ± 7.05	28/12 vs. 30/10	I-II	GA	VAS	Y	ISB: 15 ml of 0.2% ropivacaine SSAX: 10 ml of 0.2% ropivacaine + 10 ml of 0.2% ropivacaine	ISB/SSAX	PACU/6–8 h/24 h/O	[4]
30	Debnath et al. (29)	105	44 (24–70) vs. 44.5 (23–73)	30/22 vs. 30/23	I-III	GA	VAS	N	ISB: 20 ml 0.5% Chirocaine LIA: 20 ml 0.5% Chirocaine	ISB/LIA	PACU/2–4 h/24 h/O	/
31	Kim et al. (40)	93	62.39 ± 8.78 vs. 59.09 ± 7.5 vs. 62.74 ± 6.92	14/17 vs. 17/14 vs. 15/16	I-II	GA	VAS	N	ISB: 15 ml 2% lidocaine + 15 ml 2% levobupivacaine SSB: Ropivacaine 10 mg + lidocaine10 mg PCA: lidocaine 100 mg + Ropivacaine 100 mg	CISB/SSB/CG	PACU/6–8 h/24 h	/
32	Gurger and Ozer (33)	85	58.47 ± 7.18 vs. 58.21 ± 7.67	25/18 vs. 22/20	I-II	GA	VAS	N	CISB: 30 ml of 0.25% bupivacaine + 5 ml/h 0.125% bupivacaine	CISB/CG	PACU/6–8 h/24 h	/
33	Kim et al. (39)	117	63.70 ± 8.13 vs. 60.78 ± 9.38 vs. 60.90 ± 9.15	17/22 vs. 19/18 vs. 17/22	I-III	GA	VAS	N	ISB: 16 ml of 0.75% ropivacaine + 4 ml of 2% lidocaine CISB: 10 ml bolus solution of 0.75% ropivacaine	CISB/ISB/CG	PACU/24 h	/
34	Cao and Yan (27)	50	57.72 ± 7.31 vs. 56.80 ± 7.34	15/10 vs. 10/15	/	GA	VAS	Y	ISB: 20 ml of 0.2% ropivacaine SSB: 20 ml of 0.2% ropivacaine	ISB/SSB	PACU/6–8 h//2–4 h/24 h	/
35	Liu (46)	107	≥ 18	/	I-III	GA	VAS	Y	ISB: 6 ml 0.3%ropivacaine SSB: 6 ml 0.3%ropivacaine	ISB/SSB	PACU/6–8 h/24 h	[2][3][4]
36	Huang and Luo (34)	60	46.3 ± 10.2 vs. 46.6 ± 10.3	13/17 vs. 11/19	I-III	GA	VAS	Y	ISB: 20 ml of 0.5% ropivacaine	ISB/CG	PACU/6–8 h/24 h	/

ASA, American Society of Anesthesiologists; PCA, Patient controlled analgesia; PACU, Post anesthesia care unit; GA, General anesthesia; VAS, Visual analog scale; NRS, numerical rating scale; O, Opioids consumption; [1], Horner syndrome; [2], Dyspnea; [3], Hoarseness; [4], Vomiting and nausea.

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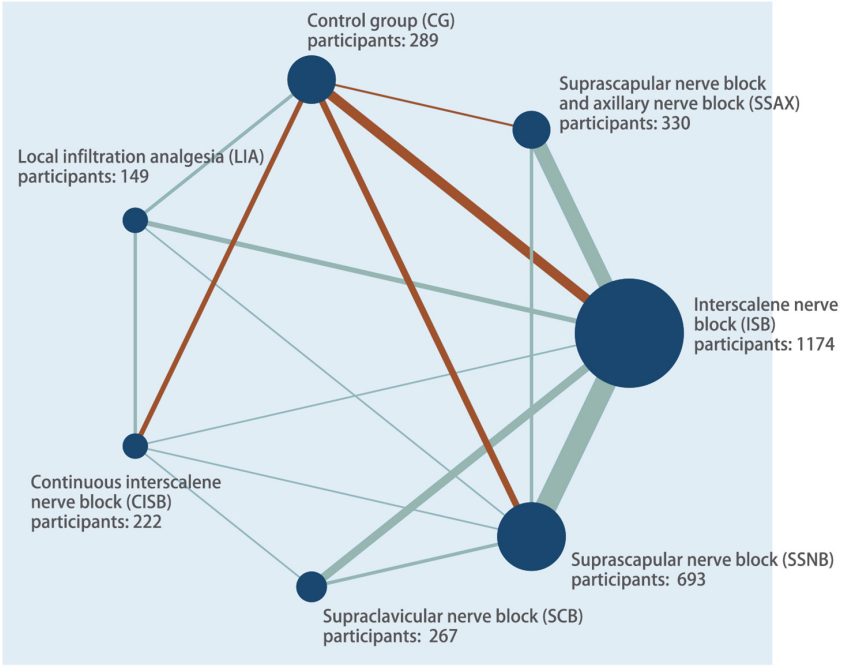

FIGURE 2
Network plot of all evidence of all the trails. The network plot of the intervention network shows the comparison of the sample size to provide anesthesia for patients undergoing arthroscopic shoulder surgery. Each node represented a different method of prevention with size of the node depending on the number of patients who received the intervention directly. The nodes were connected by lines indicating direct relationships between interventions, with the thickness of the line depending on the amount of direct evidence supporting the intervention.

of outcome assessment in detail. The assessment of quality of included studies were showed in Figures 3, 4. The funnel plot did not indicate publication bias due to its symmetrical distribution (Inverted funnel plot) (Figure 5).

Pain scores

Every study of postoperative pain scores has been associated with various nerve blocks or local analgesia. Thirty-one studies evaluated pain score by recording on a visual analog scale (VAS), a continuous scale based on a 0–10 cm (100 mm) in length. Five studies evaluated postoperative pain scores with a numerical rating scale (NRS) scoring, and the numbers (0–10) were administered in a numeric version of the VAS to evaluate pain intensity. The pain scores were evaluated at five time points (In the PACU or within 1 h after surgery, 2 or 4 h, 6 or 8 h, 24 h after surgery).

In the Post anesthesia care unit or within 1 h after surgery

A total of 36 studies reported pain scores in the PACU or within 1 h after surgery, including 7 groups (CG, ISB, CISB, SSNB, SCB, SSAX, LIA). CISB (*MD* = −3.14, 95% CI −4.47, −1.82), ISB (*MD* = −2.41, 95% CI −3.40, −1.41), SCB (*MD* = −2.34, 95% CI −3.79, −0.88), SSNB (*MD* = −1.66, 95% CI −2.73, −0.59), and SSAX (*MD* = −1.63, 95% CI −2.86, −0.39), provided significantly better analgesic effects compared to the CG group.

According to the SUCRA data (Supplementary Figure 1), CISB (SUCRA = 94.27%) and ISB (75.49%) had the highest efficacy, followed by SCB (69.36%), SSNB (39.64%), SSAX (38.79%), SSAX (31.18%), and control group (1.28%).

Within 2 or 4 h after surgery

Sixteen studies reported pain scores within 2 or 4 h after surgery and included 7 groups (CG, ISB, CISB, SSNB, SCB, SSAX, IA). ISB (MD = −2.02, 95% CI −3.49, −0.58) has significantly better outcomes than the CG group within 2 or 4 h after surgery.

According to the SUCRA data (Supplementary Figure 2), ISB (SUCRA = 85.56%) had the highest efficacy, followed by SCB (72.74%), SSNB (52.16%), CISB (48.53%), SSAX (48.23%), LIA (31.85%), and control group (10.92%).

Within 6 or 8 h after surgery

Twenty-three studies reported pain scores within 6 or 8 h after surgery and included 7 groups (Control group, ISB, CISB, SSNB, SCB, SSAX, LIA). ISB (*MD* = −1.69, 95% CI −2.54, −0.88), SCB (*MD* = −1.78, 95% CI −3.33, −0.24), SSNB (*MD* = −1.49, 95% CI −2.37, −0.63), CISB (*MD* = −1.39, 95% CI −2.50, −0.29) have significantly better outcomes than the CG group within 6 h or 8 h after surgery.

According to the SUCRA data (Supplementary Figure 3), ISB (SUCRA = 77.35%) had the highest efficacy, followed by SCB (75.37%), SSNB (62.93%), CISB (57.89%), LIA (47.02%), SSAX (27.53%), and control group (1.92%).

At 24 h after surgery

Thirty-six studies reported pain scores at 24 h after surgery and included 7 groups (Control group, ISB, CISB, SSNB, SCB, SSAX, LIA). SSNB (*MD* = −1.26, 95% CI −2.39, −0.10), SSAX (*MD* = −1.10, 95% CI −2.06, −0.11) have significantly better outcomes than the LIA group at 24 h after surgery.

The SUCRA data denoted that SSNB (SUCRA = 86.73%) and SSAX (SUCRA = 78.21%) had the highest efficacy, followed by ISB (SUCRA = 60.05%), CISB (SUCRA = 50.21%), SCB (SUCRA = 45.38%), LIA (SUCRA = 8.26%), and control group (21.16%) (Supplementary Figure 4).

Opioids consumption

Eighteen studies reported opioids consumption within 24 h after surgery and included 7 groups (Control group, ISB, CISB, SSNB, SCB, SSAX, LIA). ISB (*MD* = −12.9, 95% CI −17.15, −7.08), SCB (*MD* = −8.36, 95% CI −15.48, −1.33), SSNB (*MD* = −7.15, 95% CI −12.20, −2.15) have significantly better outcomes than the CG group within 6 h or 8 h after surgery (Supplementary Figure 5).

The SUCRA data showed that ISB (SUCRA = 97.23%) had the highest efficacy, followed by, SCB (SUCRA = 67.41%), SSNB (SUCRA = 57.91%), SSAX (SUCRA = 50.76%), CISB (SUCRA = 46.85%), LIA (SUCRA = 25.71%), and control group (21.16%).

Postoperative complications

Horner syndrome

Ten studies reported the incidence of Horner syndrome after surgery and included 5 groups (ISB, SSNB, SCB, CISB, SSAX). SSNB (OR = 0.15, 95% CI 0.01, 0.29), and SSAX (OR = 0.86, 95% CI 0.01, 0.67) significantly reduced the incidence of Horner syndrome compared to CISB group. SSNB (OR = 0.04, 95% CI 0.01, 0.13), SSAX (OR = 0.08, 95% CI 0.01, 0.32), and SCB (OR = 0.24, 95% CI 0.06, 0.58) significantly reduced the incidence of Horner syndrome compared to ISB group (Supplementary Figure 6).

Dyspnea

Twelve studies reported the incidence of dyspnea after surgery and included 5 groups (ISB, SSNB, SCB, CISB, SSAX). SSAX (OR = 0.12, 95% CI 0.02, 0.32) and SSNB (OR = 0.27, 95% CI 0.07, 0.62) significantly reduced the incidence of dyspnea syndrome compared to ISB group (Supplementary Figure 7).

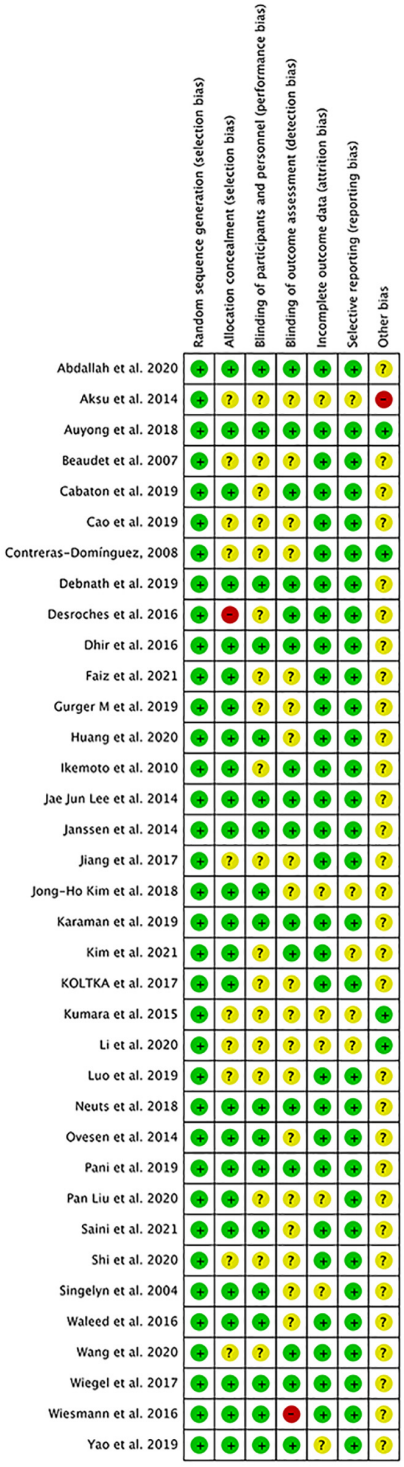

FIGURE 3
Risk of bias graph.

Hoarseness

Eleven studies reported the incidence of hoarseness after surgery and included 5 groups (ISB, SSNB, SCB, CISB, SSAX).

SSAX (OR = 0.29, 95% CI 0.03, 0.88) and SSNB (OR = 0.36, 95% CI 0.08, 0.84) significantly reduced the incidence of *hoarseness* compared to ISB group (**Supplementary Figure 8**).

Vomiting and nausea

Fourteen studies reported the incidence of vomiting after surgery and included 5 groups (ISB, SSNB, SCB, CISB, SSAX). SSNB (OR = 0.31, 95% CI 0.11, 0.71) and ISB (OR = 0.31, 95% CI 0.71, 0.84) significantly reduced the incidence of Horner syndrome compared to CISB group (**Supplementary Figure 9**).

Discussion

This NMA provides efficacy data on five variants of nerve blocks and intra-articular infiltration analgesia combined with GA, as well as the comparisons of some important complications. In the included study, all patients received nerve block before surgery. During the perioperative period, patients received GA with muscle relaxants, combined with multimodal analgesia. It is suggested that ISB are the most highly effective performed regional techniques for ASS in the early postoperative period (in the PACU or 1 h after surgery, 2 or 4 h, 6 or 8 h), while SSNB, SSAX provided provide better late postoperative shoulder analgesia (at 24 h after surgery). Moreover, SSNB, SSNB, SCB, may have a lower overall complication rate for Horner syndrome, dyspnea, hoarseness, vomiting and nausea than ISB and CISB.

ISB has been historically considered the gold standard in postoperative pain management for ASS, which was usually performed with an injection of local anesthetic at the nerve root level of the brachial plexus to block C5–7 between the anterior and middle scalene muscles (5, 57, 58). A systematic review by Warrender et al. recommend the use of ISBs as the most effective analgesic for outpatient undergoing ASS based on the evidence of 40 RCTs (4). Consistent with previous studies, our results also indicated that ISB significantly improved pain control in the early postoperative period compared with control group, particularly in the PACU or within 2 h or 4 h hours postoperatively. Following ISB, ipsilateral phrenic nerve block is a well-known complication, of which the rates of 16.6–38% have been reported in previous studies. The root cause is the interscalene insertion site is close to the phrenic nerve, and the unintended spread of local anesthesia could cause diaphragm paresis, thus reducing vital capacity and leading to dyspnea (59). Therefore, ISB would have been a relative contraindication in patients with serious pulmonary disease. Desai found that patients who received continuous interscalene infusion catheters (CISB) resulted in a clinically remarkable improvement during the first 24 postoperative hours compared with those who received a single shot ISB (5). It is indicated in our results CISB group provided a better analgesia than the ISB group in the early postoperative period.

Many studies suggested SSNB may be considered as an alternative when ISB is contraindicated to be used as an option for patients after ASS (60–62). A previous meta-analysis of 14 articles suggested that, SSNB showed inferior analgesic effect compared with ISB, particularly in the short-term period (in the PACU or within 1–2 h postoperatively) (2). At 24 h postoperative, there was no significant difference in analgesic effect between the SSNB and ISB groups. The results of this NMA are mostly consistent with previous systematic reviews. In the early postoperative time (in PACU or within 1 h), compared to the control group, the efficiency of the SSNB group was lower than that of the ISB group (ISB: *MD* = −2.41, 95% CI −3.40, −1.41; SSNB: *MD* = −1.66, 95% CI −2.73, −0.59). Additionally, compared to the ISB group, the SSNB group provided a lower analgesic effect than the ISB group (*MD* = −0.74, 95% CI −1.48, −0.01). At 24 h after surgery, the analgesic effect has no significant difference between two groups. The explanation for the imperfect early pain control of SSNB is that, the suprascapular nerve is considered to innervate about 70% shoulder joint, the other 30% is innervated by the lateral thoracic nerve and axillary nerve (2, 63). Therefore, we hypothesize that combined with axillary block, SSAX may provide improved postoperative pain control compared with SSNB alone. The results suggested that SSAX group significantly reduced pain scores compared with control group (in PACU or at 24 h) (64). However, there was no difference between the results of SSNB group and the SSAX group. Furthermore, in contrast to that of ISB, we find that the complication rates were significantly lower in the SSNB and SSAX groups.

Supraclavicular block (SCB) is also an alternative to ISB with a low incidence of side effects. Cornish found that although SCB were administered under the clavicle and above the first rib, the local anesthetics could spread cephalad between the anterior and middle scalene muscles (65). A meta-analysis by Guo et al. compared SCB with ISB in pain control after shoulder surgery, indicating that SCB provided similar analgesic efficacy compared to ISB with a low incidence of hoarseness and Horner syndrome (66), which is consistent with our results. Compared with control group, SCB group reduced significantly pain scores in PACU (*MD* = −2.34, 95% CI −3.79, −0.88).

Local infiltration analgesia (LIA) is a safe and valuable postoperative pain management technique for patients undergoing ASS, which was usually performed at the end of the shoulder surgery before wound closure. However, iatrogenic chondrolysis of the glenohumeral joint as a complication of local infiltration analgesia is a rare but recognized complication, especially in the case of high dose and long-term administration of bupivacaine (67). In our NMA, the results suggested that LIA play no significant role in reducing the pain score at all time periods.

Our study has several strengths. To our knowledge, this is the first network meta-analysis evaluating postoperative pain regimens after ASS. Additionally, high-quality meta-analysis

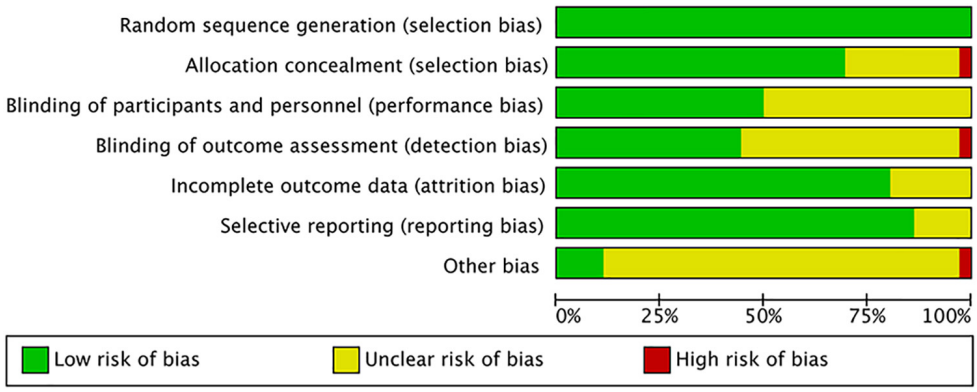

FIGURE 4
Risk of bias summary.

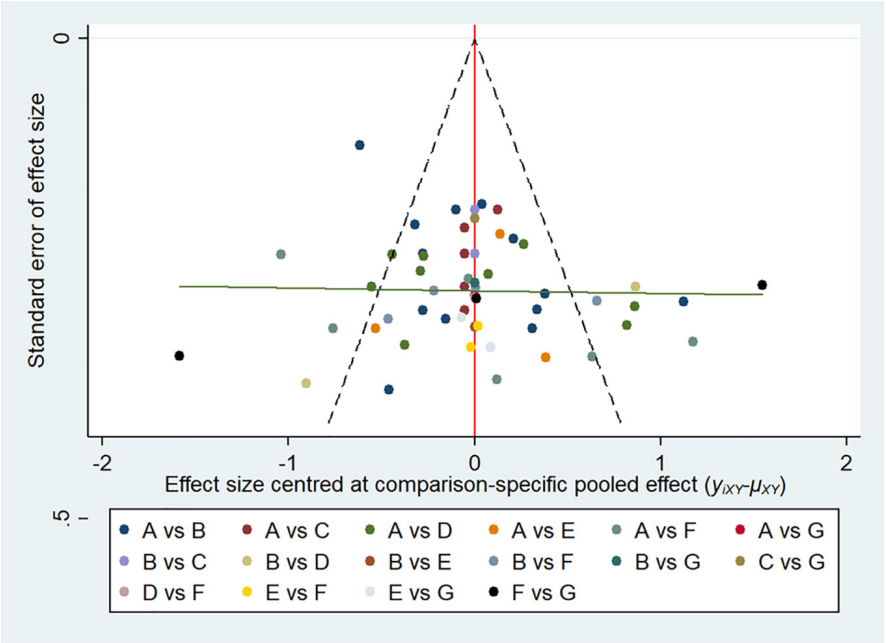

FIGURE 5
Funnel plot.

could be performed owing to that only RCTs was eligible for the present analysis. The trials were generally at low risk of bias for most ROB domains. Furthermore, in order to guarantee an accurate and thorough evaluation of the total body of data, the GRADE approach was used to grade the quality of the studies. Our NMA provided comprehensive evidence-based clinical practice guidance regarding the perioperative pain regimens in patients undergoing ASS.

There are also potential limitations in this review. Due to the limitations of the literature, some new analgesic methods and rare complications of nerve block were not analyzed in this NMA. Moreover, different types, concentrations, volumes of local anesthesia were used in these trials, which may cause some deviations. Another limitation is related to the technology used. Some nerve blocks are performed under ultrasound guidance, while others are located only by nerve stimulation. Furthermore, there was heterogeneity between the included studies in terms of quality evaluation, outcome measures, and assessment time. Finally, the proficiency of the operators, postoperative analgesia used, and patient characteristics may affect the pooled results and occurrence of complications.

Conclusion

ISB was superior in reducing pain and opioid consumption compared to other peripheral nerve blocks but had a higher frequency of adverse events.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Author contributions

ZL and J-hW helped substantial contributions to the conception or design of the work, the acquisition, analysis, interpretation of data for the work, drafting the manuscript, and revising it critically for important intellectual content. Y-bL and G-hW helped agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. P-cS helped final approval of the version to be published. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.1032253/full#supplementary-material

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The effects of intravenous tramadol vs. intravenous ketamine in the prevention of shivering during spinal anesthesia: A meta-analysis of randomized controlled trials

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Background: Shivering is a common complication after subarachnoid administration of local anesthetics. Intravenous ketamine and tramadol are widely available anti-shivering drugs, especially in developing settings. This meta-analysis aimed to compare the effects of intravenous ketamine vs. tramadol for post-spinal anesthesia shivering.

Materials and methods: PubMed/MEDLINE, Web of Science, Cochrane Library, Embase, and Google Scholar databases were used to search for relevant articles for this study. Mean difference (MD) with 95% confidence interval (CI) was used to analyze continuous outcomes, and risk ratio (RR) with 95% CI to analyze categorical results. The heterogeneity of the included studies was assessed using the I2 test. We utilized Review Manager 5.4.1 to perform statistical analysis.

Results: Thirteen studies involving 1,532 patients were included in this meta-analysis. Ketamine had comparable effects in preventing post-spinal anesthetics shivering [RR = 1.06; 95% CI (0.94, 1.20), $P = 0.33$, $I^2 = 77$], and onset of shivering [MD = −0.10; 95%CI (− 2.68, 2.48), $P = 0.94$, $I^2 = 0\%$], lower incidences of nausea and vomiting [RR = 0.51; 95%CI (0.26, 0.99), $P = 0.05$, $I^2 = 67\%$], and lower incidences of bradycardia [RR = 0.16; 95%CI (0.05, 0.47), $P = 0.001$, $I^2 = 33\%$], higher incidence of hallucinations [RR = 12; 95%CI (1.58, 91.40), $P = 0.02$, $I^2 = 0\%$], and comparable effects regarding the incidences of hypotension [RR = 0.60; 95%CI (0.30, 1.21), $P = 0.15$, $I^2 = 54\%$] as compared to tramadol.

Conclusions: Intravenous ketamine and tramadol are comparable in the prevention of post-spinal anesthetic shivering. Ketamine had a better

outcome with less occurrences of nausea, vomiting, and bradycardia. However, ketamine was associated with higher incidences of hallucinations than tramadol.

KEYWORDS

ketamine, tramadol, spinal, anesthesia, shivering

Introduction

Shivering is defined as an involuntary, repetitive activity of skeletal muscles to raise the core body temperature (1–5). Spinal anesthesia is known to decrease the shivering threshold, preceded by core hypothermia and vasoconstriction above the level of the block (6). The review of 21 studies reported that the median incidence of shivering related to neuraxial anesthesia was 55% in ranges of 40% to 64% (7).

Shivering may have beneficial thermoregulatory effects; however, it is a distressing experience and causes several undesirable detrimental effects (8). It leads to an increase in oxygen consumption and carbon dioxide production, intraocular and intracranial pressure (9–11). It may also lead to an increase in sympathetic tone that enhances the chances of myocardial ischemia (12, 13), pain (14), and bleeding (15). Shivering may impede monitoring techniques (non-invasive blood pressure, electrocardiogram, and pulse oximetry) (16–19).

A variety of pharmacologic and non-pharmacologic techniques for the prevention and treatment of shivering have been used; however, there is no globally accepted preferred technique for the treatment or prevention of post-spinal anesthetic shivering (7). Ketamine acts as a competitive N-methyl-D-aspartic acid receptor antagonist and can control post-spinal anesthetic shivering; In addition, it may decrease core-to-peripheral redistribution of heat by direct central sympathetic stimulation and by blocking inhibition of norepinephrine uptake into postganglionic sympathetic nerve endings, and it has a κ-opioid agonist property (17, 20–23). Tramadol has a μ-opioid agonist effect with minimum effect at kappa and delta receptors. Tramadol inhibits the re-uptake of serotonin and norepinephrine at the spinal cord level, which increases 5-hydroxytryptamine production. These actions of the drug make it effective in preventing and controlling post-spinal anesthetic shivering (24–27).

Intravenous tramadol and ketamine are widely available and cheap drugs, especially in the low resource settings. However, there is no high-quality data (meta-analysis) or large-sized randomized controlled trials on the relative efficacy and safety (anti-shivering agent with lesser side effects) of intravenous ketamine vs. tramadol. Hence, this meta-analysis aimed to compare the effects of intravenous tramadol vs. ketamine in preventing shivering after spinal anesthesia and associated side effects.

Abbreviations: MD, Mean difference; RR, Relative risk; CI, Confidence interval; RCTs, Randomized controlled trials.

Materials and methods

This study is reported as per Preferred Reporting Items for Systematic and Meta-analysis. Thirteen randomized controlled trials with a total of 1,532 patients were included. This meta-analysis was registered in Prospero with registration number *CRD42022342030* on July 5, 2022.

Search strategy

PubMed/MEDLINE, Web of Science, Cochrane Library, Embase, and Google Scholar databases were used for searching relevant articles. The terms used for searching were "Ketamine," "Tramadol," "Spinal Anesthesia," and "Shivering" through June 2022.

Inclusion criteria

Patients undergoing surgery under spinal anesthesia; studies that compare intravenous ketamine with intravenous tramadol on shivering; the incidence of side effects reported in both tramadol and ketamine groups; and randomized controlled trials were included.

Data extraction

The titles and abstracts of all articles were reviewed by two authors. Studies that are deemed to fall outside the inclusion criteria were excluded. Full paper copies of the remaining studies were reviewed by two authors (EF and DT) independently, and decisions made regarding

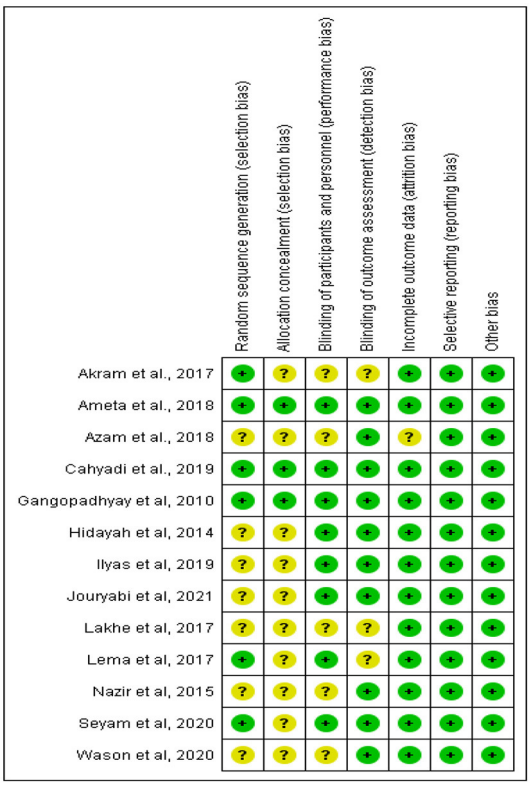

FIGURE 1
The risk of bias assessment of included studies.

selection/rejection. Any disagreements arising were resolved by a third reviewer (TT). The authors' name, publication year, characteristics of study participants, sample size, type of surgery, the dose and type of drug used for spinal anesthesia, the anti-shivering dose of intravenous ketamine and intravenous tramadol, and the outcomes of each included study were extracted.

Evaluation of the risk of bias (quality) assessment

The risk of bias was assessed using the Cochrane risk of bias tool and graded as low, unclear, or high risk of bias by two researchers independently. The included articles were rated according to random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. The disagreements between the researchers arising were resolved by a third reviewer.

Statistical analysis

We performed a meta-analysis of the effects of intravenous tramadol vs. ketamine in preventing post-spinal anesthetic shivering.

The Review Manager 5.4.1 (Cochrane Library, Oxford, UK) was used for this meta-analysis (Figure 1). The effective rate of shivering, the incidence rate of nausea and vomiting, hypotension, bradycardia, and hallucination were expressed in risk ratio (RR) with a 95% confidence interval (CI); and the onset of shivering in minutes was expressed in mean difference (MD) with 95% confidence interval (CI). If the I^2 was >50% or <50%, a fixed-effect model and a random-effect model, respectively, were utilized. The symmetry of the funnel plot showed that there was no publication bias.

Results

Characteristics of the included studies

Figure 2 demonstrates the flow chart of this meta-analysis. Thirteen RCTs (13, 18, 19, 25–34) were included in this meta-analysis, having 1,532 patients (Table 1). Eight trials (13, 26, 28–31, 33, 34) compared ketamine with tramadol; three trials (18, 32) compared ketamine with tramadol and ondansetron, clonidine (19), pethidine (27), or dexmedetomidine (25).

In six RCTs (18, 19, 25–27, 30), patients underwent lower abdominal and lower limb surgeries; patients in 2 trials (28, 31) underwent lower abdominal surgeries; patients in 3 trials (13, 29, 32) underwent cesarean section, and patients in a single trial (33) underwent lower limb surgery. However, a single trial (34) did not report the specific type of surgery.

Regarding the dose of bupivacaine used for spinal anesthesia, five trials (18, 27, 28, 31, 33) administered 15 mg of heavy bupivacaine, three studies (19, 25, 34) used 14 mg of heavy bupivacaine, and three studies (13, 30, 32) administered 12.5 mg of heavy bupivacaine, and a single trial (29) administered 9 mg of heavy bupivacaine. However, one trial (26) did not report the dose of local anesthetics used for spinal anesthesia.

The effect of ketamine vs. tramadol on the prevention of shivering

Thirteen RCTs (13, 18, 19, 25–34) reported the effective rate of shivering control. The random effects model was utilized because the value of I^2 was >50%. The effective rate of shivering control was comparable between groups (RR =1.06; 95% CI [0.94, 1.20], $P = 0.33$, $I^2 = 77\%$) (Figure 3). Sensitivity analysis was executed for the effective rate of shivering control by excluding a single study consecutively but with no source of heterogeneity detected and publication bias detected (Figure 4).

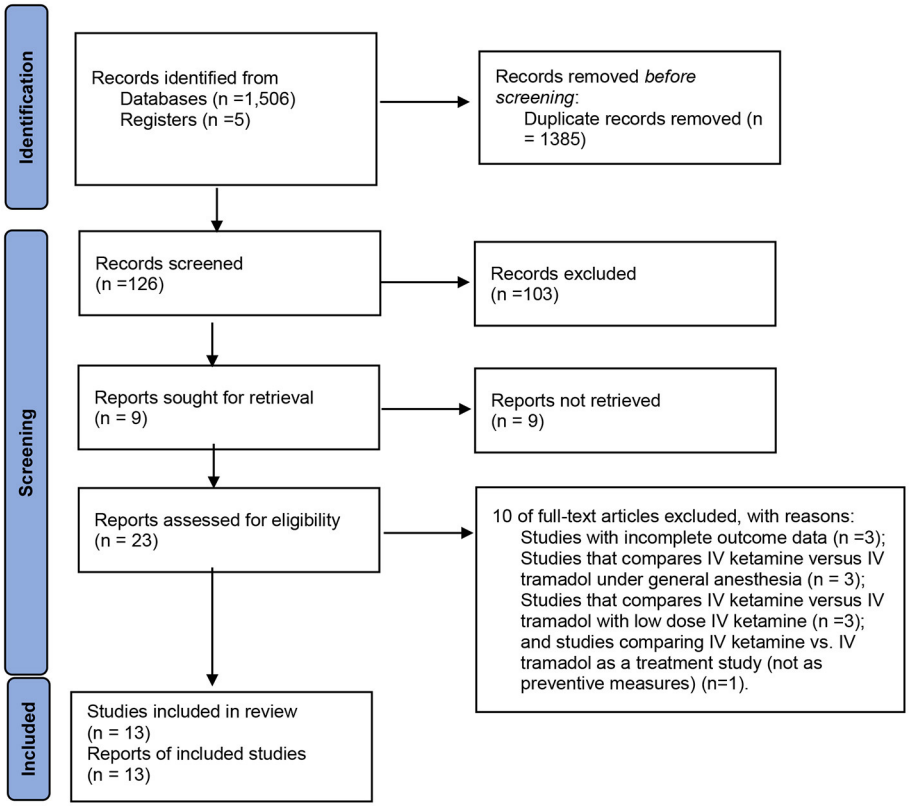

FIGURE 2
PRISMA 2020 flow diagram.

The effect of tramadol vs. ketamine on onset of shivering

Four RCTs (13, 18, 26, 34) compared time to onset of shivering of ketamine vs. tramadol. Since there was no heterogeneity detected (I^2 = 0%), the fixed effect model was utilized. The result showed that there was no significant differences regarding time to the onset of shivering time in minutes (MD = −0.10; 95%CI [– 2.68, 2.48], $P = 0.94$, $I^2 = 0\%$) (Figure 5).

The effect of tramadol vs. ketamine on the incidence of nausea and vomiting

Eight articles reported the incidence of nausea and vomiting (13, 18, 19, 25, 27, 30, 32, 34). Fifty-one patients receiving intravenous ketamine and 119 patients receiving intravenous tramadol experienced nausea and vomiting out of 428 patients in each group. Ketamine had lower incidences of nausea and vomiting than tramadol (RR = 0.51; 95%CI [0.26, 0.99], P = 0.05, $I^2 = 67\%$) (Figure 6).

The effect of tramadol vs. ketamine on the incidence of hypotension

The incidence of hypotension was reported in six trials (13, 19, 27, 32–34). Twenty-six patients receiving ketamine and 50 patients receiving tramadol experienced hypotension out of 328 patients in each group. Tramadol had comparable results with ketamine regarding the incidence of hypotension (RR = 0.60; 95%CI [0.30, 1.21], P = 0.15, I^2 = 54%) (Figure 7).

The effect of tramadol vs. ketamine on the incidence of bradycardia

The incidence of bradycardia was reported in six trials (13, 19, 25, 27, 32, 34). Three patients receiving ketamine and 22 patients receiving tramadol experienced bradycardia out of 348 patients in each group. Tramadol was associated with higher incidence of bradycardia (RR = 0.16; 95%CI [0.05, 0.47], P = 0.001, $I^2 = 33\%$) (Figure 8).

TABLE 1 Characteristics of included studies.

References	Study participants	Sample size tramadol/ Ketamine	Type of operations	Drugs used for spinal anesthesia	Dose, route of ketamine and tramadol	Outcomes
Akram et al. (28)	ASA class I–II, Age between 18 and 50 years, of either sex	32/32	Lower abdominal surgeries	3 ml of 0.5% heavy Bupivacaine	Ketamine 0.05 mg/kg IV, and Tramadol 1 mg/kg IV	Shivering was observed 6 (18.75%) in Group-K and 15 (46.88%) in Group-T (p-value = 0.01).
Ameta et al. (25)	ASA class I-II, aged 21–60 years, of either sex	50/50	Lower abdominal or lower limb surgeries	2.8 mL of 0.5% heavy bupivacaine	Ketamine 0.5 mg/kg IV, and tramadol 0.5 mg/kg IV	Shivering was seen in Group K was 46%, and Group T was 50%. No hallucinations or nausea/vomiting in both groups. Bradycardia 4% in Group K, 12% in Group T.
Azam et al. (29)	ASA I and II status, 1 aged 18–40 years	200/200	Cesarean section	1.8 ml of 0.5% heavy Bupivacaine.	0.5 mg/kg Ketamine IV, and 2 mg/kg tramadol IV	Shivering was observed in 72 (36%) patients of Group-T and 39 (19.5%) from Group-K (P = 0.000).
Cahyadi et al. (26)	ASA I and II status, aged 18-64 years	30/30	Lower abdominal or lower limb surgeries	Not specified	Ketamine IV 0.25 mg/kg, and Tramadol IV 0.5 mg/kg	Shivering was seen in 17 (56.7%) patients in Group-T and 17 (56.7%) from ketamine group ($P = 0.942$). The mean (SD) onset of shivering in minutes were 26.44 (19.708) and 25.33 (13.425) in Group-K and Group-T groups, respectively with p-value of 0.839.
Gangopadhyay et al. (27)	ASA I and II status, aged between 18 and 55 years	30/30	Infra-umbilical surgeries	3 ml of 0.5% heavy Bupivacaine	Ketamine 0.5 mg/kg IV, and tramadol 1.0 mg/kg IV, or	Shivering was seen in 4 patients of Group-T and 2 cases from ketamine. Nausea and vomiting (24 vs. 1); Pruritis (3 vs. no cases) in Group-T vs. Group-K. No evidence of respiratory depression, bradycardia, hypotension in both groups.
Hidayah et al. (30)	ASA I and II status, aged 18–70 years	50/50	Lower abdominal or lower limb surgeries	12.5 mg of 0.5% hyperbaric bupivacaine and 25 mcg fentanyl	Ketamine 0.5 mg/kg IV, and tramadol 0.5 mg/kg IV	The incidence of shivering was 4 (8%) cases in Group K, 8 (16%) patients in Group T. Hallucination (2 cases vs. 0); Nystagmus (39 vs. 0); Nausea and vomiting (9 vs. 6) from Group-K and Group-T, respectively.
Ilyas et al. (31)	ASA I and II status, aged 18–60 years	46/46	Lower abdominal procedures	15 mg of 0.5 % heavy bupivacaine.	Ketamine 0.05 mg/kg IV, and tramadol 1 mg/kg IV	Shivering was observed in 5 (10%) patients in ketamine group and 11 (24%) patients in Tramadol group.
Jouryabi et al. (32)	ASA I and II status, aged 18–40 years	127/127	Cesarean Section	12.5 mg isobaric bupivacaine.	Ketamine 0.2 mg/kg IV, and tramadol 0.5 mg/kg IV	Shivering was witnessed in 68 (53.5%), and 26 (20.5%); Nausea &vomiting [25 (19.7) vs 63 (49.6)]; Hypotension [7 (5.51) vs 28 (22.04)]; Bradycardia [0 (0) vs 14 (11)]; Hallucination [9 (7.1) vs 0 (0)]; Nystagmus [13 (10.2) vs 0 (0)]; Headache [5 (3.9) vs 10 (7.9)] in Groups- K & T respectively.

(Continued)

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TABLE 1 (Continued)

References	Study participants	Sample size tramadol/ Ketamine	Type of operations	Drugs used for spinal anesthesia	Dose, route of ketamine and tramadol	Outcomes
Lakhe et al. (18)	ASA I and II status, aged 18-65 years	30/30	General surgeries, Orthopedics or Gynecologic procedures	15 mg of 0.5 % heavy bupivacaine.	Ketamine 0.25 mg/kg IV, and tramadol 0.5 mg/kg IV	Shivering was present in 3 (10%) and 3 (10%) in Group-K & Group-T. Onset of shivering (mean ± sd) in minutes were 18.33 ± 2.88 and 16.67 ± 10.41 in Group-K & Group-T, respectively. Nausea, vomiting and hypotension were absent in both groups.
Lema et al. (13)	ASA I and II status, aged 18–39 years	41/41	Cesarean section	2.5 mL of 0.5% isobaric Bupivacaine.	Ketamine 0.2 mg/kg IV, and tramadol 0.5 mg/kg IV	Shivering was witnessed in 41.5% and 53.7%; Time to shivering in minutes was 27.5 ± 37 and 25 ± 27.7; Hypotension in 5 (12.2%) vs. 4 (9.8%); sedation 2 (4.9%) vs. 7 (17.1%), Nausea and vomiting 7 (17.1%) vs. 5 (12.2%) in Group-T & Group-K respectively; and no patient developed bradycardia and hallucinations.
Nazir et al. (33)	ASA I and II status, aged 18–60 years	30/30	Lower limb Surgeries	3 ml of 0.5% heavy Bupivacaine.	Ketamine 0.5 mg/kg IV, and tramadol 0.5mg/kg IV	Shivering was present in 3 (10%) and 2 (6.7%) in Group-K & Group-T. None of the patients had episodes of oxygen desaturation or respiratory depression, hallucinations, tachycardia, hypotension or hypertension.
Seyam et al. (34)	ASA I and II status, aged 21–60 years	50/50	Not specified	2.8 mL of 0.5% (14 mg) heavy bupivacaine	Ketamine 0.2 mg/kg IV, and tramadol 0.5 mg/kg IV	Shivering was observed in 28 (56%) and 18 (36%); Time to shivering in minutes was 31.5 ± 11 vs. 29.5 ± 9; Hypotension 11 (22%) vs 9 (18%); Nausea & vomiting 17 (34%) vs 11 (22%); Sedation (Rmsay score≤2) was 5 (10%) vs 17 (34%) in Group-T & Group-K respectively. None of the patients had bradycardia or hallucinations.
Wason et al. (19)	A total of 200 patients (50 cases in each group), ASA I and II status, aged 21–60 years	50/50	Lower abdominal or lower limb surgery	2.8 mL (14 mg) of 0.5% heavy bupivacaine	Ketamine 0.5 mg/kg IV, and tramadol 0.5 mg/kg IV	Shivering was present in 9 (18%) vs. 6 (12%); Hypotension 12% (6/50) vs. 12% (6/50); Bradycardia 1 (2%) vs. 2 (4%); and Nausea 0(0%) vs 2 (4%) patients in Group-K & Group-T respectively. Sedation score (grades 3 and 4) was significantly higher in the Group-K.

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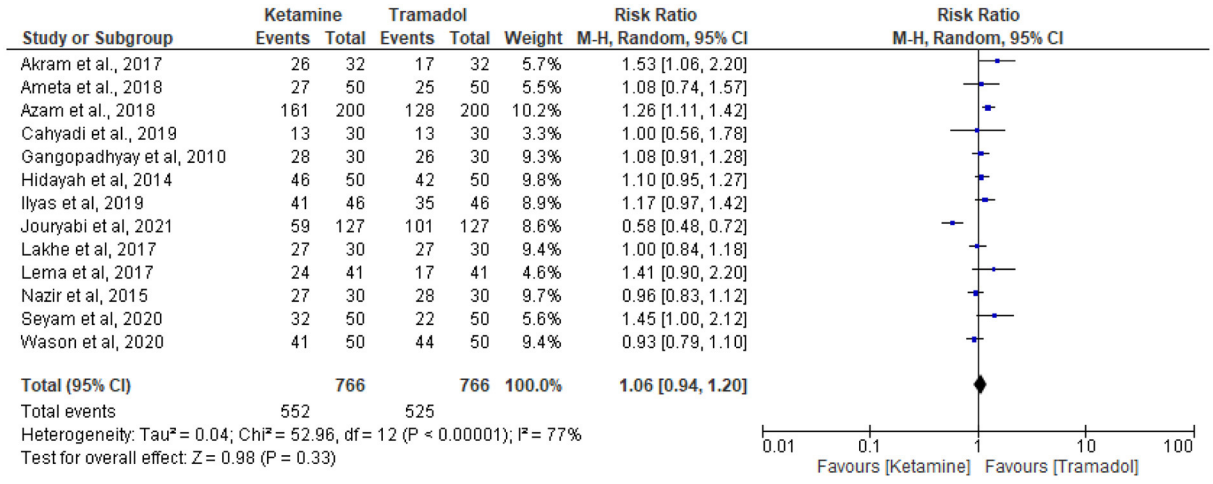

FIGURE 3
The effect of ketamine vs. tramadol on the prevention of shivering following spinal anesthesia.

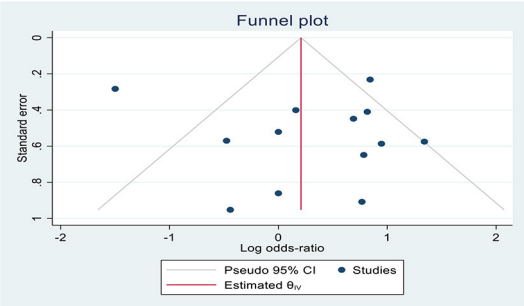

FIGURE 4
Funnel plot of the effect of tramadol vs. ketamine on prevention of shivering.

The effect of tramadol vs. ketamine on the incidence of hallucinations

The incidence of hallucination was reported in six RCTs (13, 25, 30, 32–34). Eleven patients in the ketamine group and no patient in the tramadol group experienced hallucination in a total of 348 patients in each group. Ketamine was associated with higher incidence of hallucinations (RR = 12; 95%CI [1.58, 91.40], $P = 0.02$, $I^2 = 0\%$) (Figure 9).

Discussion

Post-spinal anesthetic shivering is a common complication following subarachnoid administration of local anesthetics which results in repression of thermoregulatory mechanism for hypothermia (14, 34). In this meta-analysis, we compared the effect of intravenous ketamine and tramadol on the prevention of post-spinal anesthetics shivering.

In this meta-analysis, ketamine had comparable effects to tramadol in preventing post-spinal anesthetic shivering with a *P*-value of 0.51; and there were no significant differences regarding the onset of shivering with a *P*-value of 0.94. Tramadol inhibits the reuptake of serotonin and noradrenaline in the spinal cord and also has an effect on alpha-2 adrenergic and opioid receptors that might have anti-shivering effects (35–37). Ketamine is a competitive NMDA (N-Methyl D-Aspartate) receptor antagonist that inhibits noradrenergic and serotonergic neurons that might result in anti-shivering effects. Intravenous administration of ketamine and tramadol can be used for preventing post-spinal anesthetic shivering (19, 33, 34, 38).

The current study included a pooled analysis of the incidences of adverse events (nausea and vomiting, bradycardia, hypotension, and hallucinations) after the administration of anti-shivering agents. Ketamine showed a better outcome with less occurrences of nausea and vomiting ($P = 0.03$) and bradycardia ($P = 0.001$). Ketamine can cause a dose-dependent direct stimulation of the central nervous system that leads to an activation of the sympathetic nervous system and sustains heart rate (39). Ketamine was associated with a higher incidence of hallucinations ($P = 0.02$), and this might be due to its effect on glutamatergic signaling in psychosis that results in hallucination (40, 41). Intravenous ketamine had a comparable incidence of hypotension with intravenous tramadol with a *P*-value of 0.15. Research included in this meta-analysis (13, 19, 34) reported that ketamine was related with higher sedation scores than tramadol, despite the fact that we have not performed a pooled analysis due to variances in sedation scales employed in

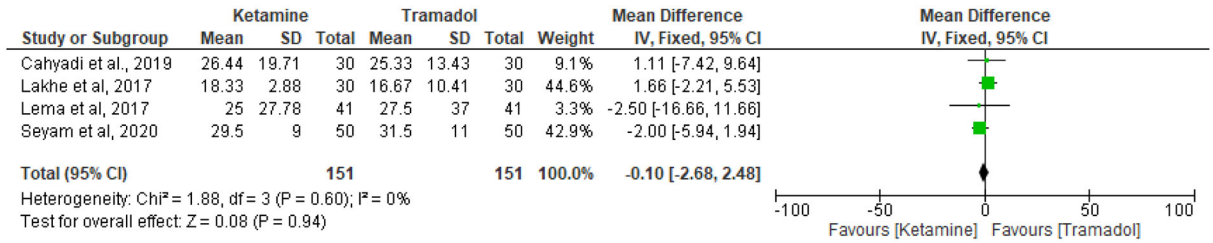

FIGURE 5
The effect of tramadol vs. ketamine on onset of shivering.

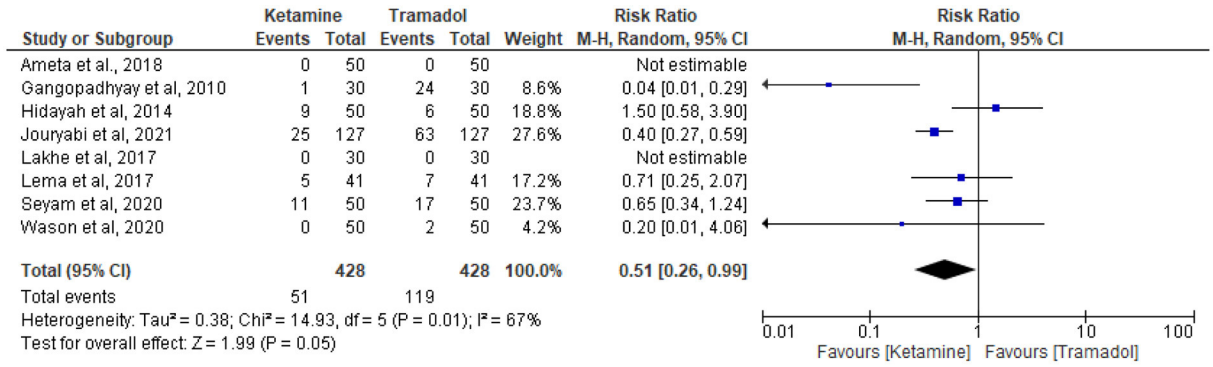

FIGURE 6
The effect of tramadol vs. ketamine on the occurrence of nausea and/or vomiting.

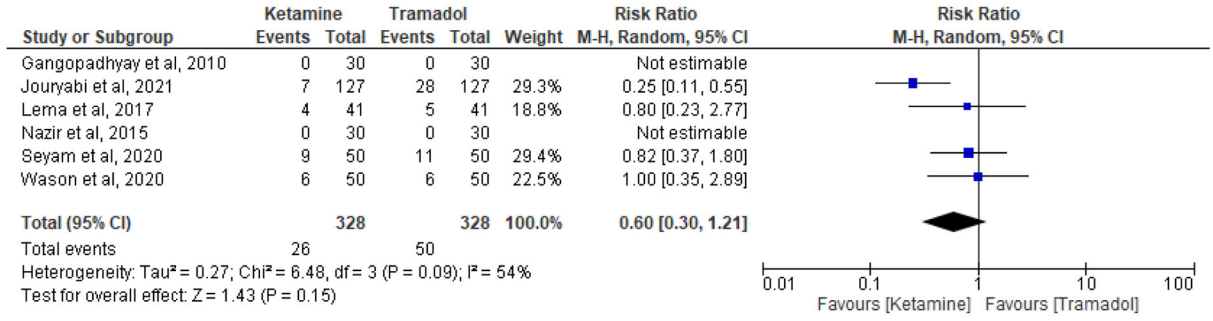

FIGURE 7
The effect of tramadol vs. ketamine on the incidence of hypotension.

the included studies. Ketamine may be a more effective anti-shivering medicine in this context than tramadol because of the higher sedation scores in the ketamine group, which may be crucial in maintaining optimal surgical circumstances and decreasing patient pain following spinal anesthesia. However, because there are variances in the types and dosages of local anesthetics used for spinal anesthesia as well as the types and durations of the procedures carried out in the included RCTs, the findings may be highly heterogeneous.

The main limitation of this meta-analysis might be the relatively inadequate sample size to make generalizations, and therefore further studies should be conducted. The other limitation of this meta-analysis could be the heterogeneity of the scales used for shivering to run a pooled analysis.

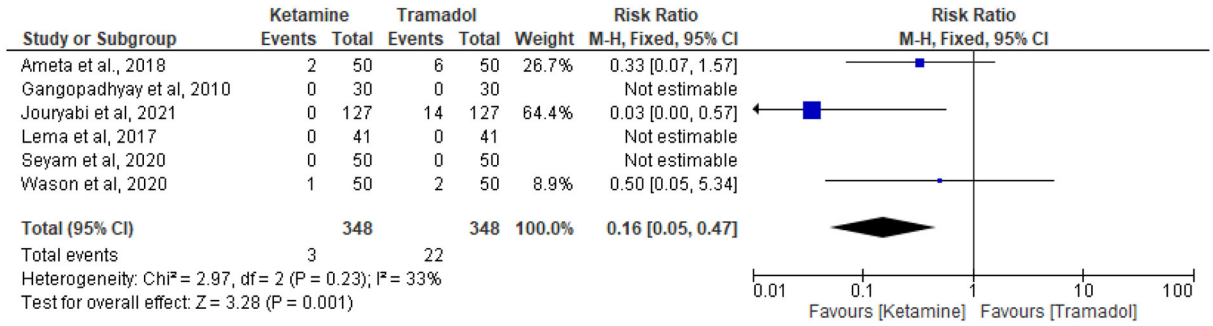

FIGURE 8
The effect of tramadol vs. ketamine on the incidence of bradycardia.

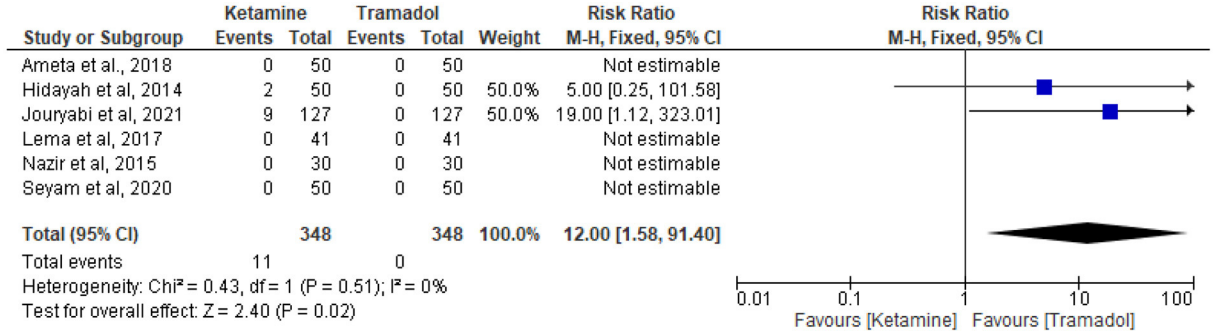

FIGURE 9
The effect of tramadol vs. ketamine on the incidence of hallucinations.

Conclusions

Intravenous ketamine and tramadol are comparable in the prevention of post-spinal anesthetic shivering. Ketamine could be a better anti-shivering agent with less occurrences of nausea, vomiting, and bradycardia. Ketamine had comparable effects regarding the incidence of hypotension. However, ketamine was associated with higher incidences of hallucinations in comparison to tramadol.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

EF, SK, MH, TT, and DT conceived the data, participated in the study design, conducted the statistical analysis, and drafted the manuscript. EF, TT, MH, and DT were involved in collecting the data, performing data analysis, and drafting the manuscript. YF and SS have also participated in the study design, data analysis, and revising of the manuscript. All authors have read and approved the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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