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Postoperative care: From pain management to delirium

Edited by
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Postoperative care: From pain management to delirium

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Editorial: Postoperative care: from pain management to delirium

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Editorial on the Research Topic
Postoperative care: from pain management to delirium

Postoperative care is important for the success of surgical operations. Pain and delirium are among the most important adverse events especially for the elderly (1). It has been reported that postoperative delirium (POD) has a negative impact on prognosis, length of stay and the burden of care. Many efforts have been made to predict the POD in the literature (2). Many novel biomarkers such as the changes in plasma tau and neurofilament light (NfL) are found to be associated with increased risk of POD (3, 4). Pain management is directly related to the development of postoperative delirium. And thus, improved control of pain can not only improve the patients' comfort but also reduce the risk of POD. Thus, the management of pain and delirium are usually inseparable. For some elderly patients with major operation, appropriate management of pain and delirium are also of vital importance to the postoperative rehabilitation (5). In this regard, I launched a special topic in Frontiers in Medicine to report most updated advances in postoperative care of pain and delirium management.

A total of 15 articles are finally published after rigorous peer review process. Zheng et al. explored nutritional status and postoperative pain outcome in elderly patients. They found that high nutritional risk/malnutrition was associated with poor postoperative pain outcomes (i.e. inadequate analgesia, cumulative consumption of analgesics) in older patients following gastrointestinal surgery, and further proposed a cut-off value of 88 for geriatric nutritional risk index (GNRI) for clinical utility. In a randomized controlled trial, Xu et al. compared dexmedetomidine combined with butorphanol or sufentanil for the prevention of postoperative nausea and vomiting (PONV) in patients undergoing microvascular decompression. The authors tested the analgesics in this special population because patients undergoing microvascular decompression are often accompanied with high risk of post-operative nausea and vomiting. They concluded that butorphanol combined with dexmedetomidine could reduce early PONV and the number of patients requiring rescue antiemetics. Acupuncture is an important component in the traditional Chinese medicine and many studies have proven its efficacy in alleviating symptoms such as postoperative delirium (6). In this special issue, Fan et al. compared transcutaneous electrical acupoint stimulation combined with auricular acupressure vs. usual care on the incidence of postoperative delirium among older patients undergoing major abdominal surgery. The postoperative delirium is significantly reduced by the use of this intervention [19/105 (18.1%) vs. 8/105 (7.6%), difference, −10.5% (95% CI, −1.5% to −19.4%); hazard ratio, 0.41 [95% CI, 0.18 to 0.95); $P = 0.023$]. In addition to clinical investigations, we also published

experimental studies. Mu et al. developed an animal model of postoperative delirium and found that interleukin-6 played an pivotal role in the pathological process.

Author contributions

ZZ design and drafted this editorial.

Conflict of interest

The author declares 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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CLINICAL TRIAL
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Dexmedetomidine Combined With Butorphanol or Sufentanil for the Prevention of Post-operative Nausea and Vomiting in Patients Undergoing Microvascular Decompression: A Randomized Controlled Trial

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Background: Patients undergoing microvascular decompression are often accompanied with high risk of post-operative nausea and vomiting (PONV). In this study, we compare the antiemetic efficacy of butorphanol or sufentanil combined with dexmedetomidine in patients undergoing microvascular decompression.

Methods: Patients undergoing microvascular decompression were randomized into two groups. The primary outcome was the occurrence and severity of PONV during the 72 h after surgery. Secondary outcomes included levels of pain intensity and sedation and consumption of opioids at 1, 2, 6, 12, 24, 48, and 72 h after surgery. We also recorded the intraoperative hemodynamics, consumption of narcotic drugs, operation and anesthesia time, estimated blood loss, infusion volume and urine output, requirements of rescue antiemetics or analgesics, the satisfaction scores of patients and surgeons, complications, and length of stay.

Results: The overall incidence rates of nausea and vomiting during the 72 h after surgery were significantly reduced in group DB (76.00 and 44.00% in group DS vs. 54.17% and 22.92% in group DB, $P < 0.05$). Patients in group DB had a lower incidence of nausea than those in group DS at intervals of 1–6 and 6–24 h ($P < 0.05$). However, patients in group DB had a lower incidence of vomiting than those in group DS only at intervals of 1–6 h ($P < 0.05$). Similarly, the number of patients requiring rescue antiemetics was also significantly reduced in group DB compared with that in group DS at intervals of 1–6 h ($P < 0.05$). The number of patients experiencing moderate to severe PONV was comparable between the two groups during 72 h after surgery ($P > 0.05$). The consumption of opioid morphine equivalent was significantly reduced in group DB ($P < 0.05$). Compared with those in group DS, the satisfaction scores of both patients and surgeons were significantly increased in group DB ($P < 0.05$).

Conclusion: Butorphanol combined with dexmedetomidine could reduce early PONV and the number of patients requiring rescue antiemetics, especially at intervals of 1–6 h, while the satisfaction scores of both patients and surgeons were significantly increased.

Keywords: post-operative nausea and vomiting, microvascular decompression, butorphanol, sufentanil, dexmedetomidine

BACKGROUND

Post-operative nausea and vomiting (PONV) is one of the most common post-operative complications in neurosurgical patients (1). It can cause electrolyte imbalance, pulmonary aspiration, elevated intracranial pressure, and delayed discharge and even result in disastrous consequences such as intracranial hemorrhage and cerebral hernia (2, 3). A previous study has reported that the incidence of PONV exceeded 50% in neurosurgical patients during the first 48 h after surgery (4). Vagal afferents of the gastrointestinal tract, chemoreceptor trigger zone in the area postrema, and the vestibular system may all have an effect on the PONV (5).

Trigeminal neuralgia (TN) is a syndrome of unilateral, paroxysmal, stabbing facial pain, originating from the trigeminal nerve and can severely affect a patient's daily lifestyle (6). Its diagnosis is extremely complicated, and careful characteristic clinical symptoms are crucial (7). The number of patients undergoing microvascular decompression (MVD), which is the best surgical modality for TN, is increasing worldwide (8). Several studies have reported that the pain-free rate was 70–80% in patients undergoing MVD at 5–10 years (9, 10). However, a previous study reported that MVD is an independent stronger risk factor for PONV even within the scope of neurosurgery (11). Though a previous study revealed that ondansetron significantly reduced PONV, the incidence of PONV was still higher than 60% within 24 h after MVD despite preventive use of ondansetron. The reason may be partly due to the operation region near the chemoreceptor trigger zone and vestibular system (12). Besides, previous study has reported that PONV may exhibit a bimodal pattern up to 48–72 h after neurosurgery (13).

Butorphanol has been widely used for musculoskeletal pain, headaches, and perioperative analgesia through the analgesia effect is only about 0.5% of sufentanil. However, there are few studies about butorphanol after neurosurgery. Dexmedetomidine (Dex), a highly selective α2-adrenergic receptor agonist, has sedative, analgesic, and anxiolytic effects (14). A recent study has also showed that sufentanil or butorphanol combined with Dex can be used safely and effectively in patients undergoing laparoscopic surgery with no increase in the incidence of adverse reactions (15). There have been no effective solutions to reduce both the incidence and severity of PONV in neurosurgery. As a result, we performed this prospective randomized clinical trial to evaluate the efficacy of butorphanol or sufentanil combined with Dex for the prevention of PONV in patients undergoing MVD.

METHODS

Patients

All patients who underwent MVD in our hospital between November 2018 and January 2020 were recruited. This study was also approved by the ethics committee in our hospital and registered in the Chinese Clinical Trial Registry (ChiCTR1800018946). All patients or their representative have provided written informed consent.

Patients were included if they met the following criteria: diagnosed as idiopathic TN (ITN) (16) and were of American Society of Anesthesiologists (ASA) grades I and II. Patients were excluded if they have diabetes mellitus; use antiemetics or glucocorticoids; have a history of PONV or motion sickness, chemotherapy, or radiation therapy; have a body mass index (BMI) >30 kg/m^2; have ischemic heart disease; have a history of long-term abuse of or addiction to alcohol, opioid(s), or sedative–hypnotic drug(s); are a smokers; have an allergy to opioids or Dex; have benign or malignant tumors or arteriovascular malformations confirmed with magnetic resonance imaging (MRI). All patients completed the Penn Facial Pain Scale (PFPS, formerly known as Brief Pain Inventory-Facial) on admission.

Randomization and Blinding

A computer-generated randomization table was used to divide patients randomly into two groups by an independent anesthetist prior to surgery [group DS: Dex 4 μg/kg with sufentanil 1.0 μg/kg in the patient controlled intravenous analgesia (PCIA) pump, $n = 50$; group DB: Dex 4 μg/kg with butorphanol 0.1 mg/kg in the PCIA pump, $n = 48$]. The study drugs in the PCIA pump were prepared by an independent anesthetic nurse, while two other anesthetic nurses were responsible for recording the results of this study. The attending anesthesiologists, surgeons, anesthetic nurses in the acute pain service (APS), and patients were all blinded to this study.

Anesthetic Management

None of the patients had received any medication before the induction of anesthesia. After patients entered the operating room, a peripheral venous access was established, and five-lead electrocardiogram, invasive arterial blood pressure, and oxygen saturation were continuously monitored by an automated system. An intravenous infusion of Dex 0.5 μg/kg was used before anesthesia induction within 15 min, followed by 0.1 mg/kg of dexamethasone, 0.3 μg/kg of sufentanil, 1–2 mg/kg of propofol, and 2.0 mg/kg of cisatracurium; we implemented trachea intubation 3 min later. Anesthesia was maintained with sevoflurane (1.5–2.5%), remifentanil (0.1–0.2 μg/kg/min), and

Dex (0.4 μg/kg/h). The bispectral index was maintained between 40 and 60. The pressure of arterial carbon dioxide ($PaCO_2$) was maintained at 35–40 mmHg during surgery. Both groups received 1 mg butorphanol and 5 mg tropisetron 30 min prior to the end of surgery. The concentrations of sevoflurane and remifentanil were adjusted according to both hemodynamic changes and the bispectral index. Under the premise of satisfactory depth of anesthesia, intraoperative vasoactive drugs (ephedrine, phenylephrine, urapidil, and atropine) were used to maintain hemodynamic stability.

All patients were extubated and observed in the postanesthetic care unit (PACU) until they meet Aldrete's criteria and then transferred to the functional neurosurgery ward. PCIA (Dex 4 μg/kg with sufentanil 1.0 μg/kg in the DS group and Dex 4 μg/kg with butorphanol 0.1 mg/kg in the DB group, up to a total volume of 100 ml) was programmed to deliver 1 ml bolus (lockout 8 min) with a continuous background infusion of 1 ml/h at the end of surgery. The PCIA was used for the first 72 h after surgery. Ten milligrams of metoclopramide was administered if the scores of PONV were >6 or if there was vomiting. Fifteen milligrams of ketorolac was administered if VRS scores of pain (VASm) were >3. The PCIA was stopped if hypoventilation (respiratory rate of <10 breaths per minute) or hypoxia (pulse oxygen saturation of <88% though intranasal oxygen inhalation at 5 L/min) happened.

MVD Procedure

The operative technique was performed according to the previous studies (17, 18). Briefly, patients were placed in a lateral position after general anesthesia, and a small retromastoid craniectomy was made behind the ear after undergoing scalp nerve block (2% lidocaine combined with 1:200,000 adrenaline) before the operation in this study; then the C-shaped dura was opened. The cerebellar hemisphere was retracted gently in a superolateral-to-inferomedial direction to visualize the trigeminal nerve. The proximal part of the nerve adjacent to the brainstem was closely examined, and any compressing artery was mobilized away from the nerve. A small piece of Teflon was then interpositioned between the nerve and the artery to prevent recontact. If venous rather than arterial compression was present, the vein was coagulated and divided. When no compressing vessel was identified, internal neurolysis was performed by separating nerve fibers longitudinally. After hemostasis, the dura was closed, and the bony defect covered with gel foam before musculofascial closure in layers. Intraoperative auditory brainstem evoked response was also monitored in this surgery. Post-operative CT was performed on the day after surgery except the patient's condition deteriorated.

Date Collection

The primary outcome was the occurrence and severity of post-operative nausea (defined as a subjectively unpleasant sensation associated with the awareness of an urge to vomit; the severity of nausea was graded using a verbal 11-point rating scale, with 0 indicating no nausea and 10 indicating the worst nausea) and vomiting (defined as a single episode of the forceful expulsion of gastric contents through the mouth) during the 72 h after surgery (19). Secondary outcomes included levels of pain intensity [visual analog scale (VAS) both at rest and with movement: 0, no pain; 10, the worst pain], sedation (LOS: recorded on a 5-point scale: 0, fully awake; 1, drowsy/closed eyes; 2, asleep/easily aroused with light tactile stimulation or a simple verbal command; 3, asleep/arousable only by strong physical stimulation; 4, unarousable), and consumption of opioids at 1, 2, 6, 12, 24, 48, and 72 h after surgery. We also recorded the intraoperative hemodynamics [recorded at the following time points: arrival at the operating room (T1); before intubation (T2); at intubation (T3); at 5 min (T4) and 10 min (T5) after intubation; at start of surgery (T6); at end of surgery (T7); at extubation (T8); and at 5 min (T9) and 10 min (T10) after arrival at the PACU], consumption of narcotic drugs, operation and anesthesia time, estimated blood loss, infusion volume and urine output, requirements of rescue antiemetics or analgesics, the satisfaction scores of patients and surgeons (11-point scale: 0, poorest; 10, excellent), complications (such as headaches, intracranial hemorrhage, wound infection, confusion, transient facial numbness, and diplopia), and length of stay.

Statistical Analysis

In our pilot study, 49% of patients receiving Dex–sufentanil experienced vomiting during the 72 h after surgery. We considered a 27% reduction to be clinically significant; 45 patients were needed in each group at a level of 0.05 and with power of 80%. Assuming a dropout rate of 10%, we included 50 patients in each group.

The Kolmogorov–Smirnov and Levene tests were used to assess data distribution and homogeneity of variance, respectively. Continuous data were expressed as mean and standard deviation or median and interquartile range (IQR). Between-group comparisons were performed using repeated-measures analysis of variance. Mann–Whitney *U* test was used for non-normal distribution of continuous data. Categorical data were expressed as frequency and percentage and analyzed using chi-square tests or Fisher's exact tests when appropriate. A probability $P < 0.05$ was considered statistically significant. Statistical analysis was performed with SPSS for Windows version 23.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Baseline Characteristics

A CONSORT diagram was used during the enrollment of patients (**Figure 1**). One hundred eighty-eight patients who underwent MVD in our hospital between November 2018 and January 2020 were recruited. Ninety patients were excluded: 25 patients with diabetes mellitus; 12 patients with an ASA grade >II; 3 patients who used antiemetics or glucocorticoids; five patients with a history of PONV or motion sickness, chemotherapy, or radiation therapy; six patients with a BMI of >30 kg/m^2; 2 patients with ischemic heart disease; 12 patients with abuse of or addiction to alcohol, opioid(s), or sedative–hypnotic drug(s); 11 patients who smoked; and 14 patients with benign or malignant tumors or

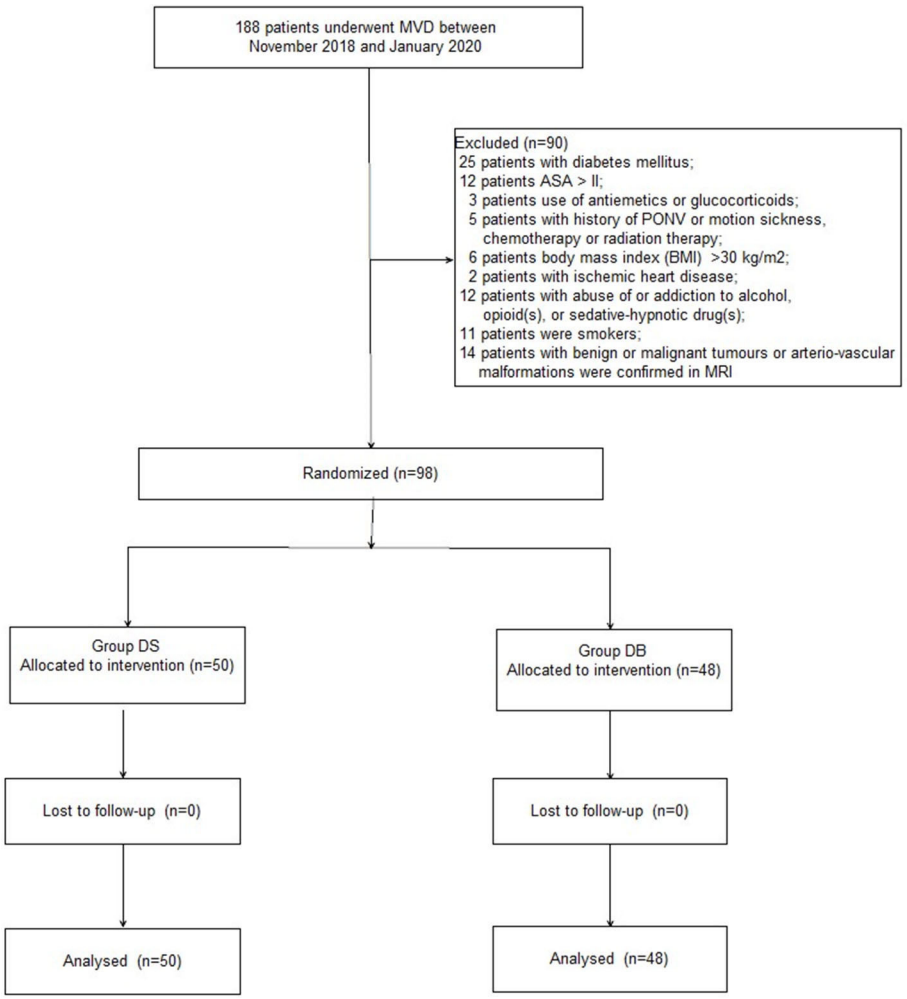

FIGURE 1 | Patient enrollment flow diagram.

arteriovascular malformations confirmed through MRI. Finally, 98 patients were included in the primary analysis and divided into two groups: 50 patients for group DS and 48 patients for group DB. Age, BMI, ASA grade, sex, comorbidity, history of TN, trigeminal nerve pain distribution, neurovascular compression, and PFPS score were all comparable between the two groups ($P > 0.05$, **Table 1**).

Intraoperative Variables

There were no significant differences between the two groups in terms of operation and anesthesia time; intraoperative hemodynamics; consumption of sevoflurane, remifentanil, Dex, and cisatracurium; estimated blood loss; infusion volume; and urine output ($P > 0.05$, **Table 2**, **Figure 2**). The number of patients using atropine, ephedrine, phenylephrine, and urapidil was also comparable between the two groups during operation ($P > 0.05$, **Table 2**).

Post-operative Variables

Compared with those in group DS, the overall incidence rates of nausea and vomiting during the 72 h after surgery were significantly reduced in group DB (76.00% and 44.00% in group DS vs. 54.17 and 22.92% in group DB, $P < 0.05$, **Table 3**). Patients in group DB had a lower incidence of nausea than patients in group DS at intervals of 1–6 and 6–24 h ($P < 0.05$, **Table 3**). However, patients in group DB had a lower incidence of vomiting than patients in group DS only at intervals of 1–6 h ($P < 0.05$, **Table 3**). Similarly, the number of patients requiring rescue antiemetics was also significantly reduced in group DB compared with group DS at intervals of 1–6 h ($P < 0.05$, **Table 3**). The number of patients who experienced moderate to severe PONV (severity of nausea >3 and vomiting) was comparable between the two groups during 72 h after surgery ($P > 0.05$, **Figure 3**).

Patients requiring rescue analgesia and length of stay were comparable between the two groups ($P > 0.05$,

TABLE 1 | Comparison of patient characteristics between the two groups.

Variable	Group DS ($n = 50$)	Group DB ($n = 48$)	*P*-values
Age (years)	58.53 ± 3.89	56.72 ± 3.21	0.069.
Body weight (kg)	68.22 ± 6.03	72.55 ± 7.70	0.281.
BMI (kg·m^{-2})	24.34 ± 1.68	24.59 ± 2.11	0.517
ASA I/II (*n*)	26/24	22/26	0.542
Sex (Male/Female)	17/33	19/29	0.567
Left-sided pain, *n* (%)	24 (60.00%)	22 (45.83%)	0.830
History of TN (month)	35.43 (21.45–55.67)	37.53 (20.34–54.56)	0.188
Comorbidity, *n* (%)			0.931
Hypertension	22 (44.00%)	18 (37.50%)	
cerebral infarction	5 (10.00%)	4 (8.33%)	
Coronary heart disease	6 (12.00%)	7 (14.58%)	
Trigeminal nerve pain distribution, *n* (%)			0.882
V1	12 (24.00%)	13 (27.08%)	
V2	43 (86.00%)	40 (83.33%)	
V2 V3	26 (52.00%)	22 (45.83%)	
Neurovascular compression, *n* (%)			0.921
Artery	35 (70.00%)	32 (66.67%)	
Vein	9 (18.00%)	11 (22.92%)	
Artery and vein	4 (8.00%)	3 (6.25%)	
None	6 (12.00%)	5 (10.42%)	
PFPS score			0.421
General function	6.38 (5.64–6.78)	6.45 (5.61–6.85)	
facial function	7.65 (6.43–8.86)	7.32 (6.29–8.71)	

Variables presented as mean ± SD, median (interquartile range) or number of patients n (%). BMI, body mass index; ASA, American Society of Anesthesiology; TN, Trigeminal neuralgia; PFPS, Penn Facial Pain Scale.

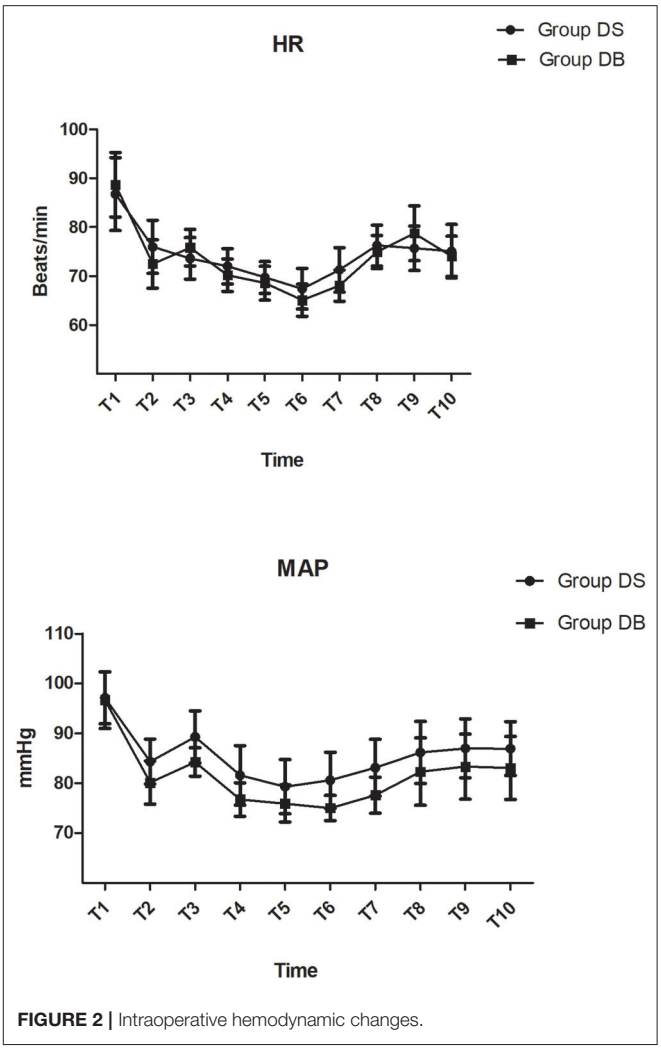

FIGURE 2 | Intraoperative hemodynamic changes.

TABLE 2 | Comparison of intraoperative variables between the two groups.

Variable	Group DS ($n = 50$)	Group DB ($n = 48$)	*P*-values
Duration of surgery (min)	163.58 (125.10–197.23)	175.57 (127.34–198.21)	0.231
Duration of anesthesia (min)	215.83 (185.99–256.83)	230.52 (196.87–270.516)	0.096
Remifentanil dosage (mg)	1.02 ± 0.29	1.12 ± 0.35	0.126
Dexmedetomidine dosage (μg)	122.38 ± 17.82	125.71 ± 23.19	0.426
Cisatracurium dosage (mg)	22.34 ± 1.89	21.83 ± 2.05	0.203
Sevoflurane (%)	1.74 (1.35–2.28)	1.59 (1.32–2.37)	0.108
Estimated blood loss (ml)	63.27 (45.38–102.74)	73.29 (52.23–109.21)	0.276
Fluids (ml)	1523.98 (683.28–2312.32)	1322.74 (836.28–2271.38)	0.075
Urine output (ml)	873.28 (462.81–1327.98)	809.72 (530.29–1529.87)	0.387
Number of patients using vasoactive drugs, *n* (%)			
Atropine	6 (12.00%)	5 (10.42%)	0.804
Ephedrine	4 (8.00%)	3 (6.25%)	1.000
Phenylephrine	17 (34.00%)	13 (27.08%)	0.458
Urapidil	6 (12.00%)	8 (16.67%)	0.509

Variables presented as mean ± SD, median (interquartile range) or n (%).

TABLE 3 | Incidence of PONV and rescued antiemetics between the two groups.

Variable	Group DS ($n = 50$)	Group DB ($n = 48$)	*P*-values
Nausea, *n* (%)			
1-6 h	29 (58.00%)	18 (37.50%)*	0.042
6–24 h	22 (44.00%)	12 (25.00%)*	0.048
24–48 h	13 (26.00%)	9 (18.75%)	0.39
48–72 h	10 (20.00%)	8 (16.67%)	0.67
Vomiting, *n* (%)			
1–6 h	15 (30.00%)	8 (16.67%)*	0.049
6–24 h	12 (16.00%)	5 (10.42%)	0.121
24–48 h	5 (10.00%)	6 (12.50%)	0.695
48–72 h	3 (6.00%)	3 (6.25%)	0.959
Rescued antiemetics, *n* (%)			
1–6 h	22 (44.00%)	11 (22.91%)*	0.027
6–24 h	16 (32.00%)	9 (18.75%)	0.133
24–48 h	9 (18.00%)	7 (14.58%)	0.647
48–72 h	8 (16.00%)	5 (10.42%)	0.415

*Variables presented as number of patients n (%). *P < 0.05 vs. Group DS.*

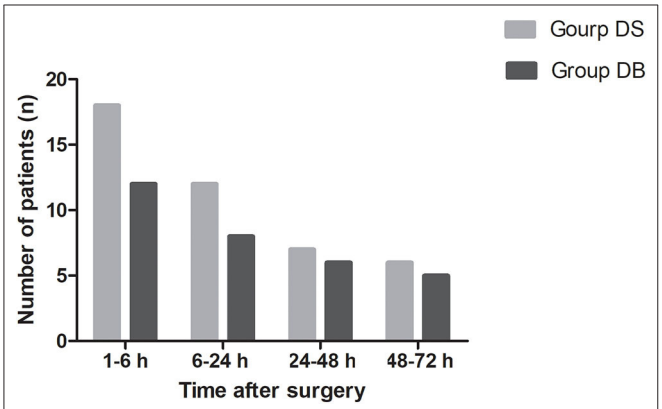

FIGURE 3 | Number of patients who experienced moderate to severe PONV between the two groups during 72 h after surgery. Moderate to severe PONV: severity of nausea >3 and vomiting.

TABLE 4 | Comparison of post-operative variables between the two groups.

Variable	Group DS ($n = 50$)	Group DB ($n = 48$)	*P*–values
Number of rescue analgesia, *n* (%)	5 (10.00%)	8 (16.67%)	0.331
Patient satisfaction score	7.50 (6.25–8.50)	8.50 (7.25–9.50)*	0.021
Surgeons satisfaction score	8.00 (7.50–9.50)	8.75 (8.00–9.75)*	0.028
Length of stay (d)	6.45 (5.53–8.24)	6.83 (5.48–8.31)	0.398

*Variables presented as number of patients n (%) or median (interquartile range). *P < 0.05 vs. Group DS.*

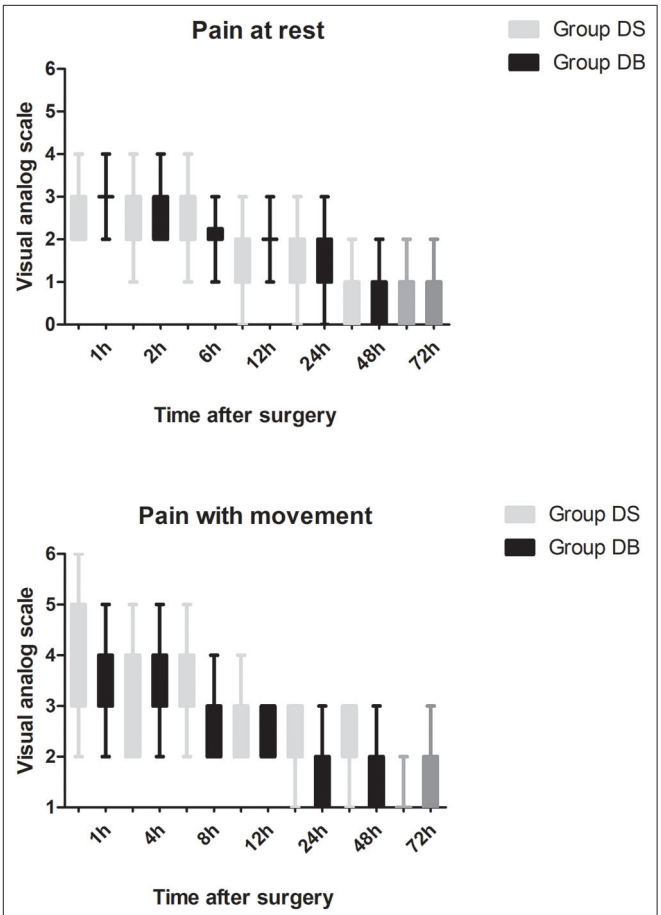

FIGURE 4 | Post-operative pain intensity (at rest and with movement) between the two groups.

Table 4). Compared with group DS, the satisfaction scores of both patients and surgeons were significantly increased in group DB ($P < 0.05$, **Table 4**). Pain scores and LOS were not significantly different between the two groups ($P > 0.05$, **Figures 4**, **5**). The consumption of PCIA was similar between the two groups. However, the consumption of opioid morphine equivalent was significantly reduced in group DB ($P < 0.05$, **Figure 6**). Complications after the surgery are summarized in **Table 5**. There were no mortalities in this study.

DISCUSSION

The results of this study indicated that butorphanol combined with Dex could reduce early PONV and the number of patients requiring rescue antiemetics, especially at intervals of 1–6 h, while the satisfaction scores of both patients and surgeons were significantly increased. At the same time, pain scores, LOS, the number of patients requiring rescue analgesia, and complications had not increased.

Although the exact etiology of PONV is unknown, female sex, non-smokers, history of PONV or motion sickness, post-operative use of opioids, and type of surgery are the most

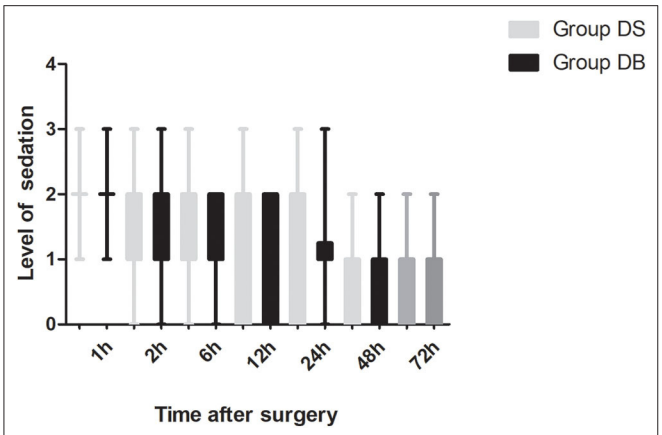

FIGURE 5 | Post-operative level of sedation between the two groups.

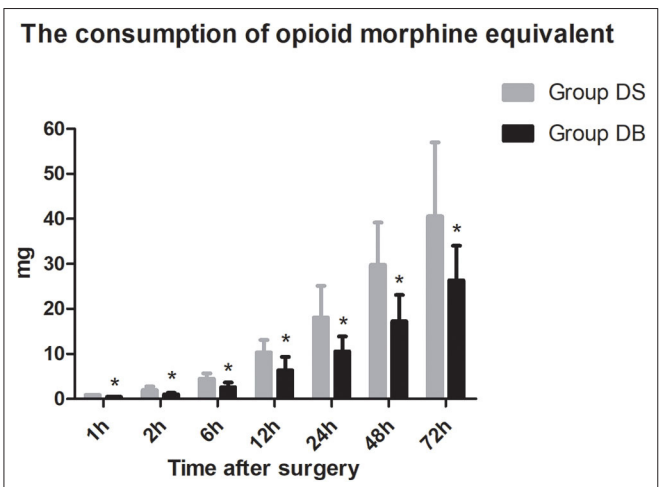

FIGURE 6 | Consumption of opioid morphine equivalent between the two groups. *$P < 0.05$ vs. group DS.

TABLE 5 | Complications of patients undergoing MVD.

Variable	Group DS ($n = 50$)	Group DB ($n = 48$)	*P*–values
Headaches	5 (10.00%)	4 (8.33%)	1.000
Dizzy	2 (4.00%)	2 (4.17%)	1.000
Transient facial numbness	3 (6.00%)	2 (4.17%)	1.000
Intracranial hemorrhage	1 (2.00%)	0 (0.00%)	1.000
Prolonged confusion	0 (0.00%)	1 (2.08%)	0.490
Cerebrospinal fluid leak	1 (2.00%)	1 (2.08%)	1.000
Diplopia	1 (2.00%)	1 (2.08%)	1.000

Variables presented as number of patients n (%).

important independent risk factors for PONV (20). As a result, we excluded patients with a history of PONV or motion sickness and smokers in this study. In consideration of the same operation and without statistical difference about sex ratio in the two groups in this study, post-operative use of opioids has become the major factor of PONV. MVD, the most effective procedure in terms of long-term pain relief for patients with TN until now, has been considered as a surgical factor for PONV according to the consensus guidelines for managing PONV (21). As a result, combination of antiemetics with different mechanisms such as histamine, 5-hydroxytryptamine type 3 (5-HT3), acetylcholine, dopamine type 2, substance P, neurokinin, several opioid receptors, and other biomolecules is recommended for PONV (22). However, there has been no effective scheme to significantly reduce the PONV of patients undergoing MVD.

Opioid-based PCIA has been widely used in post-operative analgesia for its analgetic effectiveness; however, it can also associate with a number of side effects such as PONV, respiratory depression, pruritus, and urinary retention (23). A PCIA pump was used for 72 h after surgery in this study because a previous study found that air around the surgical sites may trigger nearby-area postrema and that pneumocephalus resolves by 31% per day after craniotomy, which was also a risk factor of PONV (24). Ha et al. reported that the antiemetic efficacy of ramosetron was similar to that of ondansetron and only reduced the severity of nausea between 6 and 24 h after MVD, which suggested that ramosetron or ondansetron alone may be too weak to prevent PONV in high-risk patients (25). Although administration of dexamethasone 4 mg and ondansetron 4 mg was found to decrease the incidence of PONV, this decrease was not significantly different because MVD is a high probability in PONV (12). Fabling et al. suggested using ondansetron 8 mg at the time of wound closure for adults who underwent infratentorial craniotomy. However, patients undergoing MVD still had a high frequency of nausea (26). Palonosetron, the latest 5-HT3 receptor antagonist and more effective than ramosetron, has been proven to prevent PONV during the first 24 h after surgery when administered during anesthetic induction. This may be due to the long peak concentration time and duration of action. This study has also reported that the incidence of PONV was only significantly reduced when prophylactic palonosetron and sugammadex were used together under propofol-maintained anesthesia (27). However, most of the above studies had not focused on the post-operative use of opioids.

It has been reported that Dex at 0.5 or 1.0 μg/kg effectively reduced the incidence of PONV compared with placebo. The mechanism may involve inhibiting inflammatory mediators and enhancing the antiemetic efficacies of 5-hydroxytryptamine type (5-HT) receptor antagonists and α-adrenergic receptors (28). Besides, our previous study has also supported an opioid-sparing effect as the underlying mechanism of the antiemetic effect of Dex (29). As a result, we adopt Dex as the adjuvant drug in the opioid-dominated PCIA. The incidence of PONV was significantly reduced in our study compared with the previous study. The reason may be the preventive application of 0.1 mg/kg dexamethasone during the period of anesthesia induction and 5 mg tropisetron 30 min prior to the end of surgery. We used higher doses of dexamethasone compared with the previous study for its characters of inhibition of inflammatory mediators

and the hypothalamus–pituitary–adrenal axis, activation of α2-adrenoreceptors, and antiemetic sparing effect of Dex (11). Another possible explanation for the lower incidence of PONV may be the different anesthetic technique. Less muscle relaxants with lower doses of volatile agent and higher doses of Dex were used to allow recording of intraoperative auditory brainstem evoked response in our study. As a result, only a few patients undergoing MVD received neostigmine at the end of surgery, where it has been reported that reversal agents are associated with PONV (30). All patients underwent scalp nerve block with 2% lidocaine combined with 1:200,000 adrenaline before the operation in this study for the previous study has reported that local anesthesia or peripheral nerve block can contribute to reducing the amount of opioid used for post-operative analgesia (31). Another previous study reported that rebound pain is a very severe type of pain that appears when the peripheral nerve block wears off (32). We still observed this phenomenon, especially in the last 48–72 h post-operatively, despite adopting the multimodal analgesia regime in our study.

Butorphanol, a lipid-soluble narcotic agent with a strong κ-receptor agonist, weak u-receptor agonist/antagonist activity, and no obvious activity on δ-opioid receptors, has been widely used for musculoskeletal pain, headaches, and perioperative analgesia (33). However, there are few studies about the application of butorphanol during neurosurgery (34). In our study, we found that the consumption of opioid was significantly reduced in group DB, which may also contribute to the lower PONV and higher satisfaction scores of both patients and surgeons. Moderate sedation of patients following neurosurgery is necessary to maintain hemodynamic stability, provide sufficient analgesia, and reduce anxiety without interfering with the evaluation of the conscious state (35). As a result, the level of sedation was maintained at 1-2 in most patients during the first 12 h after surgery. Dex combined with butorphanol after neurosurgery may cause excessive sedation. However, no excessive sedation was observed during post-operative PCIA in our study. This may be due to less dosage used than the previous study (15). At the same time, pain scores and the number of patients requiring rescue analgesia had not increased. Further studies are required to establish the effect–dose balance between optimal post-operative analgesia and PONV in the Dex–butorphanol analgesic regimen.

Consistent with previous report, the age of onset for most idiopathic cases is between 50 and 60 years, and there is a higher proportion of females in our study (36). In our study, there were no mortalities or life-threatening morbidities in each group. There were still 12 vs. 10.42% patients without compressing vessel during surgery in our study, and internal neurolysis was performed by dividing the nerve. The result was similar to previous studies (7% of endoscopic MVD vs. 11% of microscopic MVD). Though endoscopic MVD has the benefit of improved visualization during surgery, the disadvantages are obvious such as having a 2D view, occupying space by itself, and generating heat that could potentially harm adjacent structures (37). The other frequently reported complications of MVD include headaches, diplopia, facial weakness, intracranial infarct/hematoma, and cerebrospinal fluid (CSF) leak. However, most of these complications are mild and transient. The incidence of complications in our study is lower than that in previous studies, the reasons for which may be the careful surgical technique (move the compressed artery distally and attach it to the dura mater using a polytetrafluoroethylene sheet, preserve the superior petrosal vein, and try to not use the retractor), absolute hemostasis, immaculate wound closure, and use of intraoperative auditory brainstem evoked response (38). It should be noted that one patient in group DB has facial paralysis immediately after surgery, which failed to resolve until discharge. However, no changes in the intraoperative auditory brainstem evoked response were observed.

There are some limitations in this study. First, we adopted the volatile-maintained anesthesia in this study due to low prices. However, a previous study reported that the incidence of PONV may be lower under propofol-maintained anesthesia in patients undergoing craniotomy (39). Second, we have no long-term follow-up about the effect of operation in this study. Third, we only reported results of patients with ITN, which are not applicable for patients with atypical and recurrent TN. Fourth, PONV decreased in the last 72 h though PCIA doses were doubled in both groups. The reasons may be complex and need further study to clarify. Finally, the result of this study only represented the practice of our center and therefore may lack generalizability to other hospitals.

In conclusion, butorphanol combined with Dex could reduce early PONV and the number of patients requiring rescue antiemetics, especially at intervals of 1–6 h, while the satisfaction scores of both patients and surgeons were significantly increased. At the same time, pain scores, LOS, the number of patients requiring rescue analgesia, and complications had not increased.

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 the Ethics Committee in Liaocheng People's Hospital and registered in the Chinese Clinical Trial Registry (ChiCTR1800018946). The patients/participants provided their written informed consent to participate in this study.

AUTHOR'S NOTE

The authors intend to share participants' data collected during the trial. This includes, study protocol, statistical analysis plan, informed consent forms, and clinical study report. It will be available based on the request of investigators whose proposed use of the data has been approved by an independent review committee by sending an email to the corresponding author.

Data are available immediately after publication and with no end date.

AUTHOR CONTRIBUTIONS

GX, JZ, ZL, and LL conceived and designed the trial. GL and LL collected the date. CR and JZ analyzed the date. GX, JZ, ZL, and YL wrote the manuscript. All authors contributed to the article and approved the submitted version.

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A Weak Response to Endoplasmic Reticulum Stress Is Associated With Postoperative Organ Failure in Patients Undergoing Cardiac Surgery With Cardiopulmonary Bypass

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Introduction: Endoplasmic reticulum stress (ERS) is involved in inflammatory organ failure. Our objective was to describe ERS, its unfolded protein response (UPR) expression/kinetics during cardiac surgery with cardiopulmonary bypass (CPB) and its association with postoperative organ failure (OF).

Methods: Prospective study conducted on patients undergoing cardiac surgery with CPB. Blood samples were taken before (Pre-CPB), 2 h (H2-CPB) and 24 h (H24-CPB) after CPB. Plasma levels of 78 kDa Glucose- Regulated Protein (GRP78, final effector of UPR) were evaluated by ELISA. The expression of genes coding for key elements of UPR (*ATF6*, *ATF4*, *sXBP1*, *CHOP*) was evaluated by quantitative PCR performed on total blood. OF was defined as invasive mechanical ventilation and/or acute kidney injury and/or hemodynamic failure requiring catecholamines.

Results: We included 46 patients, GRP78 was decreased at H2-CPB [1,328 (878–1,730) ng/ml vs. 2,348 (1,655–3,730) ng/ml Pre-CPB; $p < 0.001$] but returned to basal levels at H24-CPB [2,068 (1,436–3,005) ng/ml]. The genes involved in UPR had increased expression at H2 and H24. GRP78 plasma levels in patients with OF at H24-CPB ($n = 10$) remained below Pre-CPB levels [−27.6 (−51.5; −24.2)%] compared to patients without OF ($n = 36$) in whom GRP78 levels returned to basal levels [0.6 (−28.1; 26.6)%; $p < 0.01$]. H24-CPB *ATF6* and *CHOP* expressions were lower in patients with OF than in patients without OF [2.3 (1.3–3.1) vs. 3.0 (2.7–3.7), $p < 0.05$ and 1.3 (0.9–2.0) vs. 2.2 (1.7–2.9), $p < 0.05$, respectively].

Conclusions: Low relative levels of GRP78 and weak UPR gene expression appeared associated with postoperative OF. Further studies are needed to understand ERS implication during acute organ failure in humans.

Keywords: bypass, cardiopulmonary, cardiac surgery, endoplasmic reticulum stress, endothelium, inflammation, GRP78 protein, human

INTRODUCTION

Cardio-pulmonary bypass (CPB) is routinely used throughout the world during heart surgery. This procedure often induces an aseptic systemic inflammatory response syndrome (SIRS) associated with post-operative morbidity (1–3). This SIRS might lead to hypotension and organ dysfunction, a situation referred to as "post-pump syndrome" (4). Given the association between elevated pro-inflammatory cytokine levels and negative clinical outcomes [post-operative acute kidney injury (AKI), decreased systemic vascular resistance and lung injury], it has been postulated that modulation of inflammatory processes could improve outcomes after cardiac surgery (2, 5). Despite a progression in knowledge of CPB-induced SIRS pathophysiology, specific therapeutics to control inflammatory process are still lacking.

Endoplasmic reticulum (ER) stress and its adaptive response, the unfolded protein response (UPR), represent an archetypal example of adaptive stress responses. The ER plays a crucial role in protein folding and maturation. This folding process is finely regulated, notably by specific proteins known as chaperones, such as the 78 kDa Glucose-Regulated Protein [GRP78, a heat-shock protein coded by the Heat Shock 70kDa Protein 5 gene (*HSPA5*)], which stimulates the correct folding of polypeptide to functional protein complexes (6). Multiple disturbances observed during inflammation can result in a dysfunction of the ER, leading to the accumulation of unfolded proteins within the lumen of the ER, known as ER stress (ERS) (6, 7). The defense against ERS mainly involves the UPR which relies on three signaling pathways: Inositol-Requiring Protein-1 alpha pathway [IRE1α, involving the spliced ribonucleic acid (RNA) of X-box binding protein 1 (sXBP1)], Protein Kinase RNA-like ER kinase pathway [PERK, involving CCAAT/enhancer binding protein homologous protein (CHOP) and Activating Transcription Factor 4 (ATF4)] and Activating Transcription Factor 6 (ATF6) pathway (6). One of the roles of the UPR is to lead the synthesis of new chaperones to allow protein folding (e.g., GRP78, a final effector of UPR). However, if the ERS is severe and prolonged, UPR can lead to cell death by apoptosis (8).

Cytokine synthesis induces a massive increase in protein synthesis and, thus, an ERS which in turn activates NF-kB and thus maintains this synthesis (9). Cellular dysfunction, hallmarked by ERS, is increasingly recognized as an important contributor to the development of organ failure in critical illness, and in particular during systemic inflammation (6, 10, 11). ERS induces dysfunction and apoptosis of cardiomyocytes that can lead to heart failure and UPR have a protective effect on acute or chronic heart failure (12). ERS is associated with endothelial dysfunction and its inhibition improves endothelium-dependent relaxing function (13). In experimental sepsis, a treatment with 4-phenylbutyric acid (4BPA; a chemical chaperone which inhibits ERS) decreases the tissue expression level of inflammatory cytokines, reduces organ dysfunction and improves survival (14, 15). In human, ERS is activated in the mononuclear cells of patients with septic acute lung injury, is involved in AKI and its expression is partly correlated with organ failure in patients with septic shock (10, 14, 16). A recent work has shown the feasibility of the non-invasive detection of the ERS in urine in patients undergoing cardiac surgery with CPB and indicates that an early and robust adaptive UPR is critical for endogenous protection to acute renal failure (17).

Thus, we designed a prospective study to describe the kinetics of UPR markers and to evaluate the link between UPR expression and organ failure in patients undergoing elective cardiac surgery with CPB.

Abbreviations: 4PBA, 4-phenylbutyric acid; AKI, acute kidney injury; ATF, Activating Transcription Factor; CABG, coronary artery bypass grafting; CHOP, CCAAT/enhancer binding protein homologous protein; CPB, cardio-pulmonary bypass; Ct, cycle threshold; DNA, deoxyribonucleic acid; ER, endoplasmic reticulum; ERS, endoplasmic reticulum stress; GRP78, 78 kDa Glucose-Regulated Protein; HSPA5, Heat Shock 70kDa Protein 5; ICU, intensive care unit; IL, interleukin; IRE1α, Inositol-Requiring Protein-1 alpha; PERK, Protein Kinase RNA-like ER kinase; Pre-CPB, before cardio-pulmonary bypass; qPCR, quantitative polymerase chain reaction; RNA, ribonucleic acid; SAPS II, Simplified Acute Physiology Score II; SDHA, succinate dehydrogenase complex flavoprotein subunit A; SIRS, systemic inflammatory response syndrome; sXBP1, X-box binding protein 1; UPR, unfolded protein response; VCAM-1, Vascular Cell Adhesion Protein 1.

MATERIALS AND METHODS

Study Design

This prospective pilot study was conducted in the cardiac surgery ICU of a tertiary care University Hospital between July 2018 and April 2019. The study (N°2017/179/HP) was approved by the ethics committee *Sud-Méditerrannée II* (n° CPP 2017-A03375-48) and was performed in accordance with French laws and with the ethical standards laid down in the Declaration of Helsinki and its later amendments (18).

Inclusion and Exclusion Criteria

Adult patients (≥18 y/o) who underwent cardiac surgery with an estimated duration of CPB of more than 1 h were eligible to be included in the study. Eligible patients were contacted, and written informed consent was obtained prior to inclusion.

Exclusion criteria were: age under 18 y/o or patient under guardianship, pregnancy/breastfeeding, urgent surgery, predictable CPB of <1 h [single or double coronary artery bypass grafting (CABG) or single aortic valve replacement (VR)], surgery without sternotomy, a history of altered left ventricular systolic function (<30%), chronic autoimmune inflammatory disease, neoplasia.

Objectives

Primary Objective

The primary objective was to evaluate the variation in GRP78 plasma levels before CPB (Pre-CPB) and 2 and 24 h after the end of CPB.

Secondary Objectives

Secondary objectives were to evaluate:

- the kinetics of UPR pathway gene (*ATF6*, *ATF4*, *CHOP, HSPA5,* and *sXBP1*) expression in whole blood after CPB;
- the association between GRP78 plasma level variations and endothelial dysfunction markers [Syndecan-1, Vascular Cell

Adhesion Protein 1 (VCAM-1)], or inflammatory cytokine interleukin (IL)-6;
- the association between GRP78 level variations or UPR gene expression and organ failure 24 h after CPB (defined as presence of: invasive mechanical ventilation and/or AKI (Kidney Disease Improving Global Outcomes score $\geq$ 1) and/or hemodynamic failure requiring catecholamines) by comparing two groups: patients with and patients without organ failure 24 h after CPB.

Sample Collection and Analysis

Surgical Procedure

Induction of anesthesia was achieved with intravenous hypnotic (propofol or etomidate), opioid (sufentanil or remifentanil) and curare (cisatracrium). The anesthesia was maintained with propofol and continuous infusion of opioids. CPB was initiated with a heparinized solution. Oxygenated blood was re-injected into the arterial circulation through a cannula inserted into the aorta downstream of aortic clamping. The heart was stopped by infusion of a cardioplegia solution (potassium and beta-blockers or Custodiol© cardioplegia). During surgery, mean blood pressure was maintained between 55 and 70 mmHg. At the end of the procedure, circulating heparin was neutralized with protamine. Vasoconstrictors or inotropic agents, fluids, and transfusion products were administered at the discretion of the anesthesiologist based on clinical, echocardiographic and biological findings. Patients were transferred to post-operative cardiac ICU and monitored hourly for the first 24 h and then every 3 h for the remaining period of the ICU stay.

For each patient, baseline pre-operative characteristics were evaluated (sex, age, body mass index). The data relevant to the undertaken surgical procedure (type of surgery, surgery/CPB duration) and ICU stay [Simplified Acute Physiology Score (SAPS) II], use of catecholamine, duration of mechanical ventilation, length of ICU stay were collected.

Blood Sampling

All samples were collected from patients' arterial line, using standard hygiene protocols. The Pre-CPB sample was taken after induction of anesthesia and before incision, just after the arterial catheter was placed, postoperative samples were taken 2 and 24 h after the end of CPB, respectively. At each time point, one PAXgene® tube [allowing the conservation of ribonucleic acid (RNA) of circulating blood cells; Quiagen, Hilden, Germany; 2.5 ml of blood] and one EDTA tube (4 ml of blood) were collected. The EDTA tube was immediately centrifuged at 3,000 g for 15 min and plasma was aliquoted in microtubes. Samples were kept for a maximum of 7 days in the freezer of the ICU at −20°C and then were stored at −80°C until final analysis.

Enzyme Linked Immunosorbent Assay (ELISA)

Plasma GRP78 concentrations were determined using the commercial kit GRP78/BiP ADI-900-214 (Enzo Life Sciences, France) according to the manufacturer's protocol. After preliminary analyses, a dilution of our samples to 1:10 was chosen for optimized results. Other protein concentrations were determined using the Thermo Fisher Scientific (MA, USA) commercials kits IL-6 (ref. EH2IL6), Syndecan-1 (ref. EHSDC1) and VCAM-1 (ref. KHT0601) according to the manufacturer's protocol.

Ribonucleic Acid Extraction, Reverse Transcription, and Quantitative Polymerase Chain Reaction

RNA extraction was performed using the commercial kit PAXgene® Blood RNA System kit (Quiagen, Hilden, Germany) according to the manufacturer's protocol. Before RNA elution, residual genomic deoxyribonucleic acid (DNA) was digested using RNase-Free DNase set (Quiagen, Hilden, Germany). The integrity and quantity of the total RNA were assessed with a Nanodrop 2000 device (Thermo Fisher Scientific, Waltham, MS, USA). Total RNAs were reverse transcribed into cDNA using M-MLV Reverse Transcriptase (Invitrogen, Carlsbad, CA, USA) according to manufacturer's instructions.

A quantitative polymerase chain reaction (qPCR) was performed for:

- The mRNA of genes coding for proteins involved in UPR: *ATF6*, *ATF4*, *sXBP1*, *CHOP, HSPA5*;
- The mRNA of the gene coding for succinate dehydrogenase complex flavoprotein subunit A (SDHA). As *SDHA* has been described as a pertinent housekeeping gene in humans with inflammation and as its cycle threshold (Ct) is close to the Ct of UPR genes in qPCR, it appeared as the best housekeeping gene for our work (19).

The genes that were amplified and the primers that were used are listed in **Table 1**. Quantitative PCR was performed using the Quantstudio 12K Flex system (Applied Biosystems, Foster City, CA, USA) according to the manufacturer's instructions. The 384-well PCR plates were prepared with 1.2 μL of cDNA (16.7 ng/μL) diluted at 1:10 and 3.81 μL of reaction mix. The reaction mix contained the sense and antisense primers at a concentration of 300 nM (0.02 μL × 2), Fast Sybr Master mix (2.50 μL) and water DNase and RNase free (1.27 μL). The final volume was 5 μL per well. Samples were deposited using the Bravo Automated Liquid Handling Platform pipetting robot (Agilent Technologies, Santa Clara, CA, USA). The analysis included a first activation step for 20 s and then 40 amplification cycles consisting of a new activation phase at 95°C for 1 s followed by an elongation phase at 60°C for 20 s. Ct values were used for quantifying target gene expression relative to the housekeeping gene using the $2^{-\Delta\Delta Ct}$ method.

Statistical Analysis

In view of a previous work studying UPR expression during septic SIRS, we considered that it was necessary to include at least 45 patients to highlight a significant UPR after CPB (10). Since each subject was taken as its own control, the non-parametric Wilcoxon matched pairs signed rank test was used to assess significant variations in quantitative parameters. For group comparisons, the quantitative variables were compared using a Mann-Whitney test or a Student's test depending on the distribution of the data. The Pearson correlation test was used to assess the strength of the association between two quantitative variables. Continuous data are expressed as

TABLE 1 | Primers used for quantitative PCR.

Gene name	Sense	Sequence (5′-3′)
SDHA	Forward	GAGATGTGGTGTCTCGGTCCAT
	Reverse	GCTGTCTCTGAAATGCCAGGCA
ATF4	Forward	GTTCTCCAGCGACAAGGCTA
	Reverse	ATCCTGCTTGCTGTTGTTGG
CHOP	Forward	TCGCCGAGCTCTGATTGAC
	Reverse	CCCTGCGTATGTGGGATTGAG
sXBP1	Forward	TGCTGAGTCCGCAGCAGGTG
	Reverse	GCTGGCAGGCTCTGGGGAAG
ATF6	Forward	CCGCAGAAGGGGAGACACA
	Reverse	TCGGAGGTAAGGAGGAACTGACG
HSPA5	Forward	CGAGGAGGAGGACAAGAAGG
	Reverse	CACCTTGAACGGCAAGAACT

ATF4/6, Activating Transcription Factor 4/6; CHOP, CCAAT/enhancer binding protein homologous protein; HSPA5, Heat Shock 70kDa Protein 5; SDHA, succinate dehydrogenase complex flavoprotein subunit A; sXBP1, spliced X-box binding protein 1.

TABLE 2 | Main demographic and clinical characteristics of patients.

Demographic characteristics	
Number of patients	46
Age (years)	70 (63–76)
Sex-ratio (M/F)	3.6 (36/10)
Body Mass Index (kg/m²)	28.1 (25.7–30.5)
Length of stay in hospital (days)	13 (9–17)
Surgical characteristics	
Type of surgery:	
- coronary artery bypass grafting (CABG)	9 (19.6 %)
- mitral valve surgery	10 (21.7 %)
- Bentall or Tirone-David surgery	10 (21.7 %)
- Ross surgery	1 (2.2 %)
- aortic + mitral valve surgery	5 (10.9 %)
- aortic valve surgery + CABG	5 (10.9 %)
- mitral valve surgery + CABG	4 (8.7 %)
- aortic + mitral valve surgery + CABG	2 (4.3 %)
Duration of surgery (min)	221 (186–254)
Duration of CPB (min)	117 (92–139)
Hematocrit (%)	
- before CPB	42 (26–49)
- 2 h after CPB	35 (27–40)
- 24 h after CPB	34 (26–41)
ICU stay characteristics	
SAPS II	33 (30–40)
Duration of mechanical ventilation (hours)	6 (4–8)
Length of ICU stay (days)	3 (2–5)

Data are presented as median with interquartile range or absolute value and percentage [n (%)]. CABG, coronary artery bypass grafting; CPB, Cardiopulmonary Bypass; ICU, Intensive Care Unit; SAPS II, Simplified Acute Physiology Score II.

median with interquartile range, categorical data are presented as absolute values with percentages. All statistical tests were two-sided and the 0.05 probability level was used to establish statistical significance. The statistical analyses were performed by means of the statistical software SAS (version 9.4; SAS Institute; Cary, NC). The data were exported to GraphPad Prism 8.0 software for figure creation.

RESULTS

Clinical and Demographic Characteristics of Population

Forty-six patients were enrolled between July 2018 and April 2019. Baseline and peri-operative characteristics of included patients are detailed in **Table 2**. All patients were alive at D28.

GRP78 Plasma Levels

The plasma level of GRP78 was significantly decreased 2 h after CPB but there was no difference in GRP78 levels between pre-operative and 24-h post-CPB samples (**Figure 1A**). Relative changes in GRP78 levels 2 and 24 h after CPB are shown in **Figure 2**. There was no correlation between relative changes in GRP78 plasma level variation at 24 h and duration of CPB [$r = -0.19$ (-0.45; 0.11); $p = 0.22$]. There was no correlation between plasma level of C-reactive protein and plasma level of GRP78 at H24 [$r = 0.17$ (-0.13; 0.44); $p = 0.26$].

Syndecan-1, VCAM-1, and IL-6 Plasma Levels

The plasma level of VCAM-1 did not show any change at 2 h after CPB but was significantly increased 24 h after CPB (**Figure 1B**) while syndecan-1 and IL-6 levels were increased 2 and 24 h after CPB (**Figures 1C,D**). Relative changes in studied protein levels at 2 and 24 h post-CPB (compared to the value before CPB) are shown in **Figure 2** (as Pre-CPB IL-6 levels were undetectable, it was not possible to perform a relative analysis for this cytokine).

Twenty-four hours after CPB, there was no correlation between GRP78 plasma level variations and VCAM-1 [$r = 0.04$ (-0.33; 0.25); $p = 0.79$] and Syndecan-1 [-0.29 (-0.53; 0.00); $p = 0.05$] plasma level variations or IL-6 absolute values [$r = 0.12$ (-0.18; 0.40); $p = 0.43$].

There was also no correlation of the absolute values of GRP78 rates with those of IL-6, VCAM-1, and Syndecan-1 at H24 (**Supplemental Figure 1**).

Gene Expression of Unfolded Protein Response

The expression of *CHOP* and *sXBP1* was increased 2 h after CPB and remained stable 24 h after CPB. *ATF4* showed a small increase in expression 2 h after CPB but there was no difference in its expression between pre-operative and 24-h post-CPB samples (**Figure 3**). The expression of *ATF6* was increased 2 h after CPB and kept increasing 24 h after CPB (**Figure 3**).

Correlation Between Unfolded Protein Response and Clinical Outcome

Of the 46 patients, 10 had persistent organ failure 24 h after CPB (9 treated with catecholamines, 4 mechanically ventilated and 2 with acute renal failure; **Supplementary Table 1**). Their

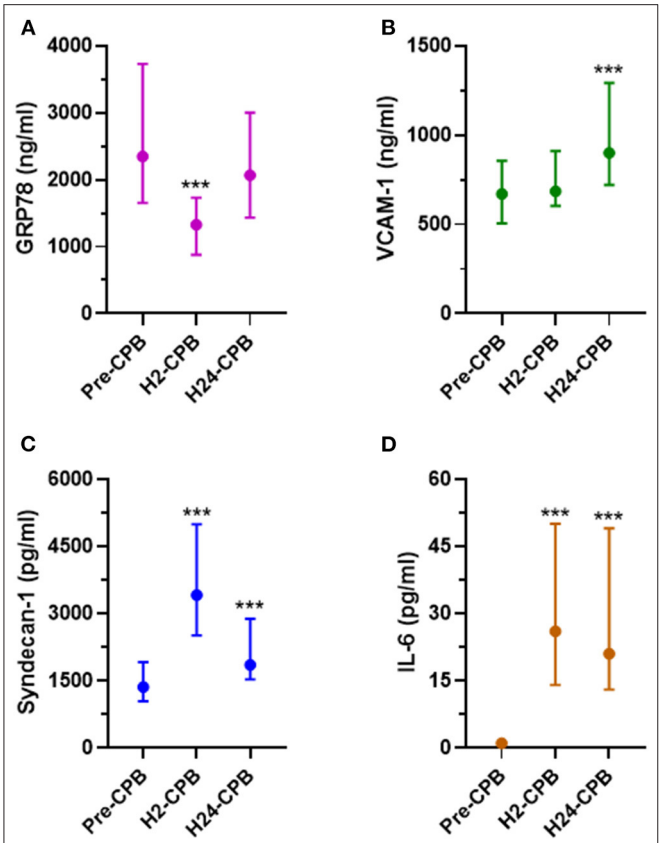

FIGURE 1 | Plasma levels of GRP78 **(A)**, VCAM-1 **(B)**, Syndecan-1 **(C)** and IL-6 **(D)** before (Pre-CPB), 2 (H2-CPB) and 24 (H24-CPB) hours after cardiopulmonary bypass (CPB). The results show a post-operative increase in IL-6, Syndecan-1 and VCAM-1 and a transient decrease (at H2-CPB only) in GRP78. Dosages were performed by Enzyme linked immunosorbent assay (ELISA). Values are presented as median with interquartile range. ***$p < 0.001$ in comparison with Pre-CPB level. GRP78, 78 kDa Glucose-Regulated Protein; IL-6, Interleukin 6; VCAM-1, Vascular Cell Adhesion Protein 1.

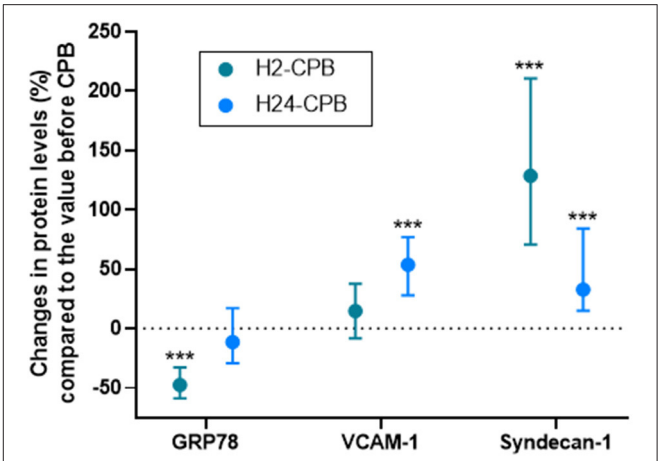

FIGURE 2 | Relative levels of studied protein 2 (H2-CPB) and 24 (H24-CPB) hours after cardiopulmonary bypass (CPB). The results show a post-operative relative increase in Syndecan-1 and VCAM-1 and a transient decrease (2 h after CPB only) in GRP78. Dosages were performed by Enzyme linked immunosorbent assay (ELISA). Values are presented as median with interquartile range. ***$p < 0.001$ in comparison with Pre-CPB level. GRP78, 78 kDa Glucose-Regulated Protein; VCAM-1, Vascular Cell Adhesion Protein 1.

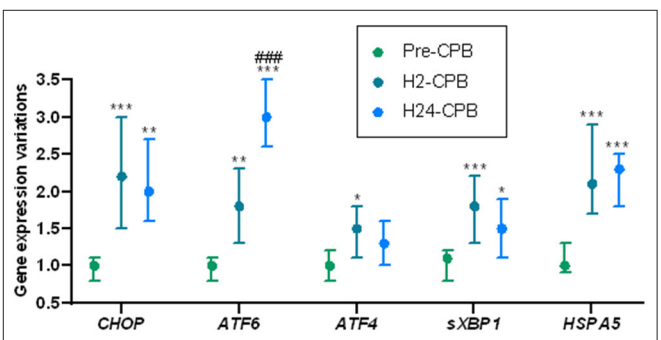

FIGURE 3 | Relative changes in Unfolded Protein Response gene expression after cardiac surgery with cardiopulmonary bypass (CPB). The results show a post-operative increase in the expression of genes coding for the key proteins of unfolded protein response, meaning a postoperative activation of the unfolded protein response. Analyses were performed by quantitative polymerase chain reaction. Gene expression prior to CPB (Pre-CPB) was averaged to 1 for each gene. For each patient, expressions at 2 h (H2-CPB) and 24 h (H24-CPB) after CPB were expressed as relative to Pre-CPB. Values are presented as median with interquartile range. Differences expressed in comparison with preoperative gene expressions: *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. Differences expressed in comparison with H2-CPB gene expressions: ###$p < 0.001$. ATF, Activating Transcription Factor; CHOP, CCAAT/enhancer binding protein homologous protein; HSPA5, Heat Shock 70kDa Protein 5; sXBP1, spliced RNA of X-box binding protein 1.

demographical and clinical characteristics are presented in the **Table 3**. There was no difference concerning Pre-CPB GRP78 levels and UPR gene expression between patients with or without organ failure (**Supplementary Table 2**). GRP78 plasma levels at 24-h post-CPB in patients with persistent organ failure remained significantly below Pre-CPB levels compared to patients without organ failure in whom GRP78 levels returned to baseline levels (**Figure 4**). To evaluate the potential bias induced by hemodilution on GRP78 levels according to the presence or absence of organ failure, we analyzed the variations in total protein levels between patients with and without organ failure and found no significant differences between groups (**Figure 4**). Among the patients with organ failure, the decrease in GRP78 levels between Pre-CPB and H24-CPB was correlated to the number of organ failures [$r = -0.76$ (-0.94 to -0.24); $p = 0.01$; **Figure 5**]. *ATF6* and *CHOP* expressions were significantly lower 24 h after CPB in patients with organ failure while there was no difference concerning *sXBP1* and *ATF4* expression (**Figure 6**).

DISCUSSION

To our knowledge, we describe for the first time the kinetics of all UPR pathways to restore ER homeostasis in patients undergoing elective cardiac surgery with CPB. We found that the plasma level of GRP78, one of the final effectors of the UPR, was decreased at the initial phase of CPB-induced SIRS and that a persistent

TABLE 3 | Comparison of demographic and clinical characteristics of patients with and without organ failure 24 h after cardiopulmonary bypass.

	No organ failure ($n = 36$)	Organ failure ($n = 10$)	*p*
Demographic characteristics			
Age (years)	71 (66–75)	69 (51–76)	0.46
Sex-ratio (M/F)	6.2	1.0	0.27
Body Mass Index (kg/m²)	27.0 (24.8–29.3)	31.5 (28.3–34.7)	0.02
Length of stay in hospital (days)	13 (9–16)	19 (11–24)	0.08
Surgical characteristics			
Type of surgery [*n* (%)]:			
- coronary artery bypass grafting (CABG)	8 (22%)	1 (10%)	0.79
- valve surgery	20 (56%)	6 (60%)	
- valve + CABG surgery	8 (22%)	3 (30%)	
Duration of surgery (min)	212 (179–254)	251 (208–260)	0.12
Duration of CPB (min)	109 (63–198)	138 (81–259)	0.70
ICU stay characteristics			
SAPS II	33 (27–38)	41 (31–49)	0.78
Duration of mechanical ventilation (hours)	5 (4–7)	11 (7–33)	0.02
Length of ICU stay (days)	3 (2–4)	5 (4–6)	0.08

Data are presented as median with interquartile range or absolute value and percentage [n (%)]. CABG, coronary artery bypass grafting; CPB, Cardiopulmonary Bypass; ICU, Intensive Care Unit; SAPS II, Simplified Acute Physiology Score II.

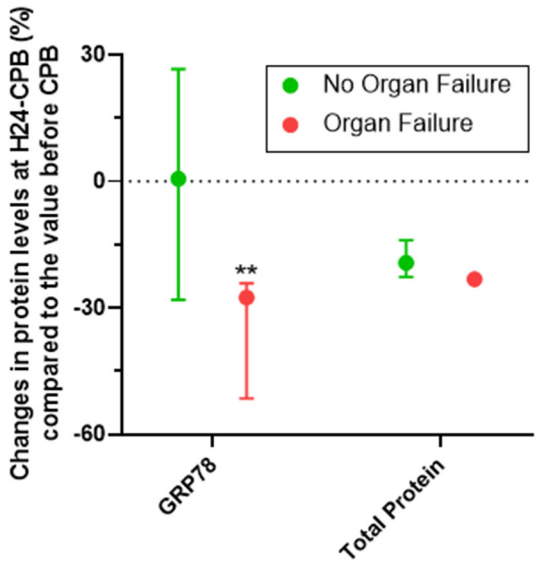

FIGURE 4 | Relative changes (%) in GRP78 levels at 24 h after cardiopulmonary bypass (CPB; H24-CPB) in patients with or without organ failure. The results show that GRP78 levels remain below baseline in patients with organ failure while they return to baseline in patients without organ failure (with no difference in proteinemia between the two groups), suggesting a less intense unfolded protein response in patients with organ failure. Dosages were performed by Enzyme linked immunosorbent assay (ELISA). Values are presented as median with interquartile range. $^{**}p < 0.01$ between groups. GRP78, 78 kDa Glucose-Regulated Protein.

decrease in GRP78 levels was associated with postoperative organ failure in this population.

Kinetics of Unfolded Protein Response

The present study demonstrates that CPB stimulated UPR, as reflected by the increased gene expression of the three UPR pathways: IRE1α, PERK, and ATF6.We observed a brief decrease in circulating GRP78 levels 2 h after CPB and a return to baseline level 24 h after CPB. We didn't find any correlation between changes in GRP78 at 24 h and duration of CPB but our range of CPB times was not wide. Future investigations should examine a broader range of CPB times before really concluding on this point. It is known that heat-shock proteins can be secreted extracellularly by many cells (dendritic cells, hepatocytes, myocytes, gut cells, lymphocytes, etc.) through several regulated pathways: lysosome-endosome pathway, secretory-like granules, extracellular vesicles (20). A previous work reported that extracellular GRP78 is mostly due to an active release from intact cells and does not result solely from the leakage of proteins from dead cells (21). It is therefore likely that the decrease in GRP78 plasma level is the result of an adaptive cellular mechanism.

Several studies have shown an increase in GRP78 plasma levels in patients with chronic systemic inflammation (cancer, obesity, atherosclerosis) (22–24). However, in acute systemic inflammation, there is increased demand for intracellular GRP78 to resolve the ERS (6, 25). This may explain the observed early decrease of extracellular GRP78 which is associated with

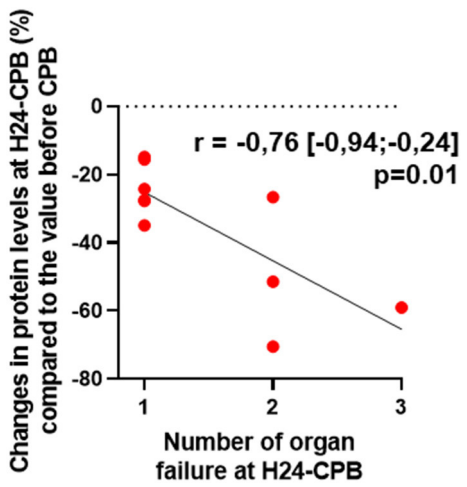

FIGURE 5 | Correlation between relative changes (%) in GRP78 levels at 24 h after cardiopulmonary bypass (CPB; H24-CPB) and the number of organ failures in the subgroup of patients with organ failure. The results show that a high number of organ failure is correlated with a significant decrease in GRP78 levels compared to the baseline level before CPB. GRP78, 78 kDa Glucose-Regulated Protein.

a rapid activation of UPR gene transcription 2 h after CPB, allowing a return of GRP78 to baseline level 24 h after CPB. It appears normal for the transcription to precede the translation

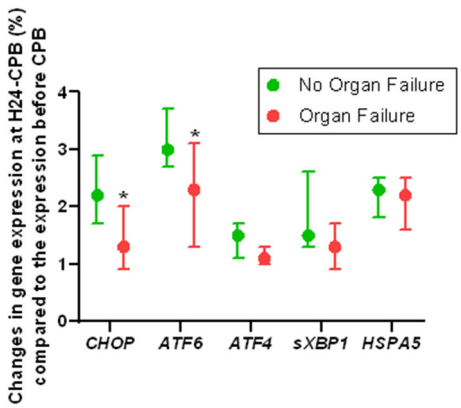

FIGURE 6 | Relative changes in Unfolded Protein Response gene expression 24 h after cardiopulmonary bypass (CPB) in patients with or without organ failure. Results show that the expression of *ATF6* and *CHOP* genes (which code for unfolded protein response key proteins) is lower in patients with postoperative organ failure than in those without organ failure, suggesting a less intense unfolded protein response in patients with organ failure. Analyses were performed by quantitative polymerase chain reaction. Values are presented as median with interquartile range. *$p < 0.05$ between groups. Gene expression at 24 h after CPB was relative to preoperative expression. ATF, Activating Transcription Factor; CHOP, CCAAT/enhancer binding protein homologous protein; HSPA5, Heat Shock 70kDa Protein 5; sXBP1, spliced RNA of X-box binding protein 1.

and it should be noted that the transcription of *HSPA5*, which codes for GRP78, is elevated early (from H2). However, the effective recovery of GRP78 plasma levels is only visualized at H24. This suggests that the activation of UPR genes is very rapid after inflammation but that its protein response in plasma is time-shifted. It has been shown that the UPR genes expression of each UPR pathway are highly correlated during ERS with variations among individual (26, 27). Our results show that the three pathways of UPR are activated during aseptic systemic inflammation in humans. However, the kinetics of these pathways appears to be different. The IRE1α (explored by *sXBP1*) and PERK (explored by *ATF4* and *CHOP*) pathways seemed to have a stable level of expression between 2 and 24 h after CPB. On the contrary, *ATF6* expression increased significantly 2 h after CPB and kept increasing 24 h after CPB. During ERS, ATF6 pathway is the first to be initiated and, due to its rapid activation (proteolytic cleavage and direct action on the genome as a transcription factor), it has the most reactive kinetics of the three UPR pathways (28, 29). ATF6 upregulates many protective genes and downregulates many potentially damaging genes, and previous studies have shown that ATF6 activation in cardiac myocytes protects the heart from ischemic damage, while inhibiting ATF6 has the opposite effect (30–32). Given our results and as previously suggested, it is possible that among UPR pathways, ATF6 is the most intensely involved pathway during acute SIRS (which could explain why its activation continued to increase 24 h after CPB) (10). The three UPR pathways have, in part, common effects to resolve ERS: chaperone synthesis, activation of ER associated degradation, activation of Nuclear Factor-Kappa B, etc. (6, 8). It is therefore difficult to propose a hypothesis on the clinical consequences of differential activation of the three pathways of UPR over time. Future works studying the activation kinetics of the UPR pathways in humans are in any case necessary to confirm or invalidate our results and to analyze more precisely the activation/return to normal delays after acute inflammation.

Unfolded Protein Response and Organ Failure

It is known that apoptosis, cytokine release and oxidative stress induced by ERS can lead to organ failure during sepsis (15). To respond to ERS, cells activate an adaptative pathway, the UPR, to synthesize chaperones (including GRP78) and restore normal ER function. It can therefore be assumed that ERS after cardiac surgery can also be a source of organ failure. Circulating GRP78 levels returned to levels comparable to baseline at H24-CPB except in patients with persistent organ failure who maintained GRP78 levels below their initial baseline. They also had a lower UPR gene expression than patients without organ failure. In a previous study, the expression of UPR mRNA gene in urine after cardiac surgery showed that patients with a rapid increase in sXBP1 mRNAs expression in urine (reflecting kidney UPR) had less AKI (17). These data suggest that a robust post-operative activation of the UPR after CPB is critical for protecting against organ failure. Moreover, pre-clinical data show that the resolution of ERS *via* chemical chaperones (e.g., 4BPA) can correct organ failure induced by a septic SIRS (14, 15). In our study, patients with a relatively strong UPR response (that probably allowed ERS resolution) returned to their baseline chaperone levels with no organ failure, while patients with a weaker UPR response failed to return to their baseline chaperone levels and had persistent organ failure. Our results are therefore consistent with previous data in human and animals on the impact of ERS and UPR on organ failure during SIRS. But, as previously stated, the prognostic value of the markers of ERS response may change with the duration of adaptive responses, which also reflect the duration of the stress (17). While a strong UPR appears necessary in the acute stress phase, excessively prolonged ERS responses promote cell death as a result of an imbalance in favor of proapoptotic pathways rather than antiapoptotic pathways (8).

Extracellular GRP78 is known to have anti-inflammatory properties by inducing the endocytosis of the Toll-Like Receptor 4, reducing the production of inflammatory cytokines and increasing the synthesis of anti-inflammatory cytokines (33, 34). It is therefore possible that patients returning to pre-operative levels of GRP78 may also benefit from its immunomodulatory effect and thus be less likely to develop persistent organ failure than patients remaining at relatively low levels of extracellular GRP78. Nevertheless, our work does not establish a causal link between organ failure after CPB and the level of GRP78, and further works are therefore necessary to confirm or invalidate our observations.

Syndecan-1, VCAM-1, and IL-6 Plasma Levels

It has been shown that ERS is implicated in endothelial dysfunction and that its inhibition in humans improves endothelial dysfunction induced by glucose ingestion (13, 35). Moreover, in a previous study conducted in septic patients, we have shown an association between expressions of *ATF6* and *ET1* (coding for endothelin-1 which is associated with endothelial dysfunction) (10). However, we did not find a link between VCAM-1, Syndecan-1 or IL-6 and GRP78 variations. With regard to the results of previous studies on the link between ERS and endothelial dysfunction, we should be cautious and not conclude the absence of a link between ERS and endothelial dysfunction in patients undergoing cardiac surgery with CPB.

LIMITATIONS

Our work has several major limitations. First, it is a pilot physiological study with a limited number of patients. We included patients with several types of surgery (valve and/or CABG) which could lead to a heterogeneity of the studied population. For example, it is known that valve surgery induces more systemic inflammation than coronary bypass surgery (36). It is therefore possible that ERS may be more pronounced in patients with valve surgery. Second, our work involved gene expression in the whole blood. As some of the proteins studied in our work cannot be measured in blood without complex cell isolation techniques, RNA quantification appeared to be the best compromise. RNA expression on whole blood measured using Paxgen tubes is strongly correlated with RNA expression in circulating leucocytes, we can thus assume that we detected variations in leucocyte gene expression (37). As it is known that UPR plays a crucial role in immune cells, including differentiation, immune activation, antibody production and cytokine expression, it seemed relevant to study the leucocyte expression of UPR genes (38, 39). However, we may have missed a potentially greater variation in gene expression in tissues and organs, as observed in animal models (14, 15). Third, we performed the first sampling after anesthetic induction. It is known that propofol has a mild inhibitory effect on ERS several hours after induction (40). Given the mechanisms involved in UPR activation (gene transcription, protein translation), it is unlikely that there would be significant variations in UPR between pre-induction period and immediate post-induction period (a few minutes). Furthermore, since all patients had a standardized anesthesia protocol, it is likely that the effects of propofol on ERS were identical for all patients. Fourth, our samples were taken at only two post-operative timepoints and it is possible that we were not able to highlight the real peak of UPR expression. Moreover, our data show that the expression of several genes involved in UPR remains high 24 h after CPB compared to baseline. Our work did not allow us to conclude when the genes involved returned to baseline expression. Fifth, we only studied patients with cardiac pathologies, some of which are associated with ERS-inducing pathologies: diabetes, atherosclerosis, obesity, metabolic syndrome (41). It is therefore not certain that GRP78 and UPR kinetics would be identical in a population without pathologies. However, it should be noted that the GRP78 plasma levels found before CPB and 24 h after CPB were very close to those recently described in a group of healthy volunteers, which probably makes our results quite extrapolable to other populations (42). Finally, we defined organ failure according to usual clinical criteria, but we did not use a standardized organ failure score such as the Sequential Organ Failure Assessment score. This complicates the interpretation of the results and makes it more difficult to compare our results with those of other works. Further studies will need to be done using this type of score to define organ failure.

CONCLUSION

We describe for the first time the kinetics of all UPR pathways during SIRS induced by cardiac surgery with CPB. We found that the plasma level of GRP78 was decreased at the initial phase of CPB-induced SIRS and that low relative GRP78 levels appeared associated with postoperative organ failure. However, further studies are needed to better understand ERS and UPR implications during systemic inflammation and acute organ failure in humans.

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 CPP Sud-Méditerranée II - Hôpital Sainte Marguerite - Pavillon 9 - 270 Boulevard Sainte Marguerite 13274 MARSEILLE. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TC was involved in the study conception and design, in acquisition of data, in analysis and interpretation of data and in manuscript draft. ZD was involved in acquisition of data, in analysis and interpretation of data and in manuscript draft. XS was involved in acquisition and in interpretation of data. CT was involved in statistical analysis and in interpretation of data. EB, JS, and FD were involved in the study conception and design, in interpretation of data and in manuscript revision. VR, BV, and FT were involved in the study conception and design, in analysis and interpretation of data and in manuscript revision. All authors contributed to manuscript revision, read and approved the submitted version.

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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.2020.613518/full#supplementary-material

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Association of Nutritional Risk Index With Postoperative Pain Outcomes in Elderly Patients Undergoing Gastrointestinal Surgeries: A Retrospective Cohort Study

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Background: Malnutrition is a major health problem, which is common in hospitalized elderly patients and is associated with an increased risk of morbidity and mortality. However, studies on malnutrition and its effect on postoperative pain outcomes in elderly patients have been largely neglected. Here we investigated the relationship between nutritional risk and postoperative pain outcomes in elderly patients.

Methods: Between April 1, 2012, and August 31, 2015, 734 elderly patients (≥65 years) who underwent gastrointestinal surgeries were recruited and assigned into two groups according to geriatric nutritional risk index (GNRI). All patients received standard anesthesia procedures and postoperative patient-controlled analgesia for 48 h. The preoperative epidemiology data and postoperative outcome data including pain intensities at rest and movement, the cumulative consumption of analgesics and its common side effects were recorded.

Results: The total number of patients with high nutritional risk (GNRI < 92) was 533 out of 734 (72.62%). When compared with low nutritional risk individuals (GNRI ≥ 92), the incidence of inadequate analgesia was significantly higher in elderly patients with GNRI < 92 at different time points. In addition, the cumulative consumption of analgesics was also significantly higher in elderly patients with GNRI < 92 at 0–6 h postoperatively. Through logistic regression analysis, high nutritional risk (OR $= 3.113$, 95% CI: 1.661–5.834, $P < 0.001$) and female gender (OR $= 0.606$, 95% CI: 0.394–0.932, $P = 0.023$) were identified as significant predictors for postoperative inadequate analgesia. Further sensitivity analyses showed high nutritional risk as a predictor for postoperative inadequate analgesia was more prominent in female patients and early elderly patients. Moreover, 88 was determined as an optimal cut-off value of GNRI for postoperative inadequate analgesia using receiver operating characteristic curve analysis.

Conclusion: High nutritional risk is associated with poor postoperative pain outcomes in gastrointestinal elderly patients. Preoperative nutritional evaluation using simple nutritional screening instruments (e.g., GNRI) with the new suggested cut-off value (GNRI = 88) might be included as a standard procedure in routine clinical practice among these patients for postoperative analgesia.

Keywords: geriatric nutritional risk index, postoperative pain, postoperative inadequate analgesia, gastrointestinal surgeries, elderly patients

INTRODUCTION

Population aging is a worldwide phenomenon. It is predicted that persons over 65 years will compose 30% of the total population by the year 2050 (1). Although these aged individuals are expected to increase demand for surgical treatments (2), management of postoperative pain in elderly patients continues to be a major challenge. It is reported that ∼50–75% of elderly patients experience inadequate postoperative pain relief (3). The under treatment of postoperative pain is associated with serious negative consequences, including increased risk of myocardial, thromboembolic or pulmonary complications, impaired rehabilitation, increased length of hospital stay, increased risk of persistent postoperative pain and elevated mortality rate (4).

The failure to provide appropriate postoperative analgesia in elderly patients is multifactorial. One of the common reasons is inadequate knowledge about physiological or pathophysiological changes and their effects on postoperative pain management in elderly patients (5). As a result of aging processes, elderly patients are at higher risk of malnutrition due to decreased gastric secretions and intestinal motility (6), which has been proven to predict morbidity and mortality among older hospitalized patients (7, 8). However, thus far, there have been no studies examining the relationship between nutritional risk and postoperative pain outcomes in elderly patients.

Geriatric nutritional risk index (GNRI) is a nutritional screening and assessment tool created to predict nutrition-related complications in hospitalized elderly patients (9). A lower value of GNRI indicates a higher nutrition-related risk. In a previous study in elderly patients with acute heart failure, it was found that GNRI < 92 is associated with poor clinical outcomes (10). In another 3-year follow-up study, a GNRI <92 was reported to associated with higher mortality and suggested as a profitable clinical trigger for routine nutritional treatment (11). However, GNRI has not been used to predict postoperative pain outcomes and its optimal cut-off value is unclear.

Accordingly, the main aim of this study was determining whether nutritional risk was associated with postoperative pain outcomes using GNRI and the optimal cut-off value of the GNRI for postoperative inadequate analgesia. Furthermore, we evaluate the influence of nutritional status on postoperative pain outcomes in gastrointestinal elderly patients receiving patient-controlled intravenous analgesia.

MATERIALS AND METHODS

Study Design and Data Sources

Institutional Review Board (IRB) approval for this retrospective cohort study was granted through the Ethic Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (TJ-IRB20190403). The requirement for informed consent from participants was waived under the regulations of IRB. Demographic data (gender, age, weight, height, etc.), preoperative data (comorbidity, serum albumin, etc.) and process data (surgical types, surgical methods, anesthesia techniques, intraoperative medication, analgesia technique, etc.) presented in the current study were extracted from the patients' electronic medical records. Outcome data (pain intensities at rest and movement, cumulative analgesics consumption, side effects of analgesics, etc.) were collected by an acute pain service group at different time points postoperatively (12–14). Approximately 82% of the patients undergoing gastrointestinal surgeries were included. All data were assessed and edited by two authors (HZ, GD). If a missing data or an extreme value occurred, the relevant raw data were double checked. Participant's name or other form of identification was deleted before analysis. The reporting of this study followed the STROBE (strengthening the reporting of observational studies in epidemiology) (15) and RECORD (reporting of studies conducted using observational routinely collected health data) (16) guidelines.

Participants

Between April 1, 2012, and August 31, 2015, elderly patients ($\geq$65 years) who underwent gastrointestinal surgeries were screened. Inclusion criteria were receiving general anesthesia and postoperative patient-controlled analgesia for 48 h. Exclusion criteria were receiving regional anesthesia, undergone repeat surgery during hospitalization and missing data for any variable.

Exposure of Interest

The exposure of interest in this study was high nutritional risk. The risk of nutritional status was assessed by the geriatric nutritional risk index (GNRI), which was designed specifically for the hospitalized elderly patients (9). The GNRI was calculated based on the patient's weight, height and serum albumin as follows: GNRI = [1.489 × albumin (g/L)] + [41.7 ×

(weight/WLo)]. The WLo is the ideal weight and was calculated using the Lorentz formula as WLo = 0.75 × height (cm) − 62.5 for men and WLo = 0.60 × height (cm) − 40 for women (17). When weight exceeded ideal weight, the ration of weight/WLo was set to 1. Similar to previous studies, the GNRI of 92 was taken as an original cut-off value (10, 11, 18).

Perioperative Pain Management and Outcome Measures

All patients were treated according to the standard procedures at Tongji Hospital. In general, anesthesia induction was performed using 0.3–0.6 μg/kg sufentanil, 0.1–0.2 mg/kg cisatracurium and 1.5–2.5 mg/kg propofol. Anesthesia was maintained with a combination of sevoflurane (1.0–2.0%), remifentanil (0.2–0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and propofol (6–10 $mg \cdot kg^{-1} \cdot h^{-1}$). At 15 min prior to the surgery, patients without contraindication were given nonsteroidal anti-inflammatory drugs (NSAIDs, 40 mg parecoxib sodium) and prophylactic antiemetics (dexamethasone 4 mg and/or tropisetron hydrochloride 2 mg). Immediately after surgery, patient-controlled intravenous analgesia (PCIA) was started with 0.7 μg/mL sufentanil and 4 mg/mL tramadol using a PCIA pump (BCM, BCDB-150, Shanghai, China). The pump was programmed to use a background infusion at 1–2.5 mL/h, a bolus dose of 1 mL, a lockout interval of 10 min, and a dose limit of 12 mL/h.

Patient outcome data were collected by the acute pain service group at 0–6, 18–24, and 42–48 h postoperatively. Pain intensities at rest and movement were assessed using a 100-mm visual analog scale (VAS, 100 being worst pain imaginable). In addition, cumulative PCIA consumption and the common side effects including postoperative nausea and vomiting, respiratory depression, abdominal distention, pruritus, urinary retention, and dizziness were also recorded. Pain trigger for rescue analgesia was VAS ≥ 40, which was defined as postoperative inadequate analgesia (13, 19). Under these circumstances, Patients without contraindication were given parecoxib sodium and PCIA parameters were upregulated. The primary outcome we used here was postoperative inadequate analgesia. As secondary outcome we investigated cumulative PCIA consumption and the side effects of PCIA.

Statistical Analysis

In the database, about 8.9% of data were missed. The missing data arose mainly in variable "postoperative cumulative PCIA consumption" but not in variables included in the regression analysis. Thus, traditional statistical analyses were performed and imputation analyses were not considered. Participants with any missing data were excluded from analysis. Demographic data (e.g., age, weight and height) and postoperative cumulative PCIA consumption were presented as median (interquartile range). These data did not pass the Shapiro-Wilk test for normal distribution and were analyzed by the Mann–Whitney *U* test. Body mass index (BMI) were presented as mean (± standard deviation) and compared using the *t* test. Dichotomous data (e.g., gender and postoperative inadequate analgesia) were expressed as absolute number (and %) and significance was calculated with the chi-square test. To evaluate the role of the preoperative factors in the prediction of postoperative inadequate analgesia during the entire 0–48 h period, a forward stepwise logistic regression model was applied. Gender, age, BMI, Charlson Comorbidity Index (CCI) score, American society of anesthesiologists (ASA) score, surgical types (gastric or intestinal), surgical methods (endoscopic or non-endoscopic), intraoperative medication and the GNRI were included in the model. Given gender and age were reported to be risk factors for postoperative inadequate analgesia in our previous study (20), sensitivity analyses were further performed in female and male subgroups, as well as in early elderly (age <75 years) and late elderly (age ≥75 years) subgroups. A receiver operating characteristic (ROC) curve analysis was used to determine an optimal cut-off value of GNRI for postoperative inadequate analgesia. A $P < 0.05$ was considered statistically significant. All of the statistical analyses were performed with SPSS software (version 17.0, SPSS Inc., Chicago, IL, USA).

RESULTS

Characteristics of the Patients

During the study period, a total of 806 patients were reviewed. Of them, 59 patients with missing data for any variable, 11 patients receiving regional anesthesia and two patients undergone repeat surgery were excluded. Finally, 734 patients were included in the analysis (**Figure 1**).

Taking GNRI of 92 as a cut-off point, the total number of patients with high nutritional risk (GNRI < 92) was 533 out of 734 (72.62%). Demographic characteristics of patients were summarized in **Table 1**. The median age of the whole population was 69 (67–74), whereas patients with GNRI < 92 were slightly older than patients with GNRI ≥ 92 (70 (67–74) vs. 68 (66–73); $p = 0.002$). Weight (57 (50–65) vs. 63 (58–71); $p < 0.001$), height (1.64 (1.58–1.70) vs. 1.65 (1.60–1.70); $p = 0.032$) and BMI (21.64 ± 3.60 vs. 23.70 ± 2.73; $p < 0.001$) were lower in patients with GNRI < 92 compared to patients with GNRI ≥ 92. In addition, less endoscopic surgeries were performed in patients with GNRI < 92 than patients with GNRI ≥ 92 (74.48 vs. 82.09%; $p < 0.030$). Gender, CCI scores, ASA scores, surgical types and intraoperative medication including dexamethasone, parecoxib and sufentanil were not different among groups.

Postoperative Pain Outcomes in Patients With Different Nutritional Risk

Firstly, we compared postoperative pain outcomes in different nutritional risk groups as classified by the GNRI, which are shown in **Table 2**. At rest, the incidence of inadequate analgesia of the whole population was 13.62% at 0–6 h, 9.54% at 18–24 h and 3.95% at 42–48 h postoperatively; the patients with GNRI < 92 had higher levels of inadequate analgesia at 0–6 h (16.51 vs. 5.97%; $p < 0.001$), 18–24 h (11.82 vs. 3.48%; $p = 0.001$), but not 42–48 h postoperatively, in comparison with the patients with GNRI ≥ 92. On movement, 20.44% patients at 0–6 h, 14.17% patients at 18–24 h and 8.99% patients at 42–48 h postoperatively presented inadequate analgesia; the incidence of inadequate analgesia in patients with GNRI < 92 was higher than the patients with GNRI ≥ 92 at 0–6 h (24.02 vs. 10.95%;

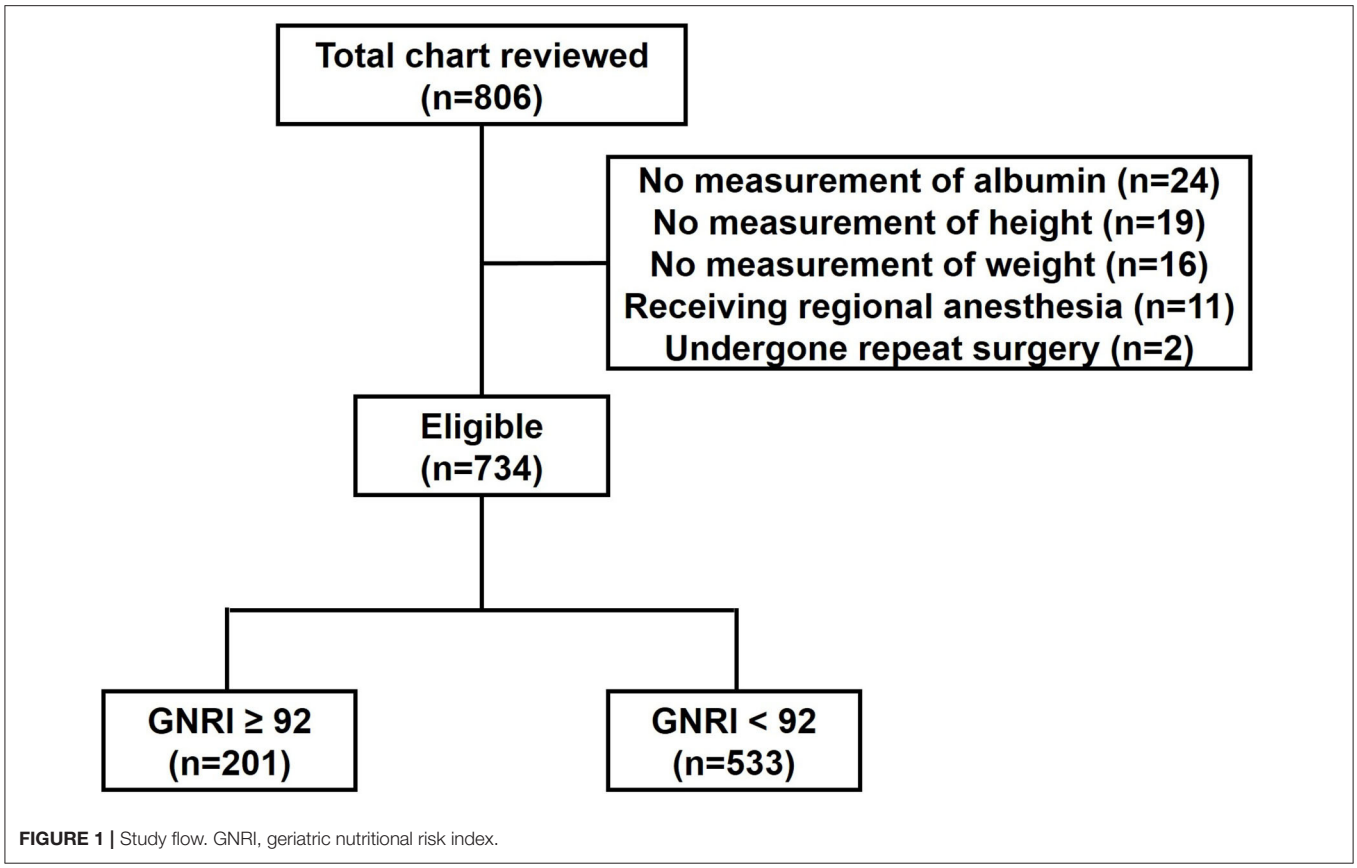

FIGURE 1 | Study flow. GNRI, geriatric nutritional risk index.

TABLE 1 | Comparison of patient characteristics in different nutritional risk groups as classified by the GNRI.

Characteristic	Total (n = 734)	GNRI ≥ 92 (n = 201)	GNRI < 92 (n = 533)	P value
Gender (male/female)	472 (64.31%)/262 (35.69%)	132 (65.67%)/69 (34.33%)	340 (63.79%)/193 (36.21%)	0.635
Age (years)	69 (67–74)	68 (66–73)	70 (67–74)	0.002
Weight (kg)	60 (51–67)	63 (58–71)	57 (50–65)	<0.001
Height (m)	1.65 (1.59–1.70)	1.65 (1.60–1.70)	1.64 (1.58–1.70)	0.032
BMI (kg/m^2)	22.20 ± 3.51	23.70 ± 2.73	21.64 ± 3.60	<0.001
CCI score (0/1/2/ ≥ 3)	276 (37.60%)/263 (35.83%)/100 (13.62%)/ 95 (12.94%)	87 (43.28%)/67 (33.33%)/28 (13.93%)/ 19 (9.45%)	189 (35.46%)/196 (36.77%)/72 (13.51%)/ 76 (14.26%)	0.140
ASA score (I/II/III/IV)	262 (35.70%)/287 (39.10%)/114 (15.53%)/ 71 (9.67%)	82 (40.80%)/74 (36.82%)/26 (12.94%)/ 19 (9.45%)	180 (33.77%)/213 (39.96%)/88 (16.51%)/ 52 (9.76%)	0.308
Surgical types (gastric/intestinal)	415 (56.54%)/319 (43.46%)	118 (58.71%)/83 (41.29%)	297 (55.72%)/236 (44.28%)	0.467
Surgical methods (E/non-E)	562 (76.57%)/172 (23.43%)	165 (82.09%)/36 (17.91%)	397 (74.48%)/136 (25.52%)	0.030
Intraoperative medication				
Dexamethasone (yes/no)	415 (56.54%)/319 (43.46%)	106 (52.74%)/95 (47.26%)	309 (57.97%)/224 (42.03%)	0.202
Parecoxib (yes/no)	421 (57.36%)/313 (42.64%)	125 (62.19%)/76 (37.81%)	296 (55.53%)/237 (44.47%)	0.104
Sufentanil (μg)	25 (20–30)	25 (20–30)	25 (20–30)	0.090

Results are presented as median (interquartile range), mean (± standard deviation) or relative numbers [n (%)]. Groups were compared by using Mann-Whitney U test, t test or chi-square test. GNRI, geriatric nutritional risk index; BMI, body mass index; CCI, Charlson Comorbidity Index; ASA, American Society of Anesthesiologists; E, endoscopic.

$p < 0.001$), 18–24 h (16.51 vs. 7.96%; $p = 0.003$) and 42–48 h (10.51 vs. 4.98%; $p = 0.019$) postoperatively.

In all patients the postoperative cumulative PCIA consumption was 0.15 (0.08–0.26) mL/kg at 0–6 h, 0.44 (0.27–0.67) mL/kg at 18–24 k and 0.64 (0.41–0.96) mL/kg at 42–48 h postoperatively. Patients with GNRI < 92 received significantly more cumulative PCIA consumption compared to patients with GNRI ≥ 92 at 0–6 h (0.16 (0.08–0.27) vs.

TABLE 2 | Comparison of postoperative pain outcomes in different nutritional risk groups as classified by the GNRI.

Outcome	Total ($n = 734$)	GNRI ≥ 92 ($n = 201$)	GNRI < 92 ($n = 533$)	*P* value
Postoperative inadequate analgesia at rest				
0–6 h	100 (13.62%)	12 (5.97%)	88 (16.51%)	<0.001
18–24 h	70 (9.54%)	7 (3.48%)	63 (11.82%)	0.001
42–48 h	29 (3.95%)	4 (1.99%)	25 (4.69%)	0.094
Postoperative inadequate analgesia on movement				
0–6 h	150 (20.44%)	22 (10.95%)	128 (24.02%)	<0.001
18–24 h	104 (14.17%)	16 (7.96%)	88 (16.51%)	0.003
42–48 h	66 (8.99%)	10 (4.98%)	56 (10.51%)	0.019
Postoperative cumulative PCIA consumption (ml/kg)				
0–6 h	0.15 (0.08–0.26)	0.15 (0.07–0.22)	0.16 (0.08–0.27)	0.036
18–24 h	0.44 (0.27–0.67)	0.41 (0.28–0.61)	0.46 (0.27–0.70)	0.103
42–48 h	0.64 (0.41–0.96)	0.60 (0.43–0.92)	0.64 (0.40–1.00)	0.246
Side effects of PCIA				
Nausea/vomiting	101 (13.76%)	21 (10.45%)	80 (15.01%)	0.110
Dizziness	36 (4.90%)	12 (5.97%)	24 (4.50%)	0.412
Abdominal distension	29 (3.95%)	6 (2.99%)	23 (4.32%)	0.409
Urinary retention	6 (0.82%)	2 (1.00%)	4 (0.75%)	0.743
Pruritus	4 (0.54%)	1 (0.50%)	3 (0.56%)	0.915
Respiratory depression	2 (0.27%)	0 (0.00%)	2 (0.38%)	0.384

Results are presented as median (interquartile range) or relative numbers [n (%)]. Groups were compared by using Mann-Whitney U test or chi-square test. GNRI, geriatric nutritional risk index; PCA, Patient-controlled analgesia.

TABLE 3 | Logistic regression analysis investigating possible predictors for postoperative inadequate analgesia.

Population	Predictors	*P* value	OR	Lower 95%CI	Upper 95%CI
Overall ($n = 734$)	Gender	0.023	0.606	0.394	0.932
Overall ($n = 734$)	GNRI	<0.001	3.113	1.661	5.834
Female ($n = 262$)	GNRI	0.003	6.349	1.901	21.201
Early elderly (Age < 75 years, $n = 587$)	GNRI	<0.001	4.302	1.932	9.579

GNRI, geriatric nutritional risk index; OR, odds ratio; CI, confidence interval.

0.15 (0.07–0.22) mL/kg; $p = 0.036$), but not at 18–24 h and 42–48 h postoperatively.

During 48 h follow-up, postoperative nausea and vomiting was the most common side effect of PCIA with the incidence of 13.76%, followed by dizziness (4.90%), abdominal distention (3.95%), urinary retention (0.82%), pruritus (0.54%) and respiratory depression (0.27%). No significant differences were noted regarding the side effects of PCIA among the two groups.

Association of Nutritional Risk With Postoperative Inadequate Analgesia

Secondly, we performed a logistic regression analyses in order to identify possible predictors for postoperative inadequate analgesia at rest during 48 h follow-up. The results showed this overall model was significant (P < 0.001). As presented in **Table 3**, high nutritional risk (OR = 3.113, 95% CI: 1.661–5.834, $P < 0.001$) but not age ($P = 0.172$), BMI ($P = 0.888$), CCI score ($P = 0.539$), ASA score ($P = 0.701$), surgical types ($P = 0.814$), surgical methods ($P = 0.859$) and intraoperative use of dexamethasone ($P = 0.698$), parecoxib ($P = 0.282$) and sufentanil ($P = 0.366$) was identified as a significant predictor for postoperative inadequate analgesia, indicating that the probability of occurrence of postoperative inadequate analgesia in patients with GNRI < 92 was higher than patients with GNRI ≥ 92. In addition, The OR for female gender was 0.606 (95% CI: 0.394–0.932, $P = 0.023$), indicating that, compared with male patients, female patients would have a higher risk to report postoperative inadequate analgesia. Furthermore, sensitivity analyses showed high nutritional risk as a predictor for postoperative inadequate analgesia was more prominent in female patients (OR = 6.349, 95% CI: 1.901–21.201, $P = 0.003$) and early elderly patients (OR = 4.302, 95% CI: 1.932–9.579, $P < 0.001$). Collectively, high nutritional risk was associated with postoperative inadequate analgesia in elderly patients after gastrointestinal surgeries, especially in female individuals and early elderly patients.

Given that GNRI was a predictor for postoperative inadequate analgesia, we used the ROC curve analysis to obtain the area under the curve and an optimal cut-off value of the GNRI. Area under ROC curve was 0.584 (95% CI: 0.531–0.637, $p = 0.007$). GNRI = 88 was determined as an optimal cut-off value with maximum discriminative power. Compared with the original cut-off value of 92, the new cut-off value of 88 had higher specificity (0.465 vs. 0.298) but lower sensitivity (0.730 vs. 0.880).

DISCUSSION

In this large sample of elderly patients after gastrointestinal surgery we showed that GNRI is a significant predictor for postoperative inadequate analgesia at rest during the first 48 h postoperatively. Elderly patients with lower GNRI values were at higher risk to experience inadequate postoperative pain relief than patients with higher GNRI values. Furthermore, we determined that 88 was an optimal cut-off value of GNRI for postoperative inadequate analgesia.

In the first part of the study, we determined the prevalence of nutrition-related risk according to an original GNRI cut-off value of 92. The results showed that majority (almost three quarters) of elderly patients in the current study were at high nutritional risk. A previous prospective cohort study reports the prevalence of severe and moderate risk of nutritional-related complication in hospitalized elderly patients is 41.2% (21). A recent retrospective study shows that 61.6% critical limb ischemia patients are at high nutritional risk (22). Another population-based survey in community-dwelling older persons finds that 69% of participants are at moderate to high nutritional risk (23). This variability is probably due to the differences of population, measurement instruments and cut-off values. Besides, our results showed that older gastrointestinal patients with high nutritional risk are not uncommon and the prevalence of high nutritional risk has always been underestimated. Thus, using of simple nutritional screening instruments (e.g., GNRI) should be included as a standard procedure in routine clinical practice (17).

Next, we compared patient characteristics and postoperative pain outcomes in different nutritional groups. As expected, we observed that patients with lower GNRI showed significantly higher values of age and lower values of weight, height and BMI. Interestingly, less patients with higher nutritional risk received endoscopic surgeries. The probable reason of this phenomenon might be the higher incidence of cardiopulmonary diseases in patients with higher nutritional risk, which was considered to be a relative contraindication to carbon dioxide pneumoperitoneum during endoscopic surgeries (24). Then, our results showed that the prevalence of postoperative inadequate analgesia at rest and movement was higher in patients with GNRI < 92 than patients with GNRI ≥ 92 at different time points. This is consist with a previous study, which shows that pain intensities was higher among patients in low nutritional status than normal patients (25). Another cross-sectional study also shows that the mean nutritional risk score is higher in patients with chronic musculoskeletal pain than patients without chronic musculoskeletal pain (23). Moreover, postoperative cumulative PCIA consumption was higher in patients with GNRI < 92 than patients with GNRI ≥ 92 in the current study. In another word, even the patients with GNRI < 92 received more analgesics, they still experienced severer postoperative pain. Collectively, high nutritional risk may lead to poor pain management in elderly patients after gastrointestinal surgeries and should not be ignored.

In the second part of the study, we explored whether high nutritional risk is a preoperative factor in the prediction of the primary outcome, postoperative inadequate analgesia. Through regression analysis, high nutritional risk was identified as having a negative effect on postoperative pain. This observation consists with the results of Takahashi et al. (25), who found a correlation between the Nutrition Risk Screening 2002 (NRS 2002) scores and the pain intensities. In community-dwelling older persons, nutritional risk was also reported as being independently associated with chronic musculoskeletal pain (23). The association between high nutritional risk and postoperative inadequate analgesia possibly refers to a systemic inflammatory response, which is triggered by undernutrition and might lead to CNS sensitization and amplification of pain through three pathways (26). Firstly, poor nutrition causes peripheral inflammation, which in turn impacts the CNS (27). Secondly, poor nutrition is associated with cell and tissue damage, which triggers Toll-like receptors activation and central immune signaling events (28). Thirdly, poor nutrition can change gut-microbiota composition that results in systemic inflammation (29). Additionally, the high levels of anxiety, depression and chronic pain in malnourished individuals, which are all risk factors for poor postoperative pain management, might contribute to postoperative inadequate analgesia as well (30–32). In addition, female gender was also identified as a predictor of postoperative inadequate analgesia and women experienced worse postoperative pain relief than men. These results agree with our previous observation in orthopedic patients, which shows that female patients represented severer postoperative pain than male patients (20). Furthermore, high nutritional risk as a predictor for postoperative inadequate analgesia was more prominent in female patients and early elderly patients. Collectively, based on the current study, a better analgesic should be considered for postoperative pain management in elderly patients with high nutritional risk, especially in female patients and early elderly patients.

Next, we determined the optimal value of GNRI using ROC curve analysis. GNRI of 88 was identified as an optimal cut-off value for postoperative inadequate analgesia, which was lower than the original cut-off value of GNRI. The original cut-off value was calculated by using the cut-off values for weight loss and albumin in the elderly (weight/WLo = 0.95 and albumin = 35 g/L) (9). The results in the current study indicate that the optimal cut-off value of GNRI might be different in different conditions. However, the trend is the same that the value of GNRI is lower, the nutrition-related risk is higher. Furthermore, the new cut-off value was more specific but less sensitive than the original cut-off value. Given that inaccurate diagnosis of malnutrition will cause unnecessary treatment and increase the cost of hospitalization, the higher specificity of the new

cut-off value is extremely important in nutritional assessment (33). Collectively, GNRI < 88 could be used as a criterion to screen patients' nutrition-related risk of postoperative inadequate analgesia in clinical practice. Early detection of nutrition-related risk before surgeries might contribute to timely nutritional care and the consequent improved postoperative pain outcomes.

Some risk factors for poor postoperative acute pain outcome were identified in previous studies. A large prospective international multicenter database analysis determined 8 risk factors for severe postoperative pain (numeric rating scale ≥ 7 points) (31). Another meta-analysis of 33 articles identified 9 predictors of poor postoperative pain management (32). However, both studies included more than 50,000 patients with appreciable heterogeneity. Thus, a particular predictor identified might not fit for certain specialties like elderly patients. Through the present analysis focusing on elderly patients, some predictors (e.g., female gender) but not others (such as younger age and higher body mass index) were confirmed. Furthermore, GNRI was added as a novel predictor. These predictors might be useful to stratify inadequate analgesia risk, develop population-specific clinical care pathways and improve pain outcomes in elderly patients. In elderly patients with high nutritional risk, standardized assessment of nutritional status, adequate implementation of nutritional support and aggressive treatment of postoperative pain should be considered.

The current study has several limitations. Firstly, the results of the current study are based on postoperative data of one single university hospital. However, the single center data may have the strength because of standard treatment, such as similar anesthesia and postoperative analgesic management. Secondly, this is a retrospective cohort study, which has relatively poor control over the exposure factor, covariates, and potential confounders. Therefore, the data obtained in the current study should be cautiously interpreted. Further prospective randomized trials to verify these results are warranted in the future. Thirdly, the new suggested cut-off value of GNRI had relative low sensitivity and specificity. Further studies are needed to evaluate its validity in larger populations. Finally, the generalizability of this study is limited to elderly patients with gastrointestinal surgery. Whether this conclusion is appropriate for patients undergoing other surgeries needs further analysis and studies in the future.

In conclusion, this retrospective cohort study demonstrated that the majority of the hospitalized elderly patients undergoing gastrointestinal surgeries had high nutrition-related risk using GNRI. In addition, lower GNRI was association with poor postoperative pain outcomes, which indicated the need for early nutritional evaluation and supplementation in elderly patients undergoing gastrointestinal surgeries.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethic Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology (TJ-IRB20190403). The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

HZ and XZ contributed to the conception of the idea and the study design. HZ prepared the data set, performed the analysis, and wrote the manuscript. GD contributed to analysis and interpretation of data. SS and XZ provided intellectual inputs for the project and critical comments on the manuscript. All authors discussed the results and commented on the manuscript.

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Clonidine as an Additive to Local Anesthetics in Caudal Block for Postoperative Analgesia in Pediatric Surgery: A Systematic Review and Meta-Analysis

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Wang Y, Guo Q, An Q, Zhao L, Wu M, Guo Z and Zhang C (2021) Clonidine as an Additive to Local Anesthetics in Caudal Block for Postoperative Analgesia in Pediatric Surgery: A Systematic Review and Meta-Analysis. Front. Med. 8:723191. doi: 10.3389/fmed.2021.723191

Background: Clonidine is an anesthetic with favorable efficacy and safety profiles for caudal epidural block, but comparisons with other adjuvants need to be confirmed in pediatric patients.

Aim: To investigate the effects of clonidine as an adjuvant in caudal epidural block to improve the intraoperative and postoperative analgesia in pediatric surgery.

Methods: PubMed, Embase, and the Cochrane Library were searched for available papers published up to February 2021. The outcomes were pain score, duration of analgesia, complications, and number of analgesic requirements. The meta-analysis was performed using random-effects models.

Results: Fifteen randomized controlled trials (RCTs) were included. There were no differences between clonidine and the control drug regarding the duration of analgesia (SMD = −0.71, 95%CI: −1.64, 0.23; I^2 = 95.5%, $P_{heterogeneity} < 0.001$), pain score (SMD = 0.35, 95%CI: −0.28, 0.98; I^2 = 80.8%, $P_{heterogeneity} < 0.001$), and requirement for additional analgesia (OR = 8.77, 95%CI: 0.70, 110.58, I^2 = 81.9%, $P_{heterogeneity} = 0.004$), but using clonidine resulted in fewer complications than the control drugs (OR = 0.33, 95%CI: 0.20, 0.54, I^2 = 21.8%, $P_{heterogeneity} = 0.217$). The sensitivity analysis showed that the results were robust. A publication bias was observed.

Conclusion: Clonidine has the same efficacy as the other adjuvants for caudal epidural block for pediatric surgery but fewer complications. These results support clonidine as an adjuvant to local anesthetic, but additional studies should be conducted.

Keywords: anesthesia, caudal, epidural, clonidine, children, meta-analysis

INTRODUCTION

Caudal epidural block is widely popular for procedures below the umbilicus since it is a simple, safe, and reliable technique in pediatric patients (1, 2). Using landmark techniques and blind insertion, the success rate is >96% in pediatric patients (3, 4). The high reliability and ease of performance make caudal block one of the most suitable blocks in pediatric surgical patients. The commonly used local anesthetics for caudal block include bupivacaine, levobupivacaine, and ropivacaine. Still, their duration of action is short, and there are concerns of infection over their repeated use or continuous infusion (5). Therefore, adjuvant drugs are necessary to optimize the action of the local anesthetics (6). Various drugs such as opioids, dexmedetomidine, epinephrine, midazolam, ketamine, and neostigmine have been used as adjuvants for caudal epidural block but with various advantages, disadvantages, and adverse effects (7–10).

Clonidine is also used for single-injection caudal blocks (7). It is an α2-adrenergic agonist that produces analgesia without causing significant respiratory depression after caudal administration in children (11–13), although its use in children <3 months is debated because of a hypothetic risk of apnea (12, 13). The use of clonidine as an adjuvant for caudal block achieves appropriate analgesia but with the advantages of prolonged analgesia, reduced residual motor blockade, and increased margin of safety (14–16). A previous meta-analysis of only four trials showed that clonidine is as effective as morphine and with a more beneficial adverse effect profile in children (17), but it did not assess other anesthetics as controls and mainly focused on the side effects. A study compared clonidine vs. dexmedetomidine and showed that adjuvant dexmedetomidine was better than clonidine in terms of sedation, analgesia, and side effects (18), but El-Hennawy et al. (19) reported no differences between the two drugs in pediatric patients undergoing abdominal surgery, and Mota Bonisson et al. (20) reported no change in morphine consumption when adding clonidine to bupivacaine, but the sedation level was higher. Saini et al. (21) reported that clonidine was better than fentanyl as an adjuvant to ropivacaine for infraumbilical pediatric surgery. Evaluating the duration of analgesia and pain are also important factors in pediatric surgery. Given the conflicting results about the use of clonidine in such patients, additional analyses are necessary.

Therefore, this meta-analysis investigated the effects of clonidine as an adjuvant in caudal epidural block to improve the intraoperative and postoperative analgesia in pediatric surgery.

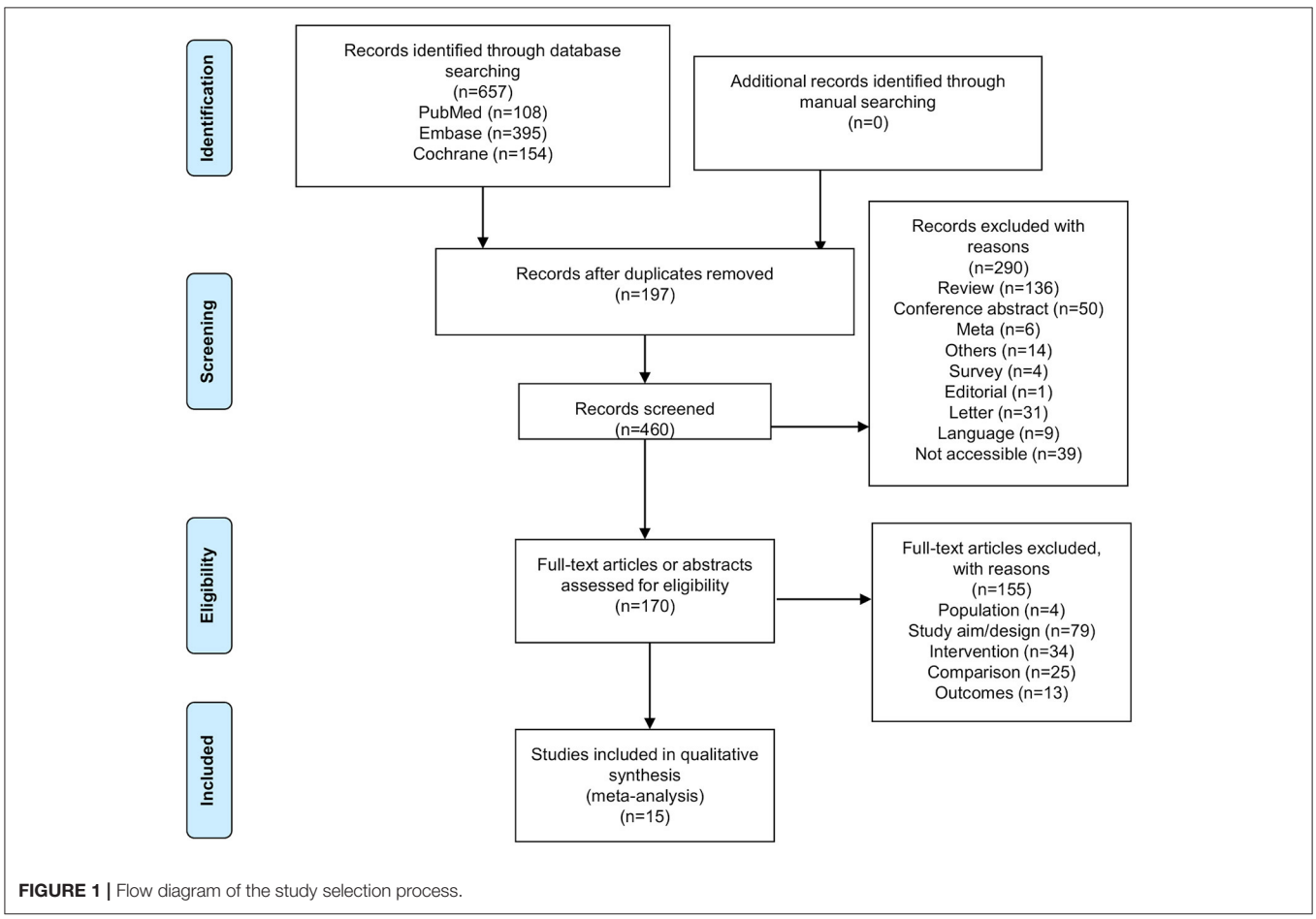

FIGURE 1 | Flow diagram of the study selection process.

TABLE 1 | Literature search and characteristics of the included studies.

References	Design	Country	Surgery	Control	Local anesthetics	Sample size		Age (year, mean, or median)		Weight, kg		Analgesic concentration and usage		
						Clonidine	Control	Clonidine	Control	Clonidine	Control	Clondine	Bupi/ropi/ levobupi	
Akbas et al. (26)	RCT	Turkey	Inguinal hernia repair and circumcision	Ketamine	Ropivacaine	25	25	6.08 (2.87)	5.92 (3.14)	20.34 (8.27)	20.36 (7.8)	1 μg/kg	0.2%, 0.75 ml/kg	lower
Amitha et al. (27)	RCT	India	Lower abdominal/lower limb surgery	Tramadol	Bupivacaine	30	30	8.26 (2.98)	9.03 (2.94)	22.16 (7.78)	26.76 (6.74)	2 μg/kg	0.25%, 0.5 ml/kg	lower
Constant et al. (30)	RCT	France	Bilateral correction of vesicoureteral reflux	Fentanyl	Bupivacaine	16	15	3.6 (0.5–9)	3.8 (1.8–6.5)	15 (5)	16 (4)	1.5 μg/kg	0.25%	lower
Cook et al. (28)	RCT	UK	Unilateral orchidopecy	Ketamine	Bupivacaine	20	20	5.02 (1.3–9)	6.03 (1.5–9)	20.1 (8.8)	23.1 (7.1)	2 μg/kg	0.25%. 1 mL/kg	lower
De Negri et al. (31)	RCT	Italy	Hernia repair/orchidopexy	S-ketamine	Ropivacaine	20	19	3 (1.5)	2.7 (1.2)	12 (7)	13 (5)	2 μg/kg	0.2%, 2 mg/kg	lower
El-Hennawy et al. (19)	RCT	Egypt	Lower abdominal surgery	Dexmedetomidine	Bupivacaine	20	20	3.8 (0.5–5.8)	3.3 (0.7–5)	16 (4.9)	14 (5.2)	2 μg/kg	0.25%, 1 ml/kg	lower
Fernandes et al. (33)	RCT	Brazil	Infraumbilical urological and genital procedures	Morphine	Bupivacaine	20	20	4.7 (2.7)	4.8 (2.6)	17.9 (7.4)	21.6 (11.2)	1 μg/kg	0.166%, 1.0 ml/kg	lower
Luz et al. (29)	RCT	Australia	Orchidopexy, hernia repair, circumcision	Morphine	Bupivacaine	18	18	2.8 (0.6–6)	2.7 (0.7–6.3)	13.9 (7.2–20)	14.2 (7.6–25)	1 μg/kg	0.18%, 1.5 ml/kg	lower
Parag et al. (36)	RCT	India	Hernia repair	Fentanyl	Bupivacaine	40	40	5.4 (2.46)	5.8 (2.63)	16.58 (3.82)	17.7 (6.3)	1 μg/kg	0.5%,	lower
Rawat et al. (35)	RCT	India	Perineal surgery	Tramadol	Levobupivacaine	22	22	4.14 (1.05)	4.23 (2.02)	11.64 (2.25)	12.2 (2.6)	1 μg/kg	0.25%. 1 mg/kg	lower
Sanwatsarkar et al. (9)	RCT	India	Infraumbilical surgery	Midazolam	Bupivacaine	25	25	6.28 (1.21)	6.16 (1.11)	15.48 (3.34)	14.96 (2.88)	1 μg/kg	0.25%. 1 mg/kg	lower
Shukla et al. (40)	RCT	Etawah	Infraumblical	Fentanyl	Ropivacaine	45	45	5.1 (3–7)	4.1 (3.3–7.8)	18 (6.2)	15 (7.2)	2 μg/kg	0.25%, 1 ml/kg	
Singh et al. (24)	RCT	Nepal	Below umbilical surgeries	Fentanyl	Bupivacaine	10	20	5.45 (2.5)	5.7 (2.8)	14.7 (3.8)	14.75 (4)	1 μg/kg	0.25%, 0.75 ml/kg	lower
Singh et al. (24)	RCT	Nepal	Below umbilical surgeries	Ketamine	Bupivacaine	10	20	5.45 (2.5)	5.3 (1.8)	14.7 (3.8)	16.85 (4.19)	1 μg/kg	0.25%, 0.75 ml/kg	lower
Singh et al. (34)	RCT	India	Upper abdominal surgery	Dexmedetomidine	Bupivacaine	25	25	2.9 (1–6)	2.8 (1.5–6)	11.3 (3.1)	11.8 (2.18)	2 μg/kg	0.2%, 1.25 ml/kg	upper
Vetter et al. (6)	RCT	USA	Ureteral reimplantation	Morphine	Ropivacaine	10	20	3.5 (1.7)	3.4 (1.8)	16 (6)	15 (4)	2 μg/kg	0.2%, 1.0 ml/kg	lower
Vetter et al. (6)	RCT	USA	Ureteral reimplantation	Hydromorphone	Ropivacaine	10	20	3.5 (1.7)	3.4 (1.8)	16 (6)	16 (5)	2 μg/kg	0.2%, 1.0 ml/kg	lower

METHODS

Literature Search

This systematic review and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (22). The research approach was designed using the PICOS principle (23). PubMed, Embase, and the Cochrane Library were searched for available papers published up to February 2021 using the MeSH terms "children," "pediatric," "bupivacaine," "levobupivacaine," "ropivacaine," "clonidine," and "analgesia," as well as relevant key words, followed by screening based on the inclusion/exclusion criteria. The records were first evaluated based on the titles, followed by an assessment based on the abstracts and full-text. In the case of multiple using the same study population, only the most recent one matching the eligibility criteria was included.

Eligibility Criteria

The eligibility criteria were (1) population: children, (2) local anesthetics: bupivacaine, ropivacaine, or levobupivacaine, (3) adjuvant in the intervention group: clonidine, (4) adjuvant in the control group: any drug other than clonidine, but not a placebo, (5) outcome: pain score, duration of analgesia, complications, and additional analgesia requirements, (6) study design: randomized controlled trials (RCTs), and (7) full-text article published in English. Reviews, meta-analyses, case reports, letters to the editor, and comments were excluded.

Data Extraction

Study characteristics (authors, year of publication, country, and study design), patient characteristics (sex, sample size, weight, and previous surgery), anesthesia characteristics (local anesthetic, analgesia in control group, analgesic concentration, and usage), outcomes (duration of analgesia, pain score, need for additional analgesia, and complications were extracted by two different investigators Qi An and Lin Zhao) according to a pre-specified protocol. In multiple arm studies (6, 24), the sample size was divided by the times it has been compared, and the generated sample size was used as the sample size of each subgroup, as previously described (25). Discrepancies were solved by discussion until a consensus was reached.

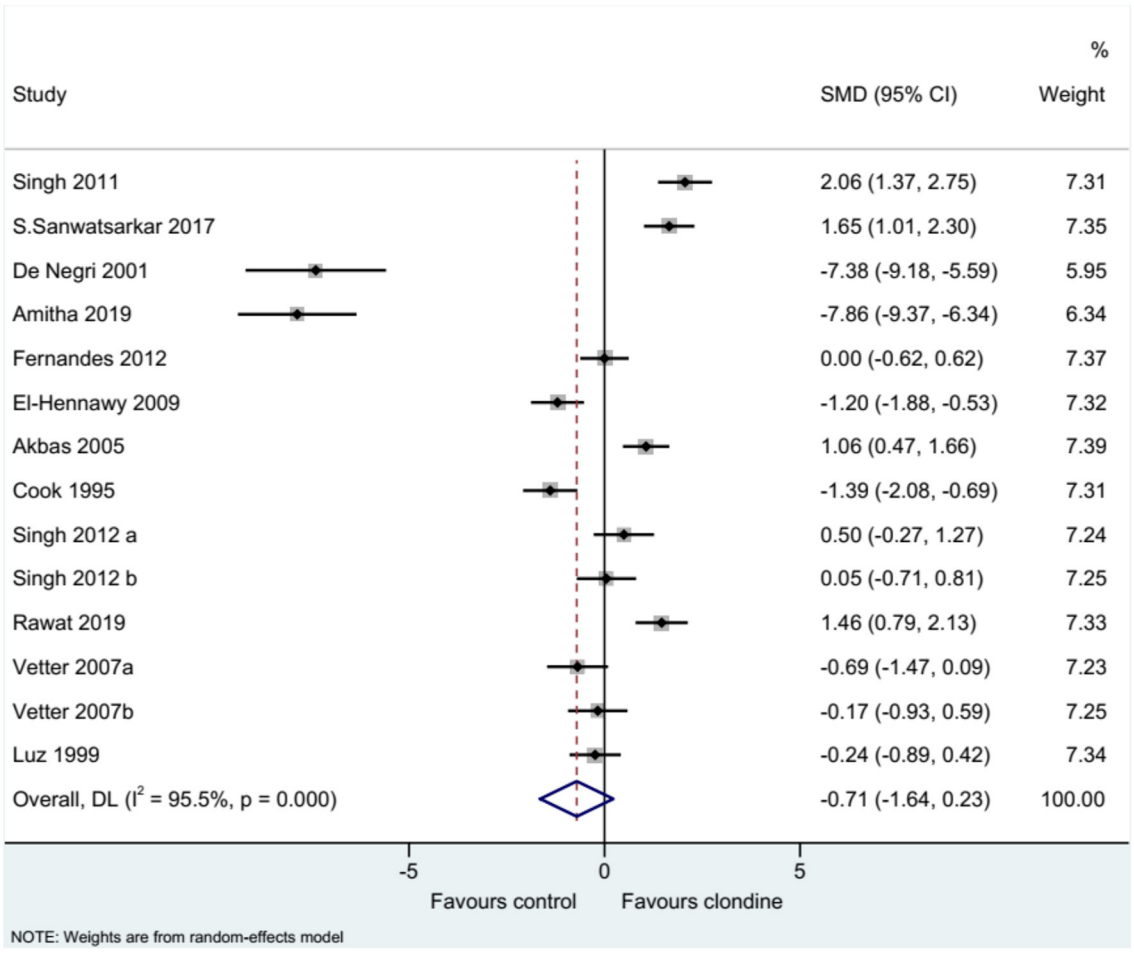

FIGURE 2 | Duration of analgesia duration.

Pain Evaluation

The pain was evaluated using the Objective Pain Score (OPS) (24, 26–29), Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) (30, 31), Face, Legs, Activity, Cry, and Consolability (FLACC) (6, 9, 19, 32–34), Children and Infants Postoperative Pain Scale (CHIPPS) (35), pinprick at each dermatome (36), or a visual analog scale (30). When possible, the pain was evaluated as a continuous variable for comparisons between the two groups. The studies that reported pain as a categorical variable were analyzed separately.

Quality of the Evidence

The level of evidence of all articles was assessed independently by two authors (YeWang and QianqianGuo) according to Version 2 of the Cochrane risk-of-bias assessment tool for randomized trials (RoB 2) (37, 38). The studies were evaluated using Grading of Recommendations Assessment Development and Evaluation (GRADE) (39). Discrepancies in the assessment were resolved through discussion until a consensus was reached.

Statistical Analysis

All analyses were performed using STATA SE 14.0 (StataCorp, College Station, Texas, USA). The standardized mean difference (SMD) and 95% confidence intervals (CI) were used for continuous variables, and odds ratio (OR) with 95%CI were used for categorical variables. Statistical heterogeneity among studies was calculated using Cochran's *Q*-test and the I^2 index. An $I^2 > 50\%$ and *Q*-test $P < 0.10$ indicated high heterogeneity. The meta-analysis was performed using random-effects models. *P*-values <0.05 were considered statistically significant. Sensitivity analyses were performed to assess the robustness of the original analyses. In addition, subgroup analyses were performed. Finally,

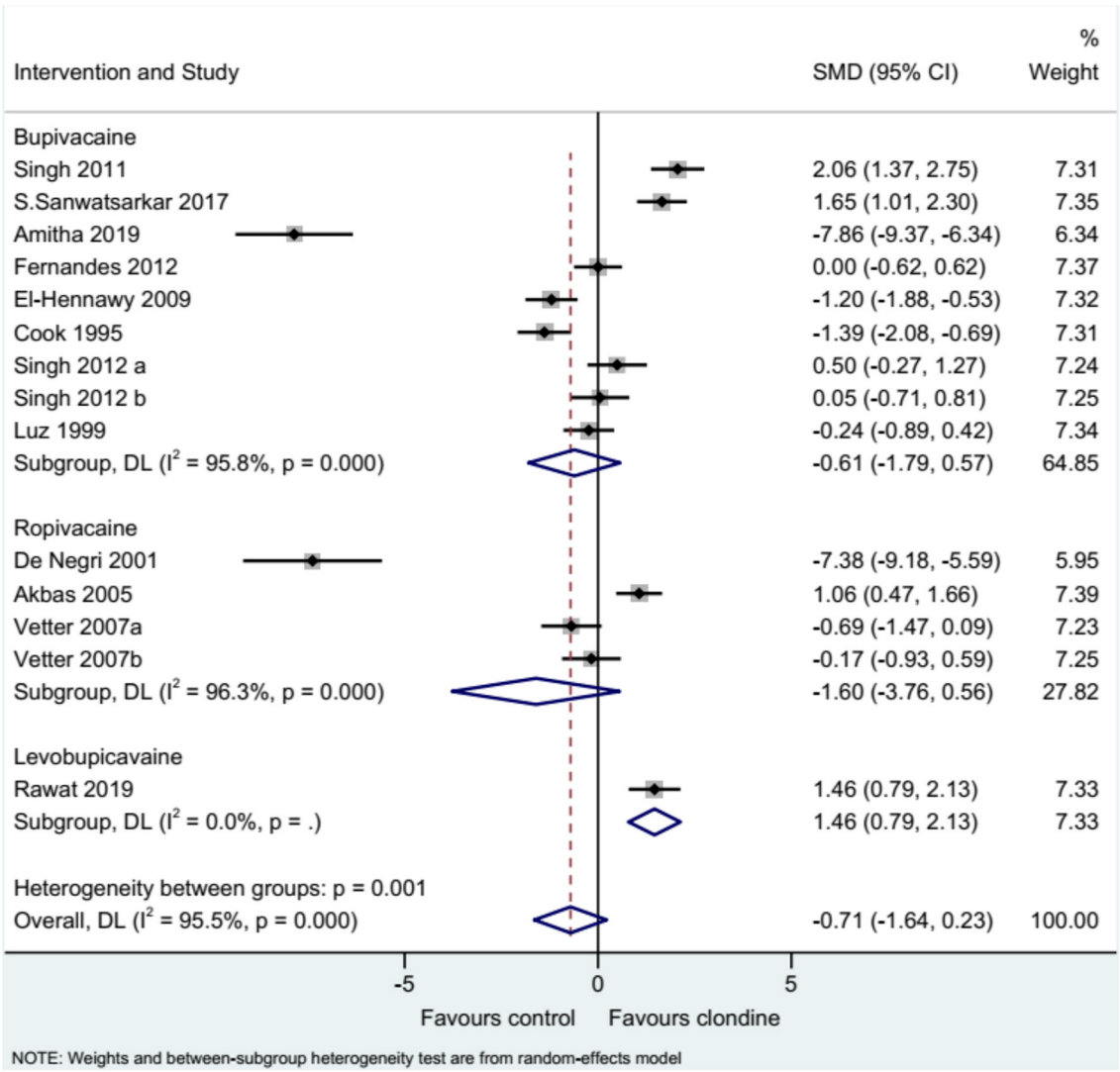

FIGURE 3 | Subgroup analysis of analgesia duration by various local anesthetics.

potential publication bias was assessed using Egger's test, Begg's test, and the trim-and-fill method (37).

RESULTS

Selection of the Studies

Figure 1 presents the study selection process. The initial database search identified 657 records. After removing the duplicates, 460 records were screened, and 290 were excluded. Then, 170 abstracts or full-text articles were assessed for eligibility, and 155 were excluded (population, $n = 4$; study aim/design, $n = 79$; intervention, $n = 34$; comparison, $n = 25$; outcomes, $n = 13$). Finally, 15 articles were included.

Table 1 presents the characteristics of the studies and patients. Fifteen studies (17 datasets; 770 patients) were included. The control groups included ketamine (24, 26, 28, 31), tramadol (27, 35), fentanyl (24, 30, 36, 40), dexmedetomidine (19, 34), morphine (6, 29, 33), midazolam (9), and hydromorphone (6). The local anesthetics included ropivacaine (6, 26, 31, 40), bupivacaine (9, 19, 24, 27–30, 33, 34, 36), and levobupivacaine (35). **Supplementary Table 1** shows the quality evaluation. Seven studies had a low risk of bias, while eight studies had an unclear risk of bias for at least one item of the RoB 2 tool. **Supplementary Table 2** shows the GRADE analysis. The pain score and the duration of analgesia had critical importance, and both showed moderate certainty. The requirement for additional analgesia was important and showed a high level of certainty. Complications were important and displayed a moderate level of certainty.

Duration of Analgesia

Twelve studies (14 datasets) reported the duration of analgesia. There was no difference between clonidine and the control drug regarding the duration of analgesia (SMD = −0.71, 95%CI: −1.64, 0.23; $I^2 = 95.5\%$, $P_{heterogeneity} < 0.001$) (**Figure 2**). A subgroup analysis was performed according to the type of local anesthetic, and there were no differences between clonidine and the control drug in the presence of bupivacaine (SMD = −0.61, 95%CI: −1.79, 0.57, $I^2 = 95.8\%$, $P_{heterogeneity} < 0.001$) or ropivacaine (SMD = −1.60, 95%CI: −3.76, 0.56,

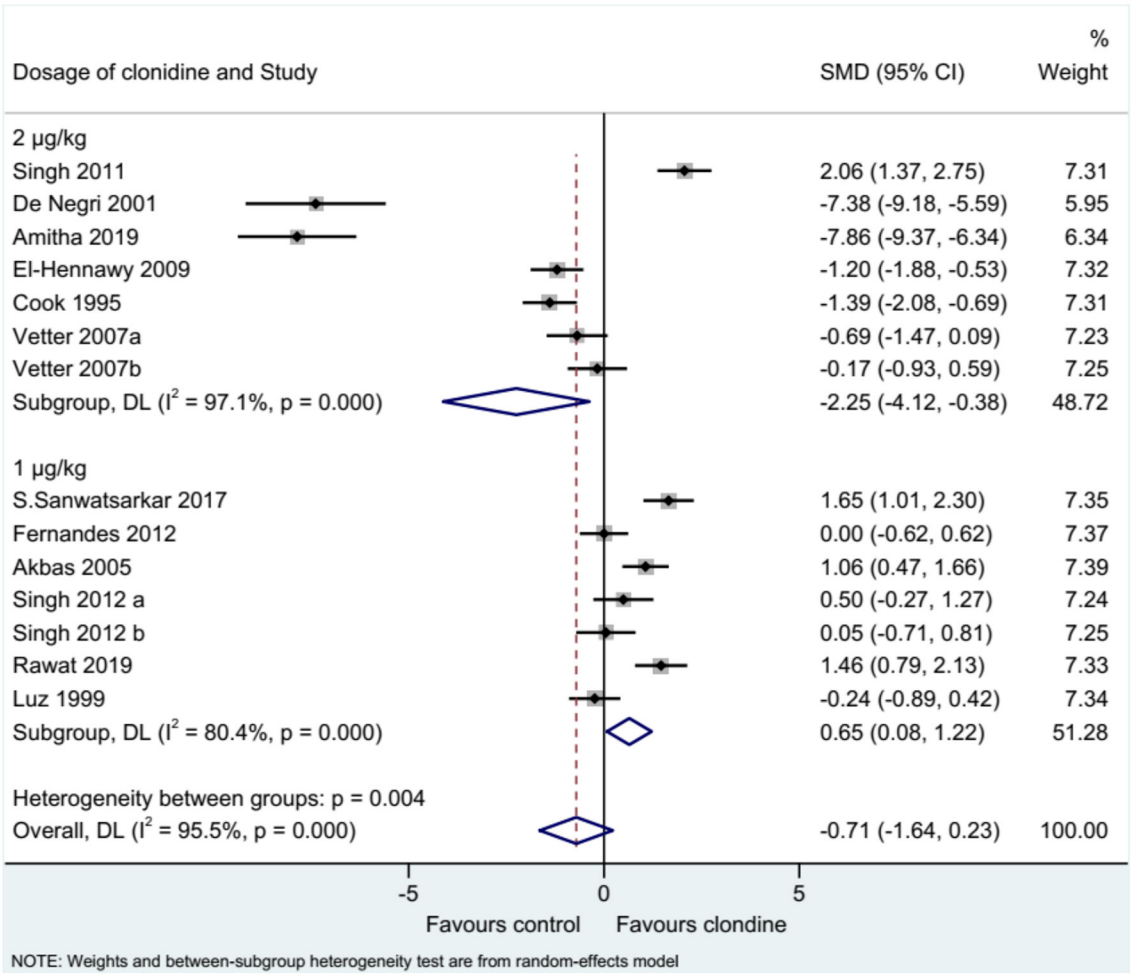

FIGURE 4 | Subgroup analysis of analgesia duration by the dosage of clonidine.

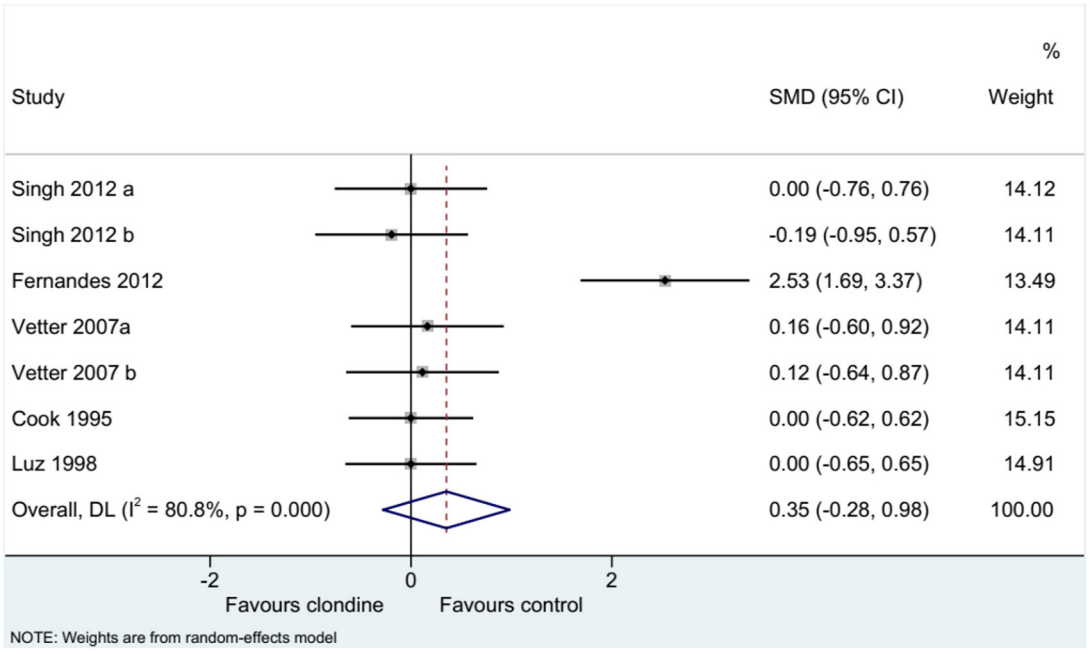

FIGURE 5 | Pain score (continuous variables).

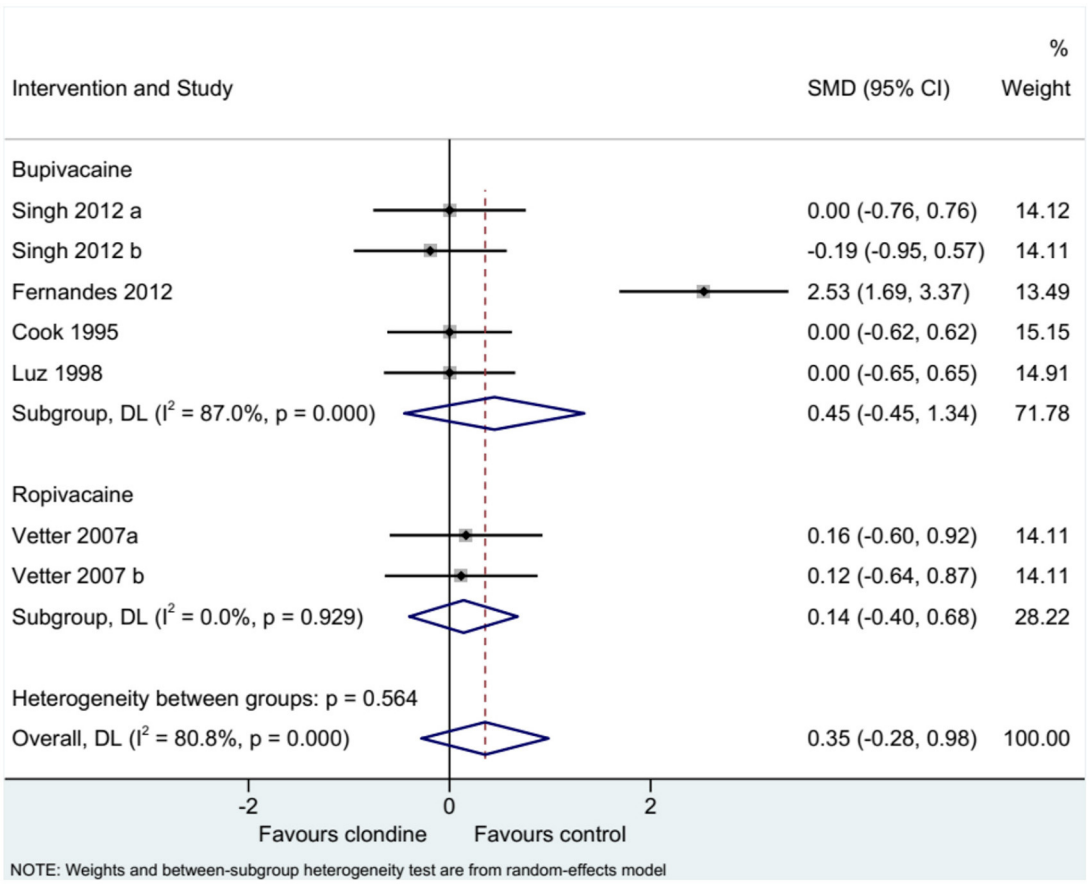

FIGURE 6 | Subgroup analysis of pain score by local anesthetic.

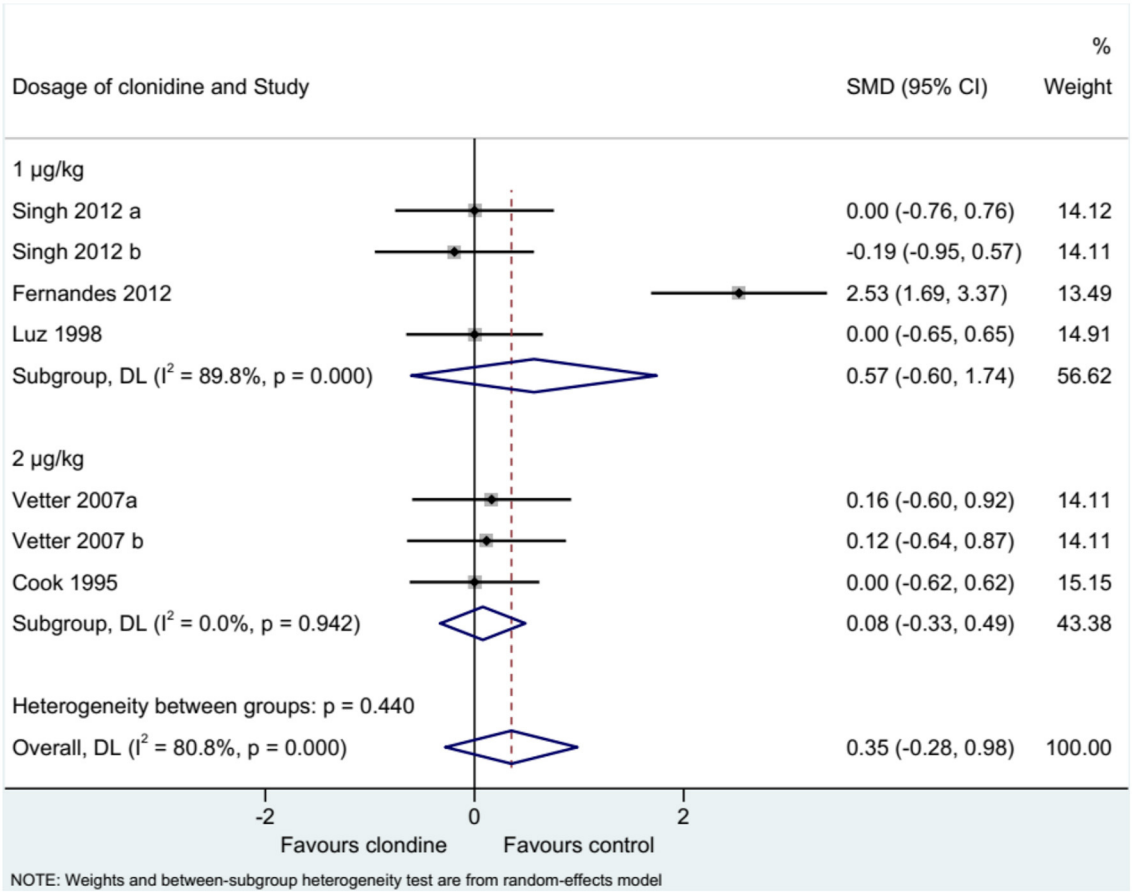

FIGURE 7 | Subgroup analysis of pain score by the dosage of clonidine.

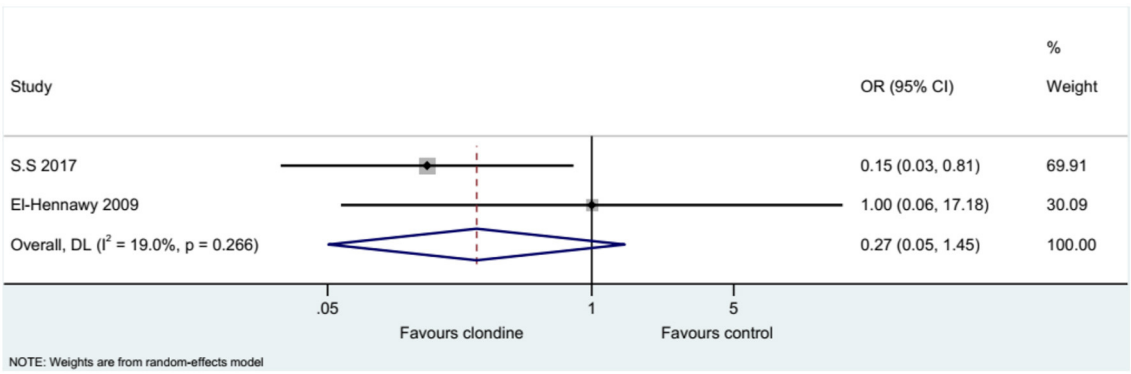

FIGURE 8 | Pain score (categorical variables).

I^2 = 96.3%, $P_{heterogeneity}$ < 0.001), but one study favored clonidine with levobupivacaine (SMD = −1.46, 95%CI: 0.79, 2.13) (**Figure 3**). Regarding the dose of clonidine, the use of clonidine 2 μg/kg favored the control drug (SMD = −2.25, 95%CI: −4.12, −0.38, I^2 = 97.1%, $P_{heterogeneity}$ < 0.001), while the use of clonidine 1 μg/kg favored clonidine (SMD = 0.65, 95%CI: −0.08, 1.22, I^2 = 80.4%, $P_{heterogeneity}$ = 0.004) (**Figure 4**).

Pain Score

Five studies (seven datasets) analyzed pain (as a continuous variable). There were no differences between clonidine and the

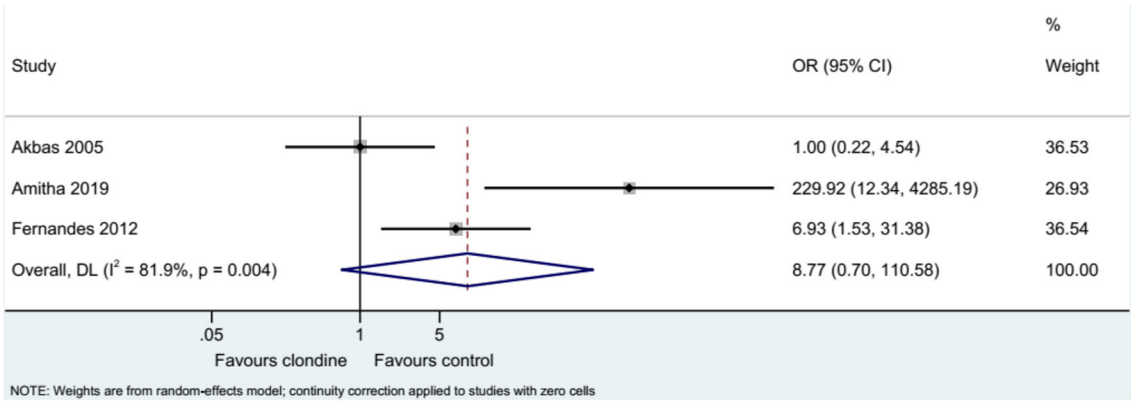

FIGURE 9 | Total numbers of analgesia of post-requirements.

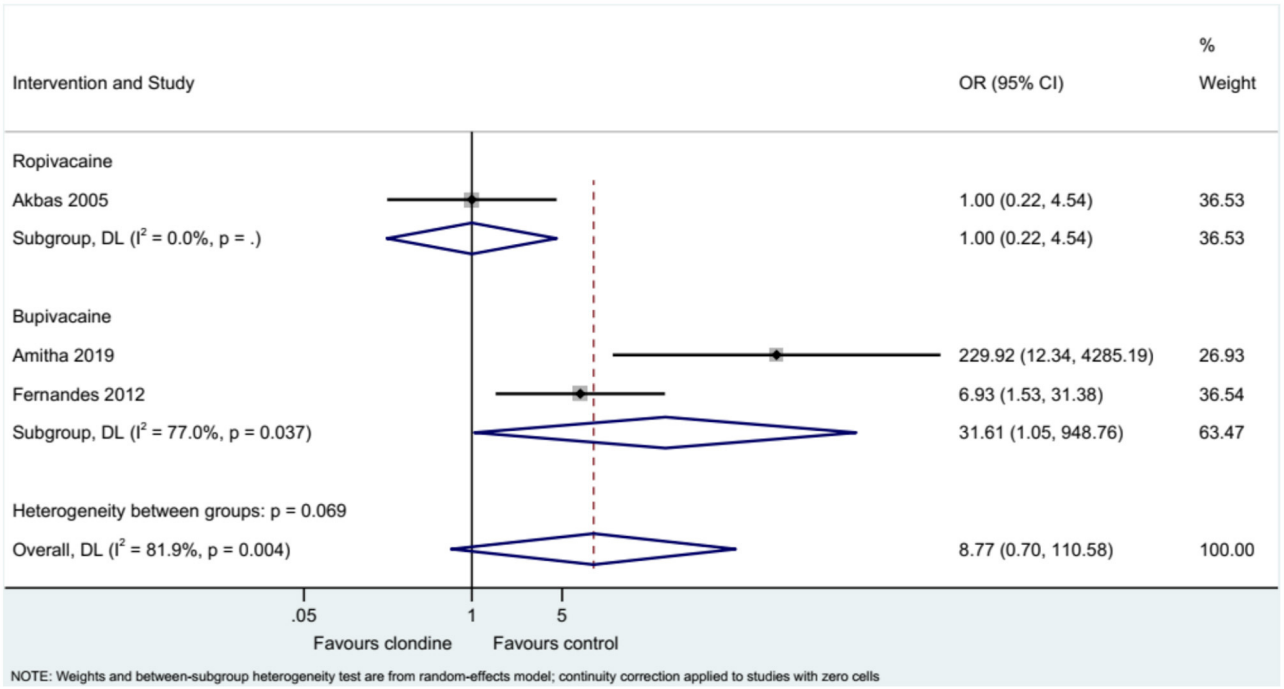

FIGURE 10 | Subgroup analysis of post-requirements by local anesthetic.

control drugs regarding pain (SMD = 0.35, 95%CI: −0.28, 0.98; I^2 = 80.8%, $P_{heterogeneity}$ < 0.001) (**Figure 5**). Similar results were obtained when considering buvicaine (SMD = 0.45, 95%CI: −0.45, 1.34, I^2 = 87.0%, $P_{heterogeneity}$ < 0.001) or ropivacaine (SMD = 0.14, 95%CI: 0.40, 0.68, I^2 = 0.0%, $P_{heterogeneity}$ = 0.929) as the local anesthetic (**Figure 6**), or when considering clonidine 2 μg/kg (SMD = 0.57, 95%CI: −0.60, 1.74, I^2 = 89.8%, $P_{heterogeneity}$ < 0.001) or 1 μg/kg (SMD = 0.08, 95%CI: −0.33, 0.49, I^2 = 0.0%, $P_{heterogeneity}$ = 0.440) (**Figure 7**). Two studies examined pain as a categorical variable showed no difference between clonidine and the control drugs (OR = 0.27, 95%CI: 0.05, 1.45, I^2 = 19.0%, $P_{heterogeneity}$ = 0.266) (**Figure 8**).

Requirement for Additional Analgesia

Three studies examined the requirement for analgesia and showed no difference between clonidine and the control drugs (OR = 8.77, 95%CI: 0.70, 110.58, I^2 = 81.9%, $P_{heterogeneity}$ = 0.004) (**Figure 9**). The requirement for analgesia was not influenced by ropivacaine (OR = 1.00, 95%CI: 0.22, 4.54), but using bupivacaine favored the control drugs in terms of the requirement for additional analgesia (OR = 31.61, 95%CI: 1.05, 948.76, I^2 = 77.0%, $P_{heterogeneity}$ = 0.037) (**Figure 10**). The requirement for analgesia was not influenced by clonidine 1 μg/kg (OR = 1.00, 95%CI: 0.22, 4.54), but using clonidine 2 μg/kg favored the control drugs in term of requirement

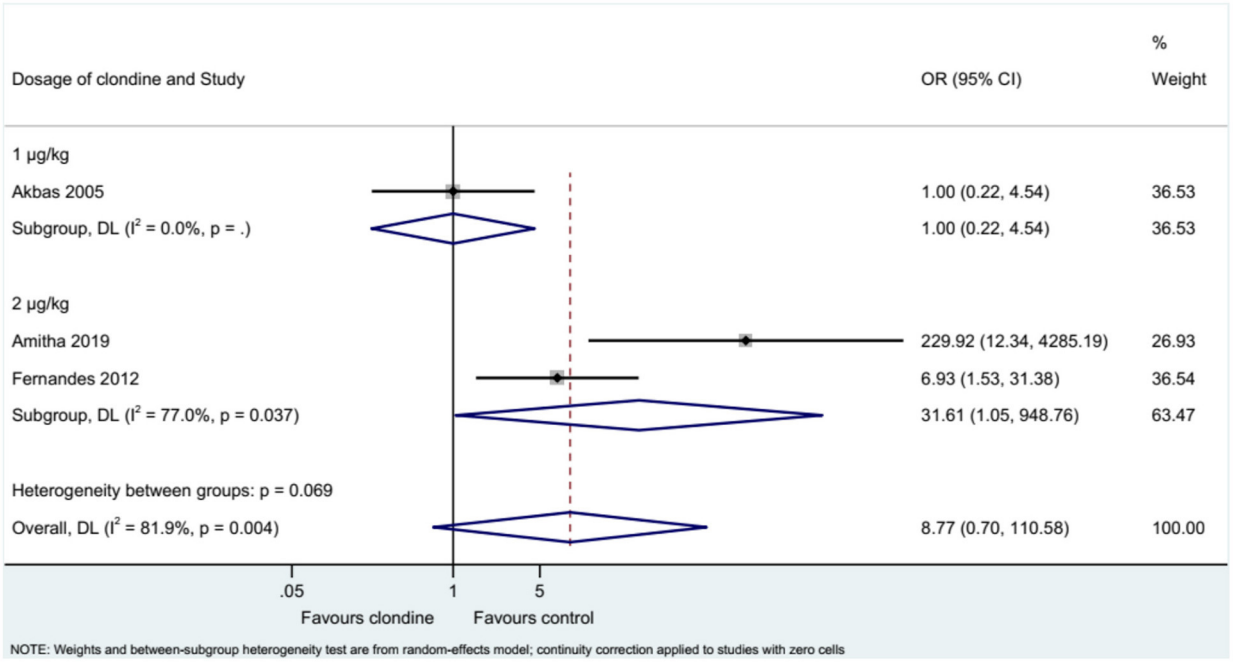

FIGURE 11 | Subgroup analysis of post-requirements by the dosage of clonidine.

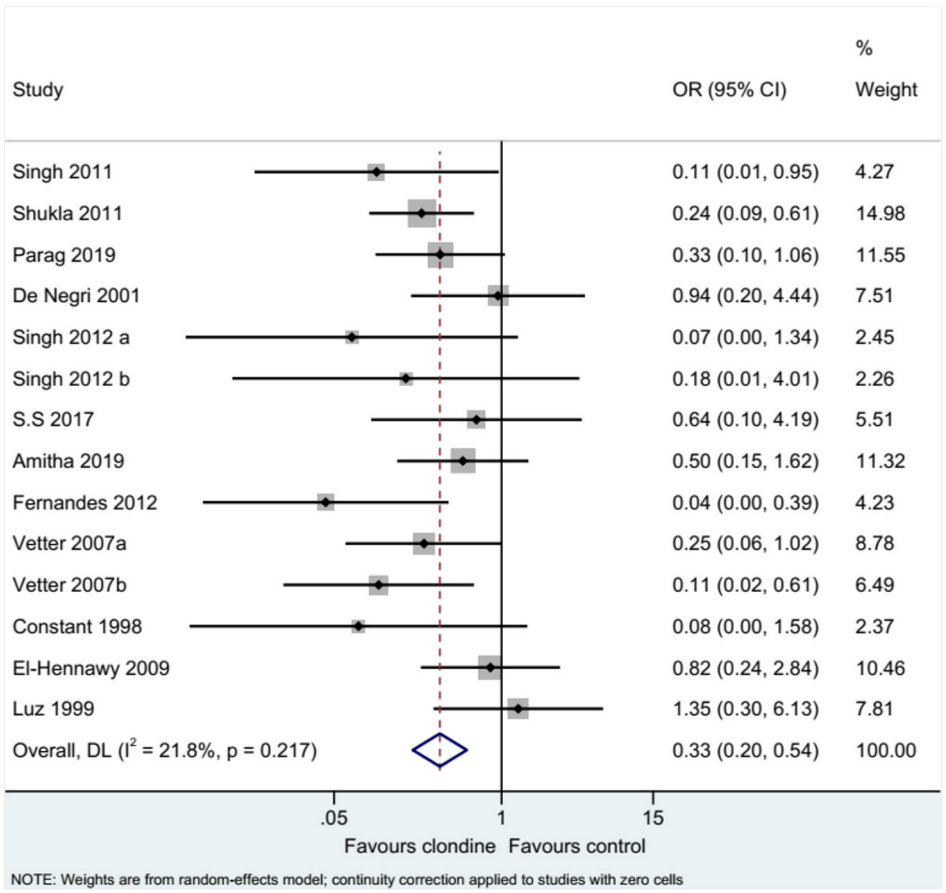

FIGURE 12 | Complications.

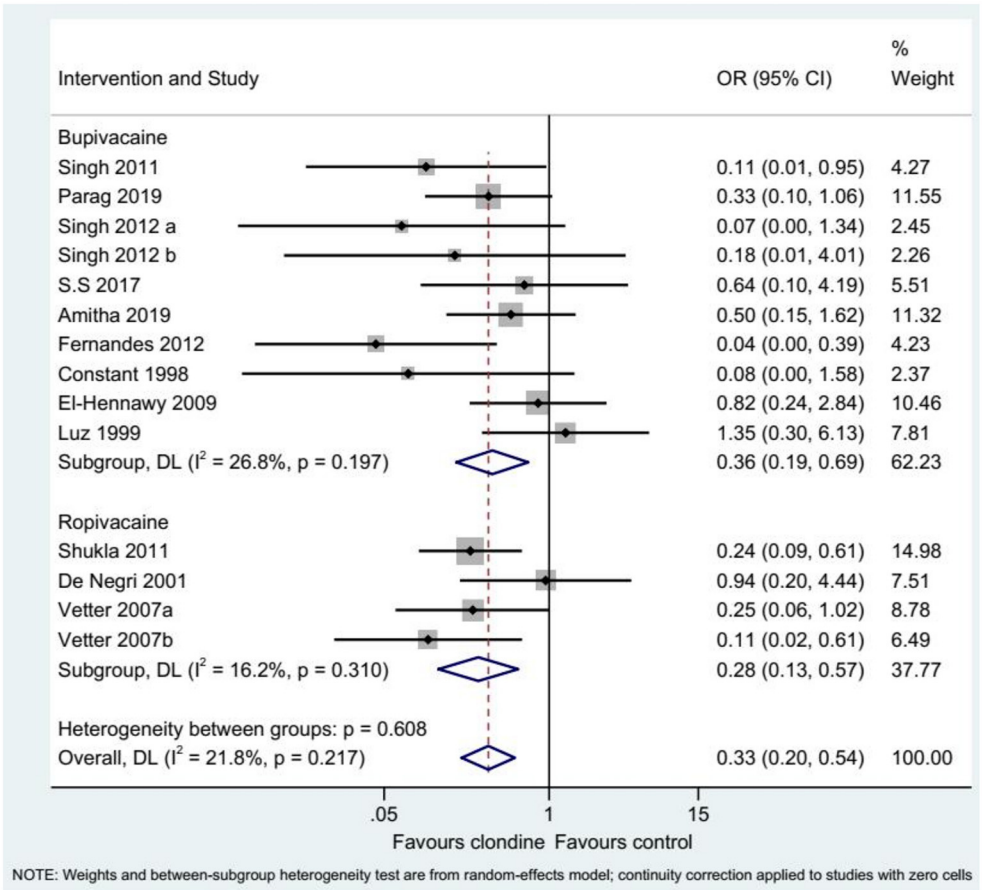

FIGURE 13 | Subgroup analysis of complications by local anesthetic.

for analgesia (OR = 31.61, 95%CI: 1.05, 948.76, I^2 = 77.0%, $P_{heterogeneity}$ = 0.037) (**Figure 11**).

Complications

Twelve studies (14 datasets) reported the complications of caudal epidural block. Using clonidine resulted in fewer complications than the control drugs (OR = 0.33, 95%CI: 0.20, 0.54, I^2 = 21.8%, $P_{heterogeneity}$ = 0.217) (**Figure 12**). Similar results were observed when using either bupivacaine (OR = 0.36, 95%CI: 0.19, 0.69, I^2 = 26.8%, $P_{heterogeneity}$ = 0.197) or ropivacaine (OR = 0.28, 95%CI: 0.13, 0.57, I^2 = 16.2%, $P_{heterogeneity}$ = 0.310) as the local anesthetic (**Figure 13**), or when using clonidine 2 μg/kg (OR = 0.35, 95%CI: 0.20, 0.61, I^2 = 19.1%, $P_{heterogeneity}$ = 0.284) or clonidine 1 μg/kg (OR = 0.31, 95%CI: 0.11, 0.86, I^2 = 39.4%, $P_{heterogeneity}$ = 0.143), but not clonidine 1.5 μg/kg (OR = 0.08, 95%CI: 0.00, 1.58) (**Figure 14**).

Sensitivity Analysis

Supplementary Figures 1–3 show that the results of analgesia duration, the requirement for additional analgesia, and complications were robust.

Publication Bias

Begg's test (P = 0.049) and Egger's test (P = 0.001) indicate the presence of a significant publication bias. The results of the trim-and-fill analysis suggest that an additional 14 RCTs would be necessary to change this conclusion (**Supplementary Figure 4**).

DISCUSSION

Clonidine is an anesthetic with favorable efficacy and safety profiles for use in caudal epidural block in children. This meta-analysis aimed to investigate the effects of clonidine as an adjuvant in caudal epidural block to improve the intraoperative and postoperative analgesia in pediatric surgery. The results suggest that clonidine has the same efficacy as the control drugs for caudal epidural block for pediatric surgery but fewer complications. Thus, these results support clonidine as an adjuvant to local anesthetic, but additional studies should be conducted.

A previous meta-analysis compared clonidine and morphine for caudal epidural block using only four studies and only morphine as control (17). Their results showed no differences regarding analgesia duration and the need for rescue analgesia,

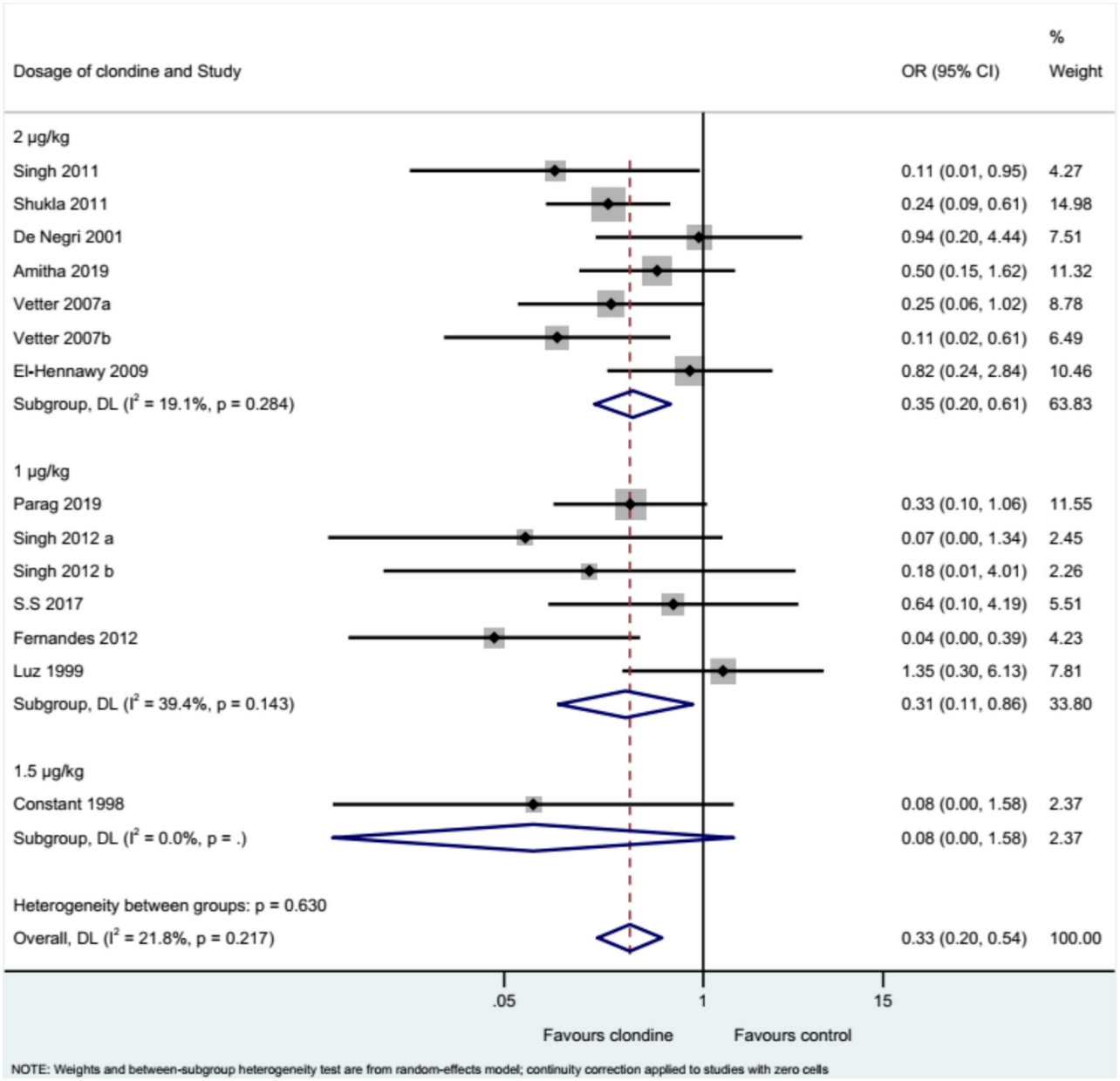

FIGURE 14 | Subgroup analysis of complications by the dosage of clonidine.

as in the present study and a meta-analysis of clonidine vs. Dexmedetomidine (18). Still, many drugs are available besides morphine for caudal block, limiting the generalizability of that previous meta-analysis. A review suggested that epidural clonidine might be more effective than opioids to manage chronic pain (41). A meta-analysis reported that dexmedetomidine had better analgesic effects than clonidine for hysterectomy (42). In the present meta-analysis, many studies reported no difference between clonidine and the comparator regarding analgesia duration (6, 24, 29, 33), while some studies favored either clonidine (9, 26, 34, 35) or the comparator (19, 27, 28, 31). Of course, the nature of the comparator might play an important role in the conclusions of the individual studies.

Clonidine inhibits the release of nociceptive neurotransmitters (33). The adverse effects of clonidine are mainly related to the excitation of α2 inhibitory neurons in the medulla vasomotor center, leading to decreased norepinephrine secretion (43). In addition, clonidine decreases the electrical activity of preganglionic parasympathetic nerves and reduces sympathetic drive, resulting in bradycardia (43, 44). Still, the other drugs commonly used for caudal epidural block also have adverse effects, like hemodynamic effects for dexmedetomidine

(45), gastrointestinal dysmotility, nausea/vomiting, pruritus, and respiratory depression for opioids (12, 46), and neuronal apoptosis for ketamine (12, 46, 47). In the present study, the complications were less important with clonidine than with the other drugs. The meta-analysis by Goyal et al. (17) also reported less nausea/vomiting with clonidine than with morphine.

In the present meta-analysis, nearly all analyses showed significant heterogeneity. This heterogeneity could be explained by differences among the included studies regarding the age of the children, the type of surgeries, the comparator drug, the local anesthetic, and the dose of clonidine. Subgroup analyses were performed regarding the local anesthetics and the clonidine dose. The results showed that using bupivacaine instead of ropivacaine was associated with a higher requirement for additional analgesia than the control group, while the choice of local anesthetic did not influence the other parameters. Regarding the dose of clonidine, using a higher dose favored the control drugs in analgesia duration and requirement for additional analgesia while having no impact on pain and complications. Therefore, using a lower dose (1 μg/kg) could be conducive to better results, especially regarding the duration of analgesia. These results are still surprising because Lee et al. (48) reported longer analgesia with a higher dose. Still, Singh et al. (24) reported that a lower dose of clonidine combined with bupivacaine fared better than the other drug combinations. Therefore, the subgroup analyses in the present study must be taken with caution, especially considering the different combinations of drugs and clonidine doses. Additional studies are necessary on this point.

Assessment of pain is complex in children and can be based only on physiological and behavioral parameters since young children cannot communicate verbally (49). The exact source of pain is difficult to determine, but understanding the various patterns of cues used by children to manifest pain is a complex undertaking (49). Different tools are recommended according to the verbal/non-verbal status of the patients (50). In addition, the included studies used various pain scale assessments, including OPS (24, 26–29), CHEOPS (30, 31), FLACC (6, 9, 19, 32–34), CHIPPS (35), pinprick at each dermatome (36), or a VAS (30), participating in heterogeneity. Even if all these assessments assess pain, they use different indicators (51). CHEOPS is validated for children of 1–7 years, FLACC for 2 months-7 years, CHIPPS for 0–5 years, OPS for 8 months-13 years, and VAS starting from 5 years (51). In addition, Sanwatsarkar et al. (9) and El-Hennawy et al. (19) presented their pain results in categorical variables based on the FLACC pain scale.

The strengths of this meta-analysis include a relatively large number of studies (only RCTs, leading to a high level of evidence) and a large number of patients. Still, this meta-analysis has limitations. As for any such study, a meta-analysis inherits the limitations of all the included studies, and caution must be applied while extrapolating the results. Two studies included multiple arms (6, 24), which were dealt with using a specific method (25). Although this method might introduce bias, it is a feasible way to deal with the problem of multiple arm studies being compared repeatedly.

In conclusion, clonidine has the same efficacy as the other adjuvants for caudal epidural block for pediatric surgery but fewer complications. These results support clonidine as an adjuvant to local anesthetic, but additional studies should be conducted because of a significant publication bias.

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

YW conceived and coordinated the study, designed, performed and analyzed the experiments, and wrote the paper. QG, QA, LZ, MW, ZG, and CZ carried out the data collection and data analysis and revised the paper. All authors reviewed the results and approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

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The Optimal Dose of Intraoperative Dexmedetomidine for Antiemetic Effects of Post-operative Nausea and Vomiting in Patients Undergoing Elective Thoracic Surgery: A Retrospective Cohort Study

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Background: Dexmedetomidine (DEX) administration decreases post-operative nausea and vomiting (PONV), but it is a lack of large-scale retrospective cohort study and is unclear whether there is a dose-relationship and optimal dose for antiemetic effects between DEX and PONV. We performed a large-scale retrospective cohort study to explore the optimal dose of intraoperative DEX for antiemetic effects of PONV.

Methods: A total of 5,310 patients aged ≥18 who underwent elective thoracic surgery from January 2016 to March 2020 under total intravenous anesthesia (TIVA) or combined intravenous and inhalation anesthesia in Henan Provincial People's Hospital. Patients were divided into two groups, those who received DEX intraoperatively and those who did not receive DEX. Patients who received DEX after surgery were excluded. Our primary outcomes were the association, the dose-response relationship, and the optimal dose for antiemetic effects between intraoperative DEX and PONV.

Results: Among the 3,878 patients enrolled, 2,553 patients received DEX and 1,325 patients did not receive DEX. The incidence of PONV in patients who received DEX was 21.3%, and the incidence of PONV in patients who did not receive DEX was 46.5% ($P = 0.001$). After the matched-pairs cohort consisted of 1,325 patients, the incidence of PONV in patients who received DEX was 23.6%, and the incidence of PONV in patients who did not receive DEX was 46.5% ($P = 0.001$). We analyzed three different models after propensity matching to validate the stability of the prediction model between intraoperative DEX and PONV. A dose-response relationship between intraoperative DEX and PONV was observed. The optimal dose range of intraoperative DEX for antiemetic effects of PONV is 50–100 μg in elective thoracic surgery.

Conclusions: Intraoperative DEX was associated with a decreased incidence of PONV in the large-scale retrospective cohort study. A dose-response relationship between intraoperative DEX and PONV was observed. The optimal dose range of intraoperative DEX for antiemetic effects of PONV is 50–100 μg in elective thoracic surgery.

Keywords: post-operative nausea and vomiting, dexmedetomidine, thoracic surgery, retrospective cohort, optimal dose

INTRODUCTION

Post-operative nausea and vomiting (PONV) include any nausea, retching or vomiting that occurs during the first 24 post-operative h (1). Vomiting can cause electrolyte imbalance and aggravate pain, even delaying discharge (2). Patients undergoing thoracic surgery experience severe pain after operation when the consumption of analgesic morphine is high, and the use of morphine is associated with nausea, vomiting, sedation and respiratory depression during acute morphine therapy (3, 4).

Fortunately, according to the fourth consensus guideline for post-operative nausea and vomiting management (5), many recommended strategies for routinely reducing the baseline risk of PONV are pointed out, including that perioperative dexmedetomidine (DEX) (evidence A1) (6). DEX 1 μg/kg before skin incision reduced the incidence of PONV after laparoscopic cholecystectomy, and PONV benefits were confirmed when DEX was added to an IV sufentanil-ondansetron PCA after thoracotomy.

However, in terms of the effect of DEX on PONV, several aspects remain unclear: (1) It is a lack of large sample size retrospective cohort study. (2) It is unclear whether there is a dose-relationship between DEX and PONV. (3) It is unclear about optimal dose of DEX for antiemetic effects.

Therefore, we hypothesized that a dose-response relationship between intraoperative DEX and PONV in elective thoracic surgery was existed. We conducted a retrospective cohort study to test this hypothesis and to explore the optimal dose of intraoperative DEX on PONV.

METHODS

Overall Design and Data Source

This was a retrospective cohort study based on the Henan Provincial People's Hospital of China. In preparing this article, the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist for cohort studies was cited. The STROBE checklist for cohort studies was referenced when preparing the article. Study design, outcome variables, and analysis plan were identified before performing the data analysis. The main page, medical record and anesthesia record sheet of each in-hospital patient was collected by Information Center Department of Henan Provincial People's Hospital and a uniform data collection system was applied. The data was obtained from an electronic medical record and collected after the fact. Anonymous data about patients' basic information, clinical diagnosis using International Statistical Classification of Diseases and Related Health Problems (10th revision) codes, surgery-relevant information, and intraoperative DEX were transferred to a specific data management institution.

Study Population

We analyzed the data of all adult (age ≥18 yr) patients who underwent elective thoracic surgery under total intravenous anesthesia (TIVA) or combined intravenous and inhalation anesthesia between January 2016 and March 2020. Patients were excluded for the following reasons: (i) data on the classification of regional anesthesia were missing; (ii) data on nausea and vomiting in the first 24 h after surgery were not recorded; (iii) DEX was used after surgery; (iv) the patient went to the Intensive Care Unit (ICU) after surgery; (v) more than 20% of patient indicators were missing; (vi) the patient had a history of alcohol, analgesic or other drug abuse and addiction; (vii) the patient had unstable angina pectoris and myocardial infarction occurring within 3 months and New York Heart Association (NYHA) grade ≥3; and (viii) the patient had severe cardiovascular and cerebrovascular diseases. For patients who had more than one thoracic surgery during the study period, only the first thoracic surgery was included.

Variables

Variables that may have an association with PONV were selected based on a literature review. Risk factors for PONV in adults included age, non-smoking, history of PONV or motion sickness, volatile anesthesia, risk surgery, female and post-operative opioid analgesics. Patients with completed data regarding age, sex, education, weight, smoking history, drinking history, American Society of Anesthesiologists (ASA) physical status, medical history (hypertension, diabetes mellitus, previous non-thoracic surgery, cerebral vascular and heart diseases and immune system diseases, coagulation dysfunction, History of PONV and Motion sickness), anesthesia method (TIVA and Combined intravenous and inhalation anesthesia), regional anesthesia, intraoperative dexamethasone, sufentanil and prophylactic antiemetics (5HT-3 antagonists), and surgical characteristics (surgical method, type and time), vascular drugs, bradycardia, hypotension, total infusion volume, red blood cell (RBC) transfusion, plasma transfusion, amount of bleeding, urine volume, length of stay (LOS) in the post-anesthesia care unit (PACU), patient controlled intravenous analgesia (PCIA), moderate-to-severe (MOS) pain at rest, moderate-to-severe (MOS) pain during activity, use of medication in PCIA, post-operative salvage opioid analgesics, rescue medication (5HT-3 antagonists) and PONV during the first post-operative 24 h were included in the study.

End Points and Confounders

Nausea and vomiting are two different phenomena; they usually coexist in a patient, post-operative nausea (PON) or post-operative vomiting (POV) notably occur in parallel to PONV. Therefore, we regarded the PONV variables as a substitute for any PON, POV or retching in the trials. The most commonly used time interval to measure the role of antiemetics is 24 h post-operatively (7). We could get the occurrence and frequency of PONV within 24 h after operation. However, we could not distinguish the degree of PON and POV in our retrospective. The primary end point in our study was the incidence of PONV during the first post-operative 24 h. Secondary end points were the dose-response relationship and the optimal dose of DEX and PONV.

Baseline factors thought to have relationships with PONV were regarded as potential confounders for the analysis. Based on clinical experiences and previous studies, we adjusted for the potential confounding effects of age, sex, surgery type, surgery time, regional anesthesia, patient controlled intravenous

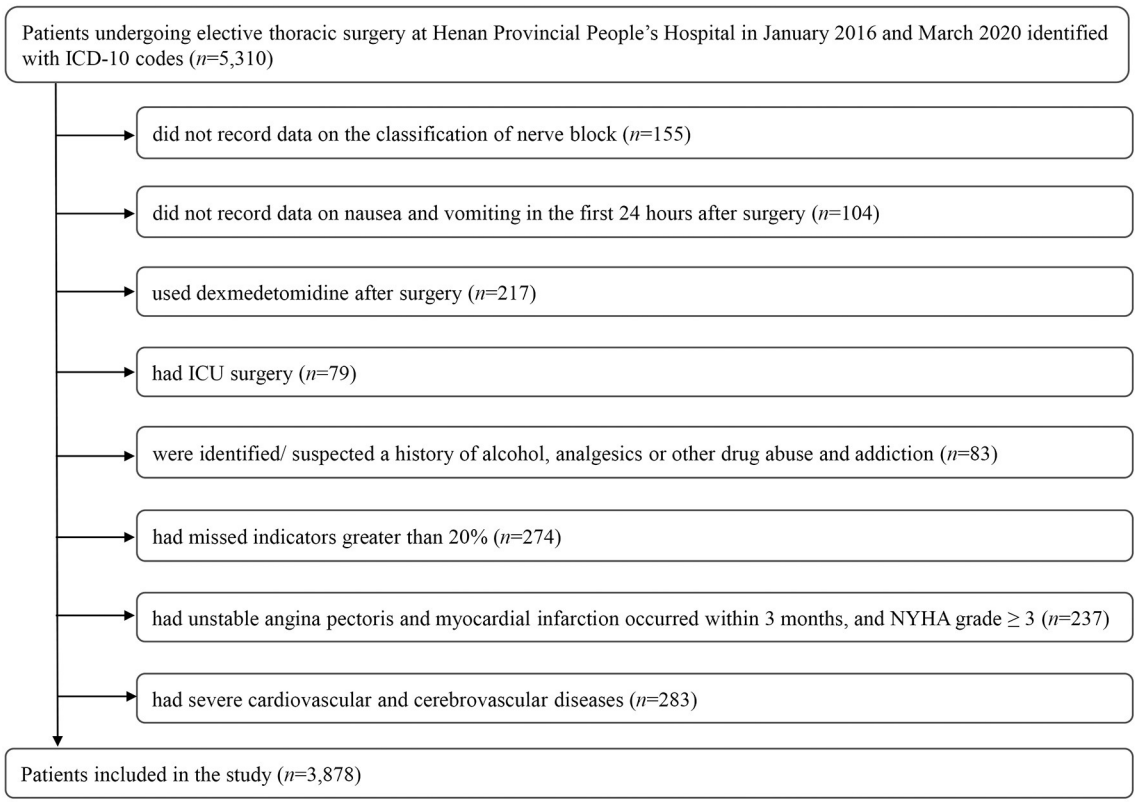

FIGURE 1 | Flow chart for final patient selection in this study. DEX, dexmedetomidine; ICU, Intensive Care Unit; NYHA, New York Heart Association.

analgesia (PCIA), education, smoking history and intraoperative sufentanil. All information concerning potential confounders was retrieved from the medical records.

Statistical Analysis

Baseline data were stratified by categorizing the study population into two groups, dexmedetomidine and non-dexmedetomidine, according to whether dexmedetomidine was used during the operation. Continuous variables of each group are presented as the mean standard deviation (if the data are normal) or quartile, and the categorical variables are expressed as absolute values and percentages. Analysis of variance was used to compare continuous variables. Categorical variables were analyzed by the chi-squared test. A 2-tailed $p<0.05$ was established as the threshold of statistical significance. We did not adjust for the probability of type I errors; hence, findings concerning secondary outcome was only considered exploratory. Data analysis was performed with R packages (R version 3.4.4).

As this was a retrospective database study, the number of eligible patients was fixed; hence, we estimated the statistical power instead of calculating the sample size. And we used propensity-score matching to exclude systematic bias. Patients were matched using 1:1 nearest-neighbor matching with a caliper size of 0.05 on a propensity score scale. To control for any residual confounding by covariates with a standardized difference >10% after matching, we included these variables as adjustment for a priori selected risk factors for PONV in the multivariable logistic regression models to analyze the association between exposure and outcome. To test the robustness of our main findings, we conducted an a priori–defined sensitivity analysis, as stated above, three analysis models were devised: "Model 1" was a crude model; "Model 2" was adjusted for age and sex; and "Model 3" included age, sex, surgery type, surgery time, anesthesia method, regional anesthesia, PCIA, education, smoking history and intraoperative sufentanil as the adjustment variables.

The associations between the different doses of dexmedetomidine and PONV were analyzed to determine whether a dose-response relationship exists, in which patients with no dexmedetomidine were excluded. Bonferroni's correction was used, and 99% confidence interval (CI) was calculated in the analysis of the dose-response relationship to adjust the type I error in the multiple comparisons. Different doses of dexmedetomidine were tested to determine whether the dose-response relationship was statistically significant using the Mann-Kendall method.

RESULTS

Of the 5,310 patients undergoing elective thoracic surgery identified in our database, 3,878 were eligible for inclusion (**Figure 1**).

TABLE 1 | Patients characteristics.

Items	Before matched				After matched			
	Without DEX ***n* = 1,325**	**DEX** ***n* = 2,553**	***P***	***SMD***	**Without DEX** ***n* = 1,325**	**DEX** ***n* = 1,325**	***P***	***SMD***
Weight (kg)	65 (57 to 72)	65 (58 to 73)	0.019	0.076	65 (58 to 73)	65 (58 to 73)	0.768	0.009
Age (year)	57 (47 to 66)	57 (49 to 66)	0.254	0.076	57 (47 to 66)	57 (49 to 66)	0.269	0.042
Sex (male)	779 (58.8)	1,583 (62)	0.064	0.064	779 (58.8)	800 (60)	0.842	0.008
ASA physical status			< 0.001	0.154			0.945	0.022
I	152 (11.5)	181 (7.1)			152 (11.5)	94 (7.1)		
II	1,016 (76.7)	2,068 (81)			1,016 (76.7)	1,073 (81)		
III	152 (11.4)	296 (11.6)			152 (11.4)	154 (11.6)		
IV	5 (0.4)	8 (0.3)			5 (0.4)	4 (0.3)		
Education			0.18	0.074			0.776	0.085
Bachelor or above	252 (19)	457 (17.9)			252 (19)	237 (17.9)		
Middle school	533 (40.2)	1,001 (39.2)			533 (40.2)	519 (39.2)		
Primary school	486 (36.7)	955 (37.4)			486 (36.7)	496 (37.4)		
Illiteracy	54 (4.1)	140 (5.5)			54 (4.1)	73 (5.5)		
Smoking history (yes)	491 (37.1)	983 (38.5)	0.414	0.029	491 (37.1)	510 (38.5)	0.842	0.043
Drinking history (yes)	443 (33.4)	888 (34.8)	0.409	0.029	443 (33.4)	461 (34.8)	0.871	0.027
History of non-thoracic surgery (yes)	496 (37.4)	978 (38.3)	0.626	0.018	496 (37.4)	507 (38.3)	0.749	0.039
Cerebral vascular disease (yes)	85 (6.4)	184 (7.2)	0.342	0.034	85 (6.4)	96 (7.2)	0.882	0.015
History of hypertension (yes)	282 (21.3)	597 (23.4)	0.14	0.051	282 (21.3)	310 (23.4)	0.819	0.014
Diabetes History (yes)	139 (10.5)	248 (9.7)	0.47	0.027	139 (10.5)	128 (9.7)	0.278	0.045
History of heart disease (yes)	85 (6.4)	245 (9.6)	0.001	0.117	85 (6.4)	87 (6.6)	0.688	0.016
History of immune system (yes)	9 (0.7)	8 (0.3)	0.121	0.061	9 (0.7)	8 (0.6)	0.117	0.070
History of coagulation dysfunction (yes)	24 (1.8)	102 (4)	<.001	0.131	24 (1.8)	53 (4)	<.001	0.090
History of PONV	49 (3.7)	71 (2.8)	0.032	0.155	49 (3.7)	31 (2.4)	0.019	0.138
Motion sickness	268 (20.3)	385 (15.1)	0.007	0.113	268 (20.3)	115 (8.7)	0.008	0.082

Data are presented as mean (SD) or n (%) or median.
SD, standard deviation; DEX, dexmedetomidine; ASA, American Society of Anesthesiologists; PONV, Post-operative nausea and vomiting.

Baseline Characteristics

Among the 3,878 patients enrolled, 2,553 patients received DEX and 1,325 patients did not receive DEX. The incidence of PONV in patients who received DEX was 21.3%, and the incidence of PONV in patients who did not receive DEX was 46.5% ($P = 0.001$). We used a propensity-score matched-pairs analysis of the cohort to evaluate the adjusted association between DEX and PONV. After the matched-pairs cohort consisted of 1,325 patients, the incidence of PONV in patients who received DEX was 23.6%, and the incidence of PONV in patients who did not receive DEX was 46.5% ($P = 0.001$). There were significant differences between the groups in terms of a history of coagulation dysfunction, history of PONV and motion sickness (**Table 1**). There were significant differences between the groups in terms of anesthesia method, regional anesthesia, surgery type, hypotension and Urine volume (**Table 2**). There were significant differences between the groups in terms of PCIA, Pain during activity (MOS), use of medication in PCIA, post-operative salvage opioid analgesics, rescue medication (5HT-3 antagonists) and PONV (**Table 3**). We analyzed three different models after propensity matching, including Model 1 (OR = 0.497, 95% CI, 0.314–0.77; $P = 0.002$), Model 2 (OR = 0.485, 95% CI, 0.305–0.755; $P = 0.002$), and Model 3 (OR = 0.489, 95% CI, 0.305–0.768; $P = 0.002$), to validate the stability of the prediction model between DEX and PONV (**Table 4**).

Dose-Response Relationship Between DEX and PONV

A dose-response relationship between DEX and PONV was observed (**Figure 2**). The ordinate of **Figure 2** is the odds ratio (0–1), and the abscissa is the dosage of DEX (0–150 μg). As is evident, the larger the dose of DEX is, the lower the incidence of PONV.

The Optimal Dose of DEX and PONV

The 95% upper confidence interval of OR was 1, and the critical value were 48.995 μg (OR = 0.0.604, 95% CI, 0.364–1.003) and 49.749 μg (OR = 0.595, 95% CI, 0.359–0.988) in the dose-response relationship (**Figure 2**). When the dose of DEX >100 μg, the OR decreases very little, and the curve is gentle (**Figure 2**). We analyzed three different dose range

TABLE 2 | Baseline data of intraoperative patients.

Items	Before matched				After matched			
	Without DEX *n* = 1,325	**DEX *n* = 2,553**	***P***	***SMD***	**Without DEX *n* = 1,325**	**DEX *n* = 1,325**	***P***	***SMD***
Anesthesia method			0.037	0.122			0.011	0.100
TIVA	325 (24.5)	835 (32.7)			325 (24.5)	412 (31.1)		
Combined intravenous and inhalation anesthesia	1,000 (75.5)	1,718 (67.3)			1,000 (75.5)	913 (68.9)		
Regional anesthesia			<.001	0.171			0.007	0.128
TPVB	966 (72.9)	2,025 (79.3)			966 (72.9)	1,051 (79.3)		
None	359 (27.1)	528 (20.7)			359 (27.1)	274 (20.7)		
Intraoperative dexamethasone (mg)	5 (4 to 6)	5 (4 to 6)	0.146	0.087	5 (4 to 6)	5 (4 to 6)	0.613	0.083
Intraoperative sufentanil (μg)	35 (30 to 40)	35 (30 to 40)	0.162	0.041	35 (30 to 40)	35 (30 to 40)	0.831	0.015
Prophylactic antiemetics (5HT-3 antagonists) (mg)	4 (3 to 5)	4 (3 to 5)	0.341	0.040	4 (3 to 5)	4 (3 to 5)	0.526	0.047
Surgical method			>.999	0.001			0.912	0.013
Open surgery	188 (14.2)	363 (14.2)			188 (14.2)	188 (14.2)		
Endoscopic surgery	1,137 (85.8)	2,190 (85.8)			1,137 (85.8)	1,137 (85.8)		
Surgery type			<.001	0.237			0.002	0.194
Lung cancer	230 (17.4)	554 (21.7)			230 (17.4)	288 (21.7)		
Lobectomy	615 (46.4)	1,136 (44.5)			615 (46.4)	589 (44.5)		
Esophageal cancer	242 (18.3)	490 (19.2)			242 (18.3)	254 (19.2)		
Mediastinal surgery	102 (7.7)	248 (9.7)			102 (7.7)	129 (9.7)		
Thoracoscopic Sympathectomy	82 (6.2)	15 (0.6)			82 (6.2)	15 (1.1)		
Other types	93 (7)	110 (4.3)			93 (7)	50 (3.8)		
Surgery time (min)	191 (135 to 255)	190 (145 to 260)	0.043	0.057	191 (135 to 255)	190 (145 to 260)	0.872	0.001
Vascular drugs (yes)	580 (43.8)	1,220 (47.8)	0.02	0.080	580 (43.8)	633 (47.8)	0.094	0.009
Bradycardia (yes)	162 (12.2)	347 (13.6)	0.232	0.042	162 (12.2)	180 (13.6)	0.527	0.009
Hypotension (yes)	440 (33.2)	661 (25.9)	<.001	0.150	440 (33.2)	343 (25.9)	<.001	0.164
Total infusion volume (ml)	1,500 (1,000 to 2,000)	1,500 (1,100 to 2,000)	0.167	0.061	1,500 (1,100 to 2,000)	1,500 (1,100 to 2,000)	0.487	0.035
RBC Transfusion (U)	1 (1 to 1)	1 (1 to 1)	0.606	0.030	1 (1 to 1)	1 (1 to 1)	0.687	0.035
Plasma Transfusion (ml)	0 (0 to 0)	0 (0 to 0)	0.697	0.015	0 (0 to 0)	0 (0 to 0)	0.224	0.017
Amount of bleeding (ml)	100 (30 to 100)	100 (50 to 150)	<0.001	0.018	100 (30 to 100)	100 (50 to 150)	0.003	0.002
Urine volume (ml)	350 (200 to 600)	400 (200 to 600)	0.001	0.107	350 (200 to 600)	360 (200 to 600)	0.028	0.055

Data are presented as mean (SD) or n (%) or median.
SD, standard deviation; DEX, dexmedetomidine; TIVA, Total intravenous anesthesia; TPVB, thoracic paravertebral regional anesthesia; LOS, Length of stay; PACU, Post Anesthesia Care Unit; RBC, red blood cell.

of dexmedetomidine for PONV, including 0–50 μg (OR = 0.776, 95% CI, 0.474–1.220; $P = 0.291$), 50-100 μg (OR = 0.247, 95% CI, 0.103–0.504; $P < 0.001$), and 100–150 μg (OR = 0, 95% CI, 0–0; $P = 0.988$) (**Table 5**). Compared with 0 μg, there was only significant difference between in range of DEX in 50–100 μg. The optimal dose range of intraoperative DEX for antiemetic effects of PONV is 50–100 μg.

DISCUSSION

In this study, we reported three main findings: first, intraoperative DEX can reduce the incidence of PONV in patients undergoing thoracic surgery; second, a dose-response relationship between intraoperative DEX and PONV was observed; third, the optimal dose range of intraoperative DEX for antiemetic effects of PONV is 50–100 μg.

Previous small sample prospective studies have shown that perioperative DEX can reduce the incidence of PONV (7–9). Some meta-analyses demonstrated that intraoperative DEX significantly lowered post-operative pain scores and opioid consumption, which could lead to a reduced opioid-related adverse events, including PONV (6, 10). These studies focused on the specific high-risk factors for PONV, especially in women (breast and gynecological surgery) and gastrointestinal surgery. Clear risk factors independently predicting PONV included female sex, post-operative opioid treatment, prior history of

TABLE 3 | Patients data within 24 h after operation.

Items	Before matched				After matched			
	Without DEX ***n* = 1,325**	**DEX** ***n* = 2,553**	***P***	***SMD***	**Without DEX** ***n* = 1,325**	**DEX** ***n* = 1,325**	***P***	***SMD***
LOS in PACU (min)	70 (55 to 95)	70 (55 to 95)	0.054	0.051	70 (55 to 95)	70 (55 to 95)	0.071	0.028
PCIA (yes)	1236 (93.3)	2231 (87.4)	<.001	0.199	1236 (93.3)	1140 (86.0)	<.001	0.146
Pain at rest (MOS)	85 (6.4)	146 (5.7)	0.412	0.035	85 (6.4)	80 (6.1)	0.114	0.035
Pain during activity (MOS)	207 (15.6)	301 (11.8)	0.002	0.103	207 (15.6)	160 (12.1)	0.002	0.084
Use of medication in PCIA (μg)	206 (16.4)	199 (8.3)	0.009	0.171	206 (16.4)	133 (10.1)	0.023	0.098
Postoperative salvageopioid analgesics (μg)	167 (12.7)	125 (7.5)	0.018	0.107	167 (12.7)	112 (8.5)	0.033	0.055
Rescue medication(5HT-3 antagonists) (mg)	413 (31.2)	398 (15.6)	0.011	0.117	413 (31.2)	246 (18.6)	0.006	0.016
PONV (yes)	616 (46.5)	544 (21.3)	0.001	0.122	616 (46.5)	312 (23.6)	0.003	0.100

Data are presented as mean (SD) or n (%) or median.
SD, standard deviation; DEX, dexmedetomidine; LOS, Length of stay; PACU, Post Anesthesia Care Unit; RBC, red blood cell; PCIA, patient controlled intravenous analgesia; MOS, moderate-to-severe (VAS score >3).

TABLE 4 | Multivariable logistic regression analysis of dexmedetomidine for PONV.

Variable	OR (95% CI)	*P*
Model 1	0.497 (0.314 to 0.77)	0.002
Model 2	0.485 (0.305 to 0.755)	0.002
Model 3	0.489 (0.305 to 0.768)	0.002

Model 1 was a crude model.
Model 2 was adjusted for age and sex using multivariable logistic regression.
Model 3 was adjusted for age, sex, surgery type, surgery time, anesthesia method, regional anesthesia, PCIA, education, smoking history and intraoperative sufentanil using multivariable logistic regression.
CI, confidence interval; OR, odds ratio; PONV, Post-operative nausea and vomiting; PCIA, patient controlled intravenous analgesia.

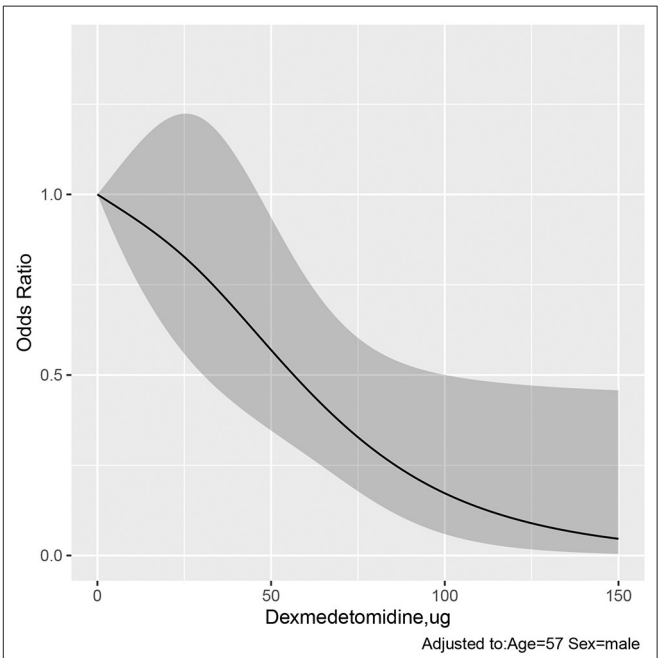

FIGURE 2 | Dose–response relationship of dexmedetomidine and PONV. The ordinate is the odds ratio (0–1), and the abscissa is the dosage of DEX (0–150 μg). Error bars represent 99% confidence intervals. The larger the dose of DEX is, the lower the incidence of PONV. DEX, dexmedetomidine; PONV, Post-operative nausea and vomiting.

motion sickness and/or PONV, and non-smokers, which can increase the risk by 20% (11). Other risk factors for PONV also included preanesthetic medication, anesthetic techniques, and post-operative pain management (12). By reviewing 4 years of patients receiving thoracic surgery in Henan Provincial People's Hospital, including esophageal surgery, lung surgery, mediastinal surgery and so on, we can further determine the relationship between intraoperative DEX and PONV. We analyzed three different models after propensity score matching and showed that perioperative DEX could reduce the incidence of PONV, further supporting that this result was very stable, and this is consistent with previous research results. To our knowledge, this is the first large-scale retrospective cohort study of intraoperative DEX and PONV in elective thoracic surgery.

The reasons why DEX could prevent PONV may be as follows: (i) Intraoperative DEX significantly lowered the demand for opioids and inhalation anesthesia during and after operation, which could help to reduce opioid-related adverse events, including PONV (13). (ii) Intraoperative DEX decreases noradrenergic activity as a result of binding to alpha-2 presynaptic inhibitory adrenoreceptors in the locus coeruleus, which may result in an antiemetic effect (14). (iii) It may be related to reducing sympathetic outflow and total catecholamine release by DEX, while high sympathetic tone and catecholamine release may trigger PONV (12).

Although some prospective studies with small sample sizes have shown that a 0.5 or 1.0 μg/kg bolus infusion could effectively decrease the incidence of PONV (7–9, 15, 16), there have been few studies on other doses, and it is not clear whether there was a dose-dependent antiemetic effect. The optimal dose

TABLE 5 | Multivariable logistic regression analysis of different dose range of dexmedetomidine for PONV.

Variable	OR (95% CI)	*P*
0–50 μg	0.776 (0.474 to 1.220)	0.291
50–100 μg	0.247 (0.103 to 0.504)	<0.001
100–150 μg	0 (0 to 0)	0.988

CI, confidence interval; OR, odds ratio; PONV, Post-operative nausea and vomiting.

of DEX for achieving antiemetic effects has not been well-documented. On the basis of the above, we explored the dose-effect relationship between DEX and PONV according to the data in our study. The intraoperative dosage of DEX ranged from 0 μg to 150 μg, and with the increase in perioperative dexmedetomidine dose, the incidence of PONV decreased. This beneficial dose-response relationship may be explained by the possible mechanism of DEX reducing the incidence of PONV.

It should be noted that bradycardia and hypotension are the most common adverse events associated with high doses of DEX, which were closely related to the rate of infusion and total dosage. Thus, when determining the optimal dose of DEX for PONV, the potential increased risk of significant hypotension and bradycardia should be balanced against optimal anti-PONV effects. We found a significant dose-response relationship between intraoperative DEX and PONV, but the range of intraoperative DEX is too extensive in **Figure 2**. When the 95% upper confidence interval of OR is just <1 in the dose-response relationship, the corresponding dose of DEX is 49.749 μg, indicating that some patients did not benefit from the DEX in terms of PONV when the DEX is <49.749 μg. When the dose of DEX was >100 μg, the OR value decreased very smoothly. This suggests that the benefit from DEX becomes smaller, at the same time, higher cardiovascular risk have to be considered very carefully. Meanwhile, we analyzed three different dose range of intraoperative DEX for antiemetic effects of PONV and showed that there was significant difference only when the dose of DEX was 50–100 μg. Based on our results, the optimal dose range of intraoperative DEX for antiemetic effects of PONV is 50–100 μg in elective thoracic surgery.

There were several limitations to this observational study, including (most notably) its retrospective nature, which prevented us from obtaining clinical details from decision-makers. First, the dose of intraoperative DEX was not reported per kilogram of body weight in our study, but we obtained the dose-response relationship between intraoperative DEX and PONV, and explored the optimal dose of intraoperative DEX which included different doses of intraoperative DEX for antiemetic effects of PONV. Second, previous studies have shown that intraoperative inhaled anesthetic dosage directly affected the frequency and degree of PONV. Due to the defects of retrospective study, we were unable to obtain the intraoperative inhaled anesthetic dosage. However, anesthesia methods did not affect the results of DEX for antiemetic effects after multivariate regression analysis. Third, PON and POV usually coexist in a patient, so we did not distinguish the two variables. The degree of PONV was not identified. Whether intraoperative dexmedetomidine can decrease the degree of PONV also requires further research.

In conclusion, intraoperative DEX was found to be significantly associated with a decreased incidence of PONV in a retrospective cohort study. We also observed a dose-response relationship: the greater the dose of intraoperative DEX is, the lower the incidence of PONV. The optimal dose range of intraoperative DEX for antiemetic effects of PONV is 50–00 μg in elective thoracic surgery.

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 the Ethical Committee of Henan Provincial People's Hospital, No. 7, Weiwu Road, Zhengzhou, Henan, China. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. Written informed consent was not obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

BL and YZ: wrote the manuscript. BL and XL conducted bioinformatics analysis, analyzed the data, and drew diagrams. YL: supervision. JZ and WZ made a lot of contributions to the design of the research, conducted data analysis, graph generation, and wrote the manuscript. All authors contributed to the refinement of the study protocol and approved the final manuscript.

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ORIGINAL RESEARCH
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Transcutaneous Electrical Acupoint Stimulation Combined With Auricular Acupressure Reduces Postoperative Delirium Among Elderly Patients Following Major Abdominal Surgery: A Randomized Clinical Trial

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Background: Postoperative delirium is common in elderly patients following major surgery. This study aimed to assess the effect of transcutaneous electrical acupoint stimulation combined with auricular acupressure on the incidence of postoperative delirium among older patients undergoing major abdominal surgery.

Methods: In this single-center, randomized controlled clinical trial, 210 patients aged 65 years or older undergoing major abdominal surgery were randomized to receive either intervention treatment (transcutaneous electrical acupoint stimulation started at 30 min before anesthesia until the end of the surgery, followed by intermittent auricular acupressure in the first three postoperative days; n = 105) or standard care (n = 105). The primary outcome was the incidence of delirium at the first seven postoperative days or until hospitalization depended on which came first. Secondary outcomes included delirium severity, opioid consumption, postoperative pain score, sleep quality, length of postoperative hospital stay, and postoperative 30-day complications. Enrollment was from April 2019 to March 2020, with follow-up ending in April 2020.

Results: All of the 210 randomized patients [median age, 69.5 years, 142 (67.6%) male] completed the trial. The incidence of postoperative delirium was significantly reduced in patients received intervention treatment (19/105 (18.1%) vs. 8/105 (7.6%), difference, –10.5% [95% CI, –1.5% to –19.4%]; hazard ratio, 0.41 [95% CI, 0.18 to 0.95]; P= 0.023). Patients in the control group had a higher postoperative Memorial Delirium Assessment Scale (4 *vs.* 3; difference, –1; 95% CI, –1 to 0; P = 0.014) and a greater increase in Pittsburgh Sleep Quality Index score from baseline to postoperative day three (2.5 *vs.* 2.0; difference, –1; 95% CI, –2 to –1; $P < 0.001$) than patients in the intervention group. No significant difference was observed as of other secondary outcomes.

Conclusion: In elderly patients undergoing major abdominal surgery, transcutaneous electrical acupoint stimulation combined with auricular acupressure reduced the incidence of postoperative in-hospital delirium compared with standard care. A multicenter, randomized clinical trial with a larger sample size is necessary to verify these findings.

Clinical Trial Registration: [https://clinicaltrials.gov], identifier [NCT03726073].

Keywords: transcutaneous electric acupoint stimulation, auricular acupressure, elderly, abdominal surgery, delirium

INTRODUCTION

Postoperative delirium is an acute neurological disorder that commonly occurs within the first three days after the operation (1, 2). Delirium prevalence ranges from 18 to 35% in general medical services and reaches 50% in elderly patients after high-risk surgery (3). It has been documented that postoperative delirium is associated with increased mortality, morbidity, and healthcare costs (4, 5). Despite efforts to decrease its occurrence, the incidence of postoperative delirium remains at 15%–54% in elderly patients after major abdominal surgery (6, 7).

The etiology of postoperative delirium is multifactorial and not fully elucidated. Cumulative evidence has shown that it may be associated with neuroinflammation, alteration in neurotransmitters, subclinical cerebral vascular events, and can be precipitated by factors such as pain, hypotension, and electroencephalogram suppression during surgery (1, 8). Acupuncture, a traditional Chinese medicine, has been reported to have anti-inflammatory and neuroprotective properties (9, 10). It also alleviates perioperative hypotension, reduces anesthetic and analgesic consumption, and improves sleep disorders (9, 11). Therefore, acupuncture and related techniques might exert a beneficial influence in reducing postoperative delirium.

Evidence supporting the use of acupuncture on delirium prevention is limited. A pilot study has shown that transcutaneous electrical acupoint stimulation applied on pre-and intraoperative has a trend of alleviating postoperative delirium in elderly patients with silent lacunar infarction undergoing spinal surgery (6.3% *vs*. 25.0%; relative risk, 0.25; 95% CI, 0.06 to 1.09) (12). Since the effect of a single session of electronic acupuncture only lasted for two or 3 h (9, 13), the transitory acupuncture protocol in the study may attribute to the limited effect of acupuncture on delirium prevention. Previous studies reported that delirium mainly occurs within postoperative three days (14, 15); thus, adding acupuncture interventions on postoperative three days may augment its preventive effects. Postoperative auricular acupuncture has shown its effect on relieving anxiety in post-cesarean section women (16) and preventing postoperative agitation in geriatric patients (17). In clinical practice, body and auricular acupuncture have been combined for synergistic effects, such as sleep improvement and opioid rescue (18, 19). However, the combined effects of body acupuncture and auricular acupuncture for delirium prevention in elderly patients have not been explored.

This study hypothesized that pre-and intra-operative transcutaneous electrical acupoint stimulation combined with auricular acupressure treatment for the first three postoperative days compared with standard care would reduce the incidence of postoperative delirium among elderly patients undergoing major abdominal surgery.

MATERIALS AND METHODS

Study Design

This was a single-center, prospective, randomized, assessor-blinded trial. Ethical approval was obtained from the Institutional Review Board of Xijing Hospital (No. KY20182080-F-1) in Xi'an, Shaanxi Province of China. The trial was registered at ClinicalTrials.gov before patient enrollment (NCT03726073, October 31, 2018[1]). Written informed consent was obtained from all patients before randomization.

Participants

Participants 65 years or older with American Society of Anesthesiologists physical status class $\leq$ III and scheduled for elective, major abdominal surgery (including hepatobiliary and pancreatic, urologic, gastrointestinal, or gynecological) were eligible for trial inclusion. Major surgery was defined by a planned more than two days hospitalization (20). Participants were required to complete a Mini-Mental State Examination and have a score higher than 20. Patients were excluded if they had a severe visual or auditory impairment, literacy deficits, mental illness, history of brain injury or neurosurgery, with a history of alcohol or drug abuse, history of acupuncture treatment, or contradicted to transcutaneous electrical acupoint stimulation or auricular acupressure (for example, planted with pacemakers, with skin lesions, or allergy to surface electrodes).

Randomization and Blinding

Participants were recruited into the study from the electronic medical record system of our hospital by research staff. After giving consent and completing the baseline assessment, eligible participants were randomly assigned to either the intervention group (transcutaneous electrical acupoint stimulation combined with auricular acupressure) or the control group (standard care) in a 1:1 ratio using simple randomization. The random allocation sequence was generated by the statistician.

Study-group assignments were concealed in opaque envelopes and revealed by a research nurse upon patients'

[1]https://clinicaltrials.gov/ct2/show/NCT03726073

arrival at the operation room. The investigators including the research coordinator, outcome assessors, data collectors, and the statistician were blinded to treatment allocation. The acupuncturist and participants were not blinded. The care team (surgeons, anesthesiologists, and nurses) were aware that an acupuncture study was undergoing but were blinded to study hypothesis and intervention protocol. Participants were informed not to discuss the group allocation or the aim of the study with investigators (except the acupuncturist) during the whole process of the study. Assessors would communicate with the ward nurses, and ask the nurses to let the patients wear an earmuff (loose enough to ensure patients could hear the assessors' questions) before every postoperative evaluation. In addition, interactions between the assessors, participants and their family members were limited to the questions on the case report form. To assess the frequency of unblinding to group allocation, the assessors were asked to guess which treatment this patient had received after a patient was discharged from the hospital.

Intervention

The acupressure protocol used in the present study was based on previous publications relating to acupoint selection in symptom management (12), investigators' previous publications (9), and clinical experience of the acupuncturist in the team who is specializing in acupuncture clinical practice with seven years.

In the intervention group, participants received transcutaneous electrical acupoint stimulation through bilateral Hegu (LI4), Neiguan (PC6), and Zusanli (ST36) acupoints after entering the operation room. The neuroprotective effects and the exact locations of these three acupoints have been previously described (12, 21, 22). After entering the operation room, Hwato brand disposable electronic pads (size 50 mm × 50 mm) were placed on these acupoints after skin disinfection and then simultaneously connected to a transcutaneous electroacupuncture apparatus (SDZ-V, Suzhou Medical Appliance Company, Suzhou, Jiangsu, China). The transcutaneous electroacupuncture apparatus was set to provide a disperse-dense wave with an alternating frequency of 2/10 Hz. The current intensity was modulated between 5 and 20 mA (5 to 10 mA for the upper limbs, 10 to 20 mA for the lower limbs) and the final stimulus current of each acupoint was regulated individually until the De Qi sensation (a composite of sensations including soreness, numbness, distention, heaviness, and others such as coldness, warmness, and pain electric-shock feeling) was achieved at each acupoint. The electrostimulation was started from 30 min before anesthesia induction and up to the end of surgery.

Postoperatively, after arriving at the post-anesthesia care unit, patients in the intervention group were tapped *Vaccaria* seeds (Hebei Heshi Medical Apparatus and Instruments Co., LTD, Hengshui, China) at seven auricular points (Shenmen, Point Zero, Sympathetic, Subcortex, Heart, Liver, and Endocrine) located on the right ear by the acupuncturist. These auricular acupoints were previously used alone or combined to manage postoperative agitation and sleep disturbances (17, 23, 24). From postoperative day one to day three, participants were instructed to manually stimulate each auricular acupoint for 30 s, five times a day, for three days (From nine AM to nine PM, around every 3 h). Participants were instructed on the procedure, stimulation techniques, duration and intensity of auricular acupressure, the methods of keeping acupressure patches in the right place and protecting them, and were asked to document the time of auricular acupressure application and any side-effects in a diary sheet. The acupuncturist verified the quality of auricular acupressure daily. The pastes with seeds were removed after three days.

Participants in the standard care group did not receive any acupuncture intervention during the study period.

Anesthesia Protocol

Anesthesia was induced with intravenous propofol (1–2 mg/kg) or etomidate (0.2–0.3 mg/kg), sufentanil (3 μg/kg), and rocuronium (1 mg/kg). After the loss of consciousness, an endotracheal tube was intubated. Anesthesia was maintained with sevoflurane inhalation (0.7–1.7 minimum alveolar concentration) and remifentanil infusion (0.05–0.2μg/kg/min). Rocuronium was administered as indicated (0.2 mg/kg). The depth of anesthesia was adjusted based on the hemodynamic indices and bispectral index (BIS). The BIS was maintained at 40–60 during surgery. Use of dexmedetomidine, midazolam, anticholinergic drugs, and haloperidol was avoided unless they were indicated for delirium rescue therapy. Standard monitoring procedures included electrocardiography, pulse oximetry, capnography, and inspiratory and expiratory sevoflurane concentrations. Invasive blood pressure monitoring was applied when necessary. A lung-protective ventilation strategy and multimodal analgesia were applied intraoperatively. Analgesia was assisted by intravenous administration of parecoxib sodium (40 mg) and oxycodone (0.1 mg/kg) preoperatively and local anesthetic infiltration in the surgical wound (0.5% ropivacaine) postoperatively. Postoperative intravenous patient-controlled analgesia was applied to patients during postoperative three days based on anesthesiologists' clinical experience. Patient-controlled intravenous analgesia was established with 100 ml of 1 μg/ml sufentanil and 80 μg/ml butorphanol, programmed to deliver a background infusion of 0.015 ml/kg/h and 0.5 mL bolus with a lockout interval of 10 min. Parecoxib sodium (40 mg) was given intravenously every 12 h during the postoperative three days. An intravenous bolus of rescue oxycodone (0.05–0.1 mg/kg) was available every 6 h if the pain was intolerable.

Outcomes

Two trained investigators who were not involved in the study intervention, anesthesia, and clinical care of patients performed outcome assessment. The primary outcome was the incidence of delirium during the first seven postoperative days or hospitalization if patients were discharged within seven days postoperatively. The diagnosis of delirium and its subtype were based on the Confusion Assessment Method or Confusion Assessment Method-intensive care unit for intubated patients, the Richmond Agitation Sedation Scale, reports from family members, and medical records review (5, 25, 26). Delirium was assessed daily at around 6 PM. The Confusion Assessment Method algorithm required the identification of both an

acute onset and fluctuating course and inattention and either disorganized thinking or an impaired level of consciousness (25). As ward nurses and surgeons would assess patients' mental status at least once daily and describe the results in their notes, medical records would be reviewed. For delirium patients in the ward, a mix-type delirium would be diagnosed if the patients manifested a fluctuation of mental status and behaviors during the day. Delirium patients in the intensive care unit were classified using the Richmond Agitation Sedation Scale score (RASS) (26): (1) hyperactive type, consistently positive RASS score remains at + 1 to + 4; (2) hypoactive type, consistently neutral or negative Richmond Agitation Sedation Scale remains at –3 to 0; (3) mixed type, alternative positive and negative.

Secondary outcomes included delirium severity measured by the Memorial Delirium Assessment Scale, intraoperative opioid consumption, pain intensity both at rest and at movement assessed by the Numeric Rating Scale at 24 h, 48 h, and 72 h after surgery, sleep quality within the first three postoperative days by the Pittsburgh Sleep Quality Index, length of postoperative hospitalization, the occurrence of non-delirium and complications within postoperative 30 days.

Statistical Analysis

The incidence of postoperative delirium was reported to be up to 23.9% in elderly patients after major surgery (5, 7). We assumed that the incidence of postoperative delirium would be reduced from 23.9% in the control group to 8.9% in the intervention group based on the effect reported in a small randomized controlled trial (12). With significance set at 0.05 and a power of 80%, 95 patients in each group were required (PASS 15.0 software, NCSS, Kaysville, UT) to detect the differences. Considering a loss to follow-up rate of 10%, we planned to enroll 210 participants, with 105 in each group.

Analyses of primary and secondary outcomes were performed both in the intention-to-treat and per-protocol populations. We did not plan an interim analysis. We did not conduct the missing data imputation as there were no missing data for the primary outcome and less than 5% for all secondary outcomes.

Categorical variables are presented as frequencies or proportions and analyzed using the chi-squared test or Fisher exact test. Continuous variables are presented as mean (standard deviation) or median (interquartile range) depending on distribution (the Shapiro-Wilk test was used to assess normality) and analyzed with independent samples *t*-test or Mann–Whitney *U* test. The relative risk and 95% confidence interval (CI) are used to describe the differences in dichotomous outcomes. The difference (and 95% CI) between medians were calculated with the Hodges–Lehmann estimator.

The primary endpoint was analyzed using the chi-squared test. The cumulative postoperative delirium incidence was calculated with the Kaplan–Meier estimator, with differences between groups assessed using the log-rank test. The hazard ratio and 95% CI estimated with a Cox regression model were used to describe differences if the proportional assumption was not violated. The Cox regression model was adjusted for age and sex.

The Memorial Delirium Assessment Scale within seven postoperative days was compared using a generalized linear mixed-effect model, with results presented as mean and 95% CI. Treatment assignment, time, and interaction between treatment assignment and time effects were included as fixed effects. Participants were included as random effects. The model covariates were unadjusted.

Sensitivity analysis included analysis of the primary and secondary outcomes in the per-protocol populations. We performed *post hoc* subgroup analyses using a Cox proportional hazards model to investigate the intervention effects on the cumulative delirium incidence in specific subgroups, including sex (male *vs.* female), age ($<$ 70 years old *vs.* $\geq$ 70 years old), the education level ($\leq$ 9 years of schooling or no qualification *vs.* $>$9 years of schooling), surgery type (upper abdominal surgery *vs.* lower abdominal surgery), and history of operation. We tested for treatment effect heterogeneity across various subgroups and reported the corresponding *P* values for interaction.

Statistical analyses were performed using SPSS 24.0 (IBM Corp., Armonk NY). Two-tailed tests were used in all analyses, and $P < 0.05$ was considered statistically significant.

RESULTS

Trial Population and Baseline Characteristics

From April 17, 2019, to March 10, 2020, 334 patients scheduled for major abdominal surgery were screened for eligibility at Xijing Hospital, Xi'an, Shaanxi Province of China. Among them, 210 patients were enrolled and randomly assigned to either the intervention group (n = 105) or the standard care group (n = 105). Eight patients (two in the intervention group and three in the standard care group violated anesthesia protocol, three in the intervention group violated acupuncture protocol) were excluded from the per-protocol analysis (**Figure 1**).

Overall, most of the patients were male (142/210, 67.6%), and the median age was 69.5 (interquartile range, 67.0–73.0) years (**Table 1**). The types of surgery included hepatobiliary and pancreatic (52.4%), urologic (33.8%), gastrointestinal (10.5%), and gynecological (3.3%) procedures (**Table 1**). Baseline characteristics and surgical parameters did not differ between the two groups (**Table 1**). Forty-nine (23.3%) patients were discharged within postoperative six days, five (2.4%) patients (three in the control group and two in the intervention group) were transferred to the intensive care unit after surgery, and there were no differences between groups. The final visit of the last randomized patient took place on April 10, 2020.

Primary and Secondary Outcomes

In the intention-to-treat population, the incidence of postoperative delirium during postoperative seven days was 7.6% (8/105) in the intervention group and 18.1% (19/105) in the control group (difference, −10.5% [95% CI, −1.5% to −19.4%]; relative risk, 0.42 [95% CI, 0.19 to 0.92]; P = 0.023; number needed to treat = 10 [95% CI, 5 to 64]; **Table 2**). The proportion of postoperative delirium-free patients significantly differed

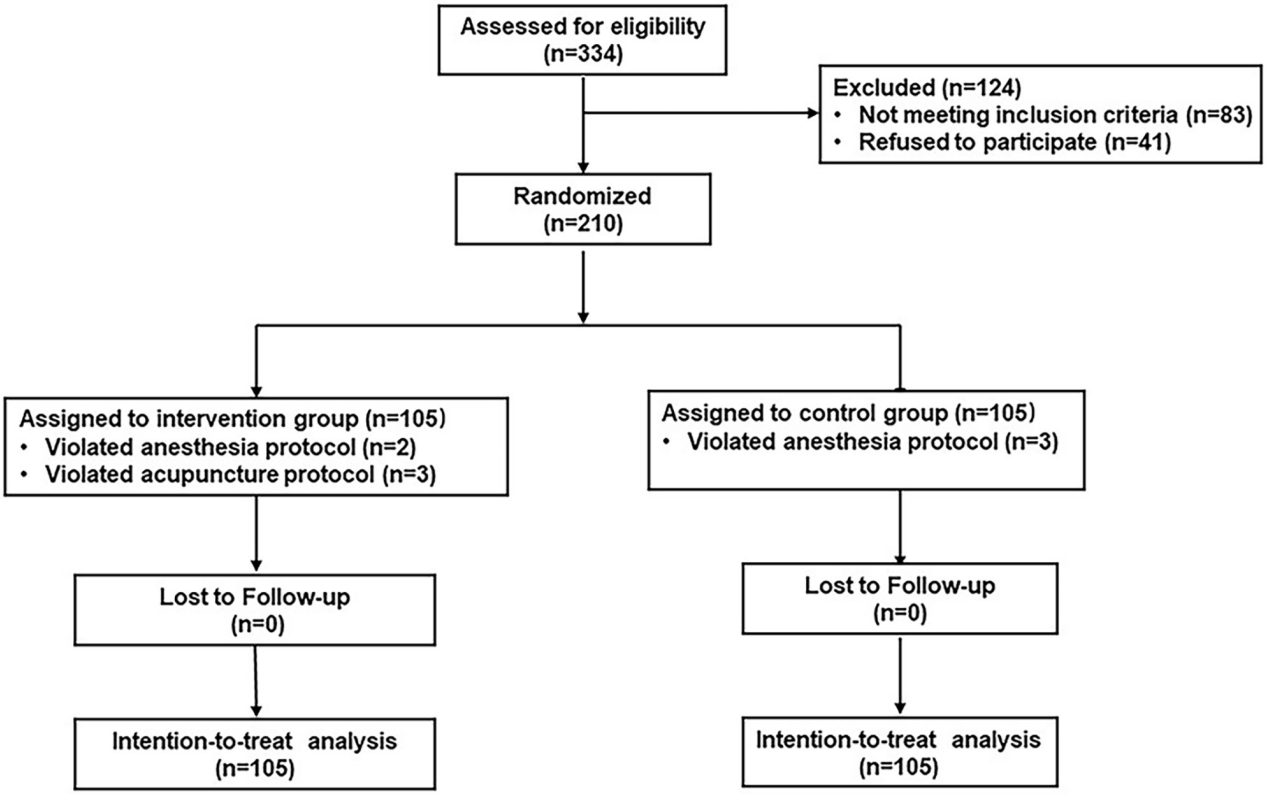


FIGURE 1 | Trial profile. The intention-to-treat analysis included all randomized patients in the groups in which they were randomly assigned.

between the two groups (hazard ratio, 0.41; 95% CI, 0.18 to 0.95; $P = 0.023$) (**Figure 2**).

Subgroup analyses using the Cox model showed that the interaction between surgery sites and treatment was statistically significant ($P = 0.005$, **Figure 3**). Patients who underwent upper abdominal surgery benefited more from the intervention than those who underwent lower abdominal surgery (hazard ratio, 0.16; 95% CI, 0.04 to 0.71).

The incidence of delirium on the day of surgery was 5.7% (6/105) in the intervention group and 15.2% (16/105) in the control group (relative risk, 0.38; 95% CI, 0.15 to 0.92; P=0.024). Delirium severity measured by Memorial Delirium Assessment Scale was lower in the intervention group than in the control group (3 *vs.* 4; difference, −1; 95% CI,−1 to 0; $P = 0.010$), with significant differences on postoperative day two ($P = 0.007$), day three ($P < 0.001$) and day four ($P = 0.037$) (**Figure 4**). The control group had a significantly greater increase regarding Pittsburgh Sleep Quality Index score change from baseline to postoperative day three than the intervention group (2.5 *vs.* 2.0; difference, −1; 95% CI, −2 to −1; $P < 0.001$). The two groups did not differ significantly with respect to the duration of delirium, the intraoperative consumption of sufentanil and remifentanil, the Numeric Pain Rating Scale at rest and movement at postoperative 24 h, 48 h, and 72 h, the patient-controlled intravenous analgesia drug consumption during postoperative 0–24 h, 24–48 h, and 48–72 h, and the length of postoperative hospitalization (**Table 2**).

The per-protocol analysis yielded similar results (**Supplementary Table 1**).

Adverse Events

Thirty-three surgery-related adverse events (12 in the intervention group and 21 in the control group) were documented within 30 days postoperatively. Adverse events (anastomotic leakage or bleeding, pneumonia, delayed feeding, readmission, sepsis, re-operation, death, acute kidney failure, new arrhythmia, and ileus), whether viewed individually (P for each > 0.20) or collectively (11.4% *vs.* 20.0%; relative risk, 0.57; 95% CI, 0.30 to 1.10; $P = 0.088$), did not significantly differ between the two groups (**Table 3**). Two patients in the control group died of postoperative septic shock, but no difference was found in all-cause 30-day mortality between groups.

Skin temporary pain or paranesthesia was considered an expected adverse event with transcutaneous electrical acupoint stimulation and auricular acupressure treatment. One patient in the intervention group reported mild leg numbness, which was alleviated within three days. There was no withdrawal from adverse events.

The Effectiveness of Assessor-Blinded

Outcome assessors were able to get a 54.3% rate for correctly guessing patients' received therapy (59.0% for the intervention

TABLE 1 | Baseline characteristics and surgical details of the intention-to-treat population.

Variables	Total (*n* = 210)	Control group (*n* = 105)	Intervention group (*n* = 105)
Age (years)	69.5 (67.0–73.0)	69.0 (67.0-73.0)	70.0 (67.0-72.0)
Sex			
Male	142 (67.6)	70 (66.7)	72 (68.6)
Female	68 (33.4)	35 (33.3)	33 (31.4)
ASA class			
II	181 (86.2)	90 (85.7)	91 (86.7)
III	29 (13.8)	15 (14, 2)	14 (13.3)
Body mass index (kg/m^2)	23.3 ± 2.8	22.7 ± 2.9	23.6 ± 2.9
Length of education (years)	9 (5.8 – 12)	8 (4.5 – 12)	9 (6 – 12)
Level of education			
Illiteracy	14 (6.7)	9 (8.6)	5 (4.8)
Primary school	55 (26.2)	28 (26.7)	27 (25.7)
Middle school	59 (28.1)	31 (29.5)	29 (27.6)
High School	36 (17.1)	17 (16.2)	19 (18.1)
University	45 (21.4)	20 (19.0)	25 (23.8)
Mini-Mental State Examination score	27 (25 – 29)	27(25 – 29)	28 (25 – 29)
Carlson score	2 (2 – 4)	2 (2 – 4)	2 (2 – 3)
Number of previous operations	1 (0 – 2)	1 (0 – 2)	1 (0 – 2)
Comorbidities			
Hypertension	88 (41.9)	45 (42.9)	43 (41.0)
Coronary artery disease	23 (11.0)	12 (11.4)	11 (10.5)
Diabetes	37 (17.6)	23 (21.9)	14 (13.3)
Chronic bronchitis	9 (4.3)	5 (4.8)	4 (3.8)
Arrhythmia	24 (11.4)	10 (9.5)	14 (13.3)
Stroke	21 (10.0)	12 (11.4)	9 (8.6)
Current smoking	36 (17.1)	17 (16.2)	19 (18.1)
Alcoholism	6 (2.9)	4 (3.8)	2 (1.9)
Surgical procedure			
Hepatobiliary and pancreatic	110 (52.4)	54 (51.4)	56 (53.3)
Urologic	71 (33.8)	35 (33.3)	36 (34.3)
Gastrointestinal	22 (10.5)	11 (10.5)	11 (10.5)
Gynecological	7 (3.3)	5 (4.8)	2 (1.9)
Open surgery	121 (57.6)	56 (53.3)	65 (61.9)
Duration of anesthesia (min)	216 (165285)	227 (170 – 285)	210 (160 – 282)
Duration of surgery (min)	175 (129 – 244)	175 (132 – 239)	175 (125 – 245)
Transferred to ICU after surgery	5 (2.4)	3 (2.9)	2 (1.9)
Discharged within postoperative six days	49 (23.3)	24 (22.9)	25 (23.8)
Number of patients using PCIA	156 (74.3)	77 (73.3)	79 (75.2)

Data are presented as number (%), mean (SD), or median (interquartile range). Differences between groups were compared using the chi-squared, Mann–Whitney U, or Fisher's exact test as appropriate. ASA: American Society of Anesthesiologists. ICU: Intensive care unit. PCIA: Patient-controlled intravenous analgesia.

group and 49.5% for the control group). Outcome assessors' perception of patients' accepted treatment did not affect the primary outcome (**Supplementary Table 2**).

DISCUSSION

In this single-center, prospective, randomized trial, transcutaneous electrical acupoint stimulation combined with auricular acupressure reduced the incidence and severity of postoperative delirium and improved postoperative sleep quality in elderly patients undergoing major abdominal surgery.

Postoperative delirium developed in 18.1% of patients in the standard care group. This was in line with previous studies for non-cardiac surgeries, which range from 13 to 50% (3), but slightly lower than the reported rate that we used to estimate sample size (23.9%) (5). There are several reasons for this. First, compared with those in the previous study (5), patients in the current study were younger (median age: 69.5 years *vs.* 77.0 years) and higher delirium risk patients (such as American Society of Anesthesiologists physical status class > III and Mini-Mental State Examination score ≤ 20) were excluded. Second, anesthesia management was different between the two studies. Delirium risk factors such as midazolam, anticholinergic drugs, and haloperidol were avoided, and Bis-guided anesthesia management was applied during surgery in the present study. These reasons may explain the slightly lower incidence of delirium in this trial (1, 3).

A trend of reduced incidence of postoperative delirium (6.3% *vs.* 25%; relative risk, 0.25; 95% CI, 0.06 to 1.09) was reported when transcutaneous electrical acupoint stimulation was applied pre- and intraoperatively to 64 geriatric patients with silent lacunar infarction undergoing spine surgery (12). This was consistent with the delirium-prevention effect observed in our study (relative risk, 0.42; 95% CI, 0.19 to 0.92). The mechanisms of the delirium-sparing effect produced by transcutaneous electrical acupoint stimulation and auricular acupressure remain undetermined. Gao et al. demonstrated that transcutaneous electrical acupoint stimulation at bilateral LI4 and PC6 reduced neuroinflammation by lowering the permeability of the blood-brain barrier (12). Studies reported that one potential mechanism by which auricular acupressure may exert its anti-delirium effect is activating the locus coeruleus noradrenergic system, which is one of the central vagal relay centers and plays a critical role in the generating and regulating of delirium (27, 28). By stimulating the ear branch of the vagus nerve, auricular acupressure may exert an add-on neuroprotective effect by direct and indirect modulation of the activity and connectivity of the locus coeruleus noradrenergic system, thus modulating the release and uptake of noradrenaline and dopamine in some key brain regions, including the prefrontal cortex and hippocampus, which are postulated to be associated with attention, memory, and other cognitive dysfunction (27–29). As postoperative delirium has been speculated to be a harbinger for postoperative cognitive dysfunction, the mechanism of acupuncture to prevent postoperative delirium may be similar to those of acupuncture to prevent postoperative cognitive dysfunction, which is by attenuating systemic inflammation and neuroinflammation, reducing oxidative stress levels, improving synaptic plasticity, and reducing neuronal injury (10, 12, 30).

TABLE 2 | Effectiveness outcomes analyzed in the intention-to-treat population.

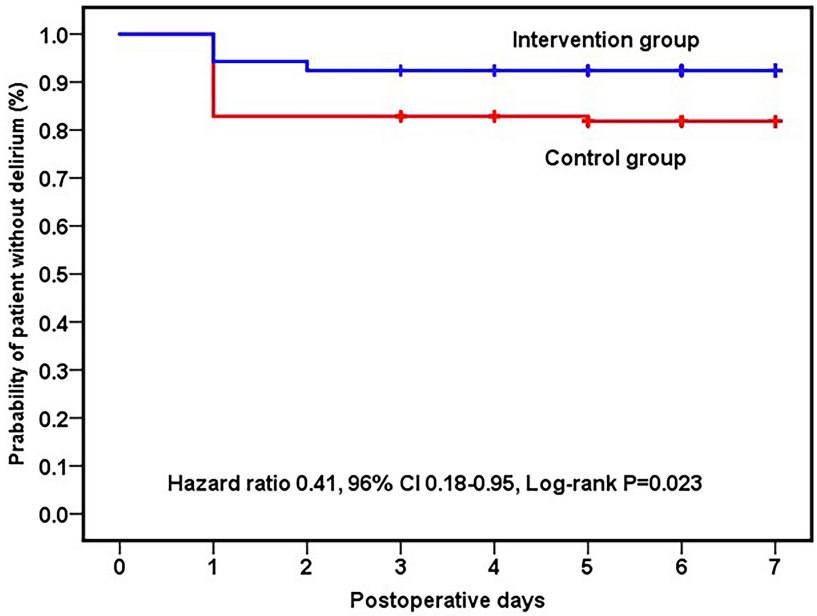
Variables	Control group (n = 105)	Intervention group (n = 105)	Relative risk or difference (95% CI)	P value
Primary outcome				
[1]Overall incidence of delirium	19 (18.1)	8 (7.6)	0.42 (0.19 to 0.92)	0.023
Secondary outcomes				
Memorial Delirium Assessment Scale	4 (2–6)	3 (2–5)	−1 (−1 to 0)	0.010
The motoric subtype of delirium				0.025
Hypoactive	9 (8.6)	6 (5.7)		
Hyperactive	7 (6.7)	0 (0)		
Mixed	3 (2.9)	2 (1.9)		
Delirium on the day of surgery	16 (15.2)	6 (5.7)	0.38 (0.15 to 0.92)	0.024
[2]Delirium duration	3.0 (2.0–3.0)	2.0 (1.3–3.0)	0 (−1 to 1)	0.449
Intraoperative consumption of sufentanil (ng/kg/min)	2.4 (1.7–3.4)	2.4 (1.8–3.0)	−0.07 (−0.37 to 0.20)	0.642
Intraoperative consumption of remifentanil (μg/kg/min)	0.13 (0.11–0.14)	0.12 (0.10–0.14)	-0.01 (−0.01 to 0)	0.136
Pain score at rest				
Postoperative day 1	0 (0–1)	0 (0–2)	0 (0 to 0)	0.248
Postoperative day 2	0 (0–1)	0 (0–1)	0 (0 to 0)	0.679
Postoperative day 3	0 (0–1)	0 (0–1)	0 (0 to 0)	0.901
Pain score with movement				
Postoperative day 1	3(1–4)	3 (2–4)	1 (0 to 1)	0.290
Postoperative day 2	2 (1–4)	3 (1–4)	0 (0 to 1)	0.137
Postoperative day 3	2 (1–4)	3 (1–4)	0 (0 to 1)	0.390
PCIA Drug Consumption (ml)				
Postoperative 0–24 h	21.5 (18.2–25.8)	22.4 (16.5–25.1)	0.2 (–2.2 to 2.1)	0.859
Postoperative 24–48 h	20.8 (8.3–24.3)	21.5 (7.1–25.5)	0.1 (–2.5 to 2.9)	0.938
Postoperative 48–72 h	6.4 (0–22.5)	3.2 (0–21.6)	0 (–2.1 to 0)	0.302
Pittsburgh Sleep Quality Index				
Baseline	7 (5–10)	7(4.5–10)	0 (−1 to 1)	0.567
During postoperative three days	11 (8–14)	8 (6–13)	−2 (−3 to -1)	0.001
Changes from baseline	2.5 (2.0–4.8)	2.0 (1.0–3.0)	−1 (−2 to -1)	< 0.001
Length of postoperative hospitalization (days)	8 (7–10)	8 (7–10)	0 (−1 to 1)	0.988
[3] Incidence of non-delirium complications	21 (20.0)	12 (11.4)	0.57 (0.30 to 1.10)	0.088

Data are presented as number (%) or median (interquartile range). Differences between groups were compared using the chi-squared, Mann–Whitney U, Fisher's exact test, or generalized linear mixed effect models as appropriate. [1]Occurrence of delirium at any time during the first seven postoperative days or hospitalization if the patient was discharged within seven postoperative days. [2]Delirium duration was calculated only for patients who experienced delirium. [3]Occurrence of any non-delirium complication within 30 days postoperatively. PCIA: Patient-controlled intravenous analgesia. PCIA therapy was applied to seventy-seven patients in the control group and seventy-nine patients in the intervention group.

Subgroup analysis of our data suggested that patients who underwent upper abdominal surgery benefitted more from the intervention than patients who underwent lower abdominal surgery. It is unclear why this occurred, but this heterogeneity may be related to the acupoints we selected and the individual response differences toward acupuncture treatment. Kim et al. suggested that individual differences in acupuncture analgesia are associated with inherited genetic factors, adenosine monophosphate-activated protein kinase expression in the hypothalamus, spinal levels of neurotransmitters and pro-inflammatory cytokines, and the density of cholecystokinin receptors (31). The difference of acupuncture's delirium-prevention effects between upper and lower abdominal surgery may share similar mechanisms and warrant further study. Our results also raise the question of whether the specificity of needling sites is essential to the therapeutic benefits of acupuncture.

Psychological distress, pain, and insomnia are often intertwined (32). Pain and sleep disorders are possible confounders of delirium severity, and thus attenuated the extent of postoperative pain and improved sleep quality might reduce the incidence of postoperative delirium (1, 33). Inconsistent with the previous studies (34, 35), acupuncture did not decrease intraoperative opioid consumption and postoperative pain in this trial. This may be related to the high opioid doses and a multi-model analgesia protocol adopted in the present trial.

The change from baseline to postoperative day three in the Pittsburgh Sleep Quality Index score was more significant in the control group than in the intervention group (2.5 *vs.* 2.0; between-group difference, –1; 95% CI, –2 to –1; $P < 0.001$), indicating that the acupuncture intervention in the present study has a beneficial effect on postoperative sleep quality. The improved sleep quality within the first three postoperative days in the present study may be attributed to



Number at risk								
Control group	105	105	89	87	84	81	73	63
Intervention group	105	105	99	97	96	94	89	74

FIGURE 2 | Kaplan–Meier curve showing the probability of a patient being delirium-free within seven postoperative days.

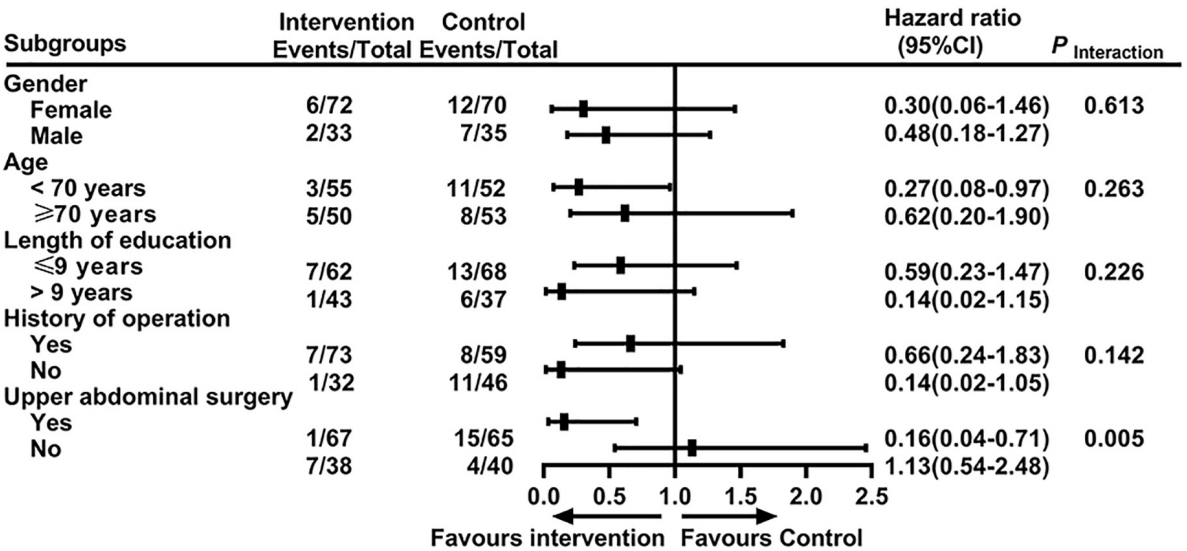


FIGURE 3 | Forest plot of the subgroup analysis for the primary outcome.

auricular acupressure, as indicated in the previous studies that auricular acupoint stimulation improves sleep quality (36). The rationale of the auricular acupoints selected in this trial was based on their effects of calming the mind, relieving anxiety, and improving sleep quality (23). Hou et al. showed that auricular acupressure normalized disturbed sleep patterns and improved sleep quality via regulating the neuroendocrine system, neuroimmunological factors, neuroinflammation, and neural reflex, as well as antioxidation (37). However, whether auricular acupressure reduces postoperative delirium directly or indirectly

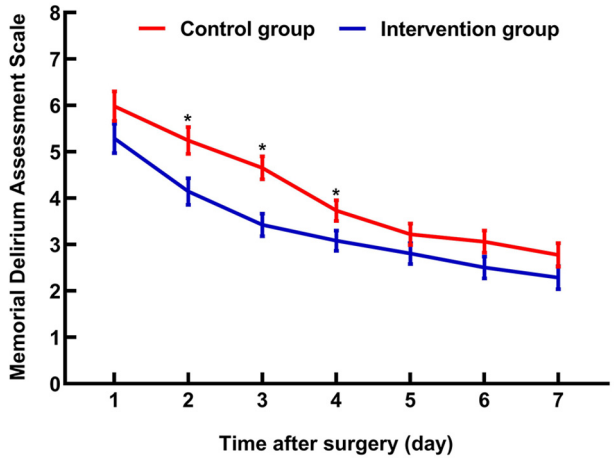


FIGURE 4 | Changes in Memorial Delirium Assessment Scale during the first postoperative seven days. Makers indicate means, and error bars indicate standard errors. *Significant difference between groups.

TABLE 3 | Postoperative complications within 30 days analyzed in the intention-to-treat population.

Variables	Control group (*n* = 105)	Intervention group (*n* = 105)	*P value*
Anastomotic leakage or bleeding	3 (2.9)	1 (1.0)	0.621
Pneumonia	3 (2.9)	3 (2.9)	1.000
Delayed feeding	2 (1.9)	1 (1.0)	1.000
Readmission	5 (4.8)	1 (1.0)	0.212
Sepsis	2 (1.9)	0 (0)	0.498
Re-operation	2 (1.9)	3 (2.9)	0.681
Death	2 (1.9)	0 (0)	0.498
Acute kidney failure	1 (1.0)	1 (1.0)	1.000
New arrhythmia	1 (1.0)	1 (1.0)	1.000
Ileus	0 (0)	1 (1.0)	1.000

Data are presented as number (%). Differences between groups were compared using Fisher's exact test.

by improving postoperative sleep quality is unclear, which needs to be elucidated in future studies.

The Confusion Assessment Method and Confusion Assessment Method-intensive care unit were used in this study to diagnose delirium as they are commonly used for postoperative delirium identification and easy to learn for non-psychiatrists, with high sensitivity (94% to 100%) and high specificity (90% to 95%) (25). As each assessment may take 20 min to 30 min, and assessments were conducted for postoperative seven days, a once-daily assessment was chosen in this study to improve participants' compliance. However, it is possible that short periods of fluctuating mental status, inattention, disorganized thinking, or altered consciousness level may not be detected at the time of assessment. Additional medical records review was used in this study to minimize the risk of delirium misclassification, which has been accepted in previous studies (5, 38). Further research should add other screening methods such as the Consortium to Establish a Registry of Alzheimer's Disease (39) and the Montreal Cognitive Assessment tests (40) to assess other diverse cognitive domains and verify the robustness of anti-delirium effects exerted from electrical acupoint stimulation combined with auricular acupressure.

This study has several limitations. First, this is a single-center study, while internal validity is not impacted, the external validity and generalizability of the results may be affected by clinical practice and therapeutic measures in various medical centers. The sample size is relatively small, the power of this intervention should be tested in a clinical trial with a larger sample size. Second, the enrolled patients and the acupuncturist were not blinded. Thus, an inherent risk of the Hawthorne effect cannot be ruled out in this study. The outcome assessors, data collectors and the statistician were blinded to reduce the risk of bias. Third, a sham acupuncture group was not used to eliminate the placebo effect. Future studies are needed to distinguish the specific and non-specific effects of acupuncture intervention for postoperative delirium. Fourth, the subgroup analysis was *post hoc*. Therefore, these findings should be interpreted as exploratory. In addition, the number of events in most subgroups was relatively small, which may limit the power to detect the difference among subgroups. Fifth, the dosage of postoperative rescue analgesic drugs was not recorded. However, perioperative pain management was strictly controlled, postoperative pain scores were lower, and the analgesic effect was comparable between the two groups. Standardized perioperative pain management and preservation of randomization would be expected to minimize the confounding from rescue drug consumption differences. Furthermore, although anesthesia management was conducted under the guidance of the BIS, the BIS and frequencies of burst suppression during surgery were not recorded and compared, potentially confounding and biasing the results (41).

Acupuncture is an important supplementary strategy for perioperative management (9), applications of acupuncture before, during, and after surgery as an adjuvant therapy will have a great clinical application. Future acupuncture studies should investigate how to best implement acupuncture in real-world clinical settings, such as setting up an acupuncture protocol and selecting the appropriate acupoints for specific surgeries and populations. To investigate the mechanisms of how acupuncture prevents postoperative delirium could provide essential insights in preventing postoperative delirium. As postoperative delirium and postoperative cognitive dysfunction share risk factors (30), a long-term follow-up to investigate the preventive effects of acupuncture intervention on postoperative cognitive dysfunction should also be included in future studies.

In conclusion, in this single-center, prospective, randomized study, transcutaneous electrical acupoint stimulation combined with auricular acupressure reduced the incidence of postoperative delirium in elderly patients undergoing major abdominal surgery. A multicenter randomized clinical trial with a larger sample size is necessary to verify these findings.

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 the Institutional Review Board of Xijing Hospital (No. KY20182080-F-1) in Xi'an, Shaanxi Province of China. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

QF, CL, ZL, HD, and LX contributed to the concept and design of the study and data interpretation. QF and ZL performed the study registration. QF and JF performed the screen of patients. NY performed the acupuncture intervention. YW and LW performed the outcome assessment and data collection. CL performed the data analysis. QF, CL, ZL, and HD prepared the primary manuscript. All the authors read and approved the final version of the manuscript.

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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.2022.855296/full#supplementary-material

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Effect of Preoperative Thoracic Paravertebral Blocks on Emergence Agitation During Tracheal Extubation: A Randomized Controlled Trial

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Objective: This study aims to compare the effects of preoperative thoracic paravertebral blocks (TPVB) with intercoastal nerve blocks (ICNB) on emergence agitation (EA) during tracheal extubation in patients who underwent thoracoscopic lobectomy.

Design, Setting, and Participants: A randomized clinical trial was conducted in patients undergoing thoracoscopic lobectomy at Beijing Chest Hospital between June 2019 and December 2020.

Interventions: Patients were randomly assigned 1:1 to receive either ultrasound-guided preoperative TPVB or ICNB.

Main Outcomes and Measures: The primary outcome was the occurrence of emergency agitation, which was evaluated by Aono's four-point scale (AFPS). Secondary outcomes included hemodynamics [mean arterial pressure (MAP) and heart rate (HR)]; and post-operative pain intensity [visual analog scale (VAS), Ramsay sedation score (RSS), and patient-controlled analgesia (PCA) demand times].

Results: Among the 100 patients aged 55–75 years old, 50 were randomized to each group; 97 patients completed the trial. Compared to the ICNB group, the occurrence of EA in the TPVB group was significantly lower [31.3% (15/48) vs. 12.2% (6/49), relative risk = 1.276, 95% CI: 1.02–1.60, $P = 0.028$]. For patients in the TPVB group, the MAP and HR at 5, 10, and 30 min after extubation were significantly lower; the intraoperative details including emergence time, extubation time, and consumption of sufentanil were significantly shorter than that in the ICNB group. Additionally, patients in the TPVB group

showed significantly lower VAS at rest or coughing and significantly lower RSS at 60 and 240 min after extubation than patients in the ICNB group (all $P < 0.05$).

Conclusion: Preoperative TPVB was associated with less EA during tracheal extubation when compared with ICNB in patients undergoing thoracoscopic lobectomy.

Clinical Trial Registration: [http://www.chictr.org.cn/index.aspx], identifier [ChiCTR1900023852].

Keywords: emergence agitation, thoracoscopic, thoracic paravertebral block, intercostal nerve blocks, randomized controlled trial

INTRODUCTION

Emergence agitation (EA) in adults is manifested as psychomotor excitement with purposeless thrashing, restlessness, and disorientation, and is a common complication in the waking stage of general anesthesia. It is commonly seen in thoracoscopic lobectomy (1) and the occurrence might reach 19% in non-cardiac surgery (2). EA may cause self-extubation or accidental removal of catheters, cardiac-cerebral vascular events (3), or even death (4). Multiple factors have been demonstrated to contribute to EA such as acute pain, urinary catheterization, tracheal intubation, and psychological stress (5). Previous studies had identified that one of the highest risk factors is post-operative acute pain (6–8). Intravenous opioids can reduce the occurrence of EA, but those drugs may lead to a high occurrence of drowsiness, dizziness, nausea, vomiting, delayed recovery, respiratory depression, and chest wall muscle rigidity (9). Therefore, approaches to prevent EA are important to identify.

The intercostal nerve block is a convenient and effective method to improve post-operative pain in thoracic surgery and has been widely used in clinical practices. Previous studies showed that intrapleural intercostal nerve block with mini-thoracotomy could reduce the post-operative pain and contribute to improving post-operative outcomes after major pulmonary resections (10, 11).

Thoracic paravertebral analgesia is similar to epidural analgesia with fewer side effects and is increasingly utilized in clinical practices (12). Studies have shown that a two-point paravertebral injection can spread the solution to a wider area and is more effective than single-point injection for analgesia (13). Due to significant difficulties in defining the paravertebral space (PVS), the failure rate of the traditional approach is around 10.1% (14). With the rapid advancement of ultrasound use in recent years, ultrasound-guided, thoracic paravertebral block (TPVB) has been shown to increase the success rate of block significantly (15). Several systemic reviews suggested that both TPVB and intercostal nerve blocks (ICNB) could play a role in ameliorating post-thoracotomy pain (16–18).

This study aims to compare the effects of preoperative thoracic paravertebral blocks (TPVB) with intercoastal nerve blocks (ICNB) on EA during tracheal extubation in patients who underwent thoracoscopic lobectomy.

MATERIALS AND METHODS

Study Design and Participants

Ethical approval for this trial was obtained from the Institutional Review Board of Beijing Chest Hospital [ID: (2018) Ethical Review of Clinical Trial Recommended Project No. 03-01]. Written informed consents were obtained from all participants.

This randomized controlled trial was conducted on patients who underwent thoracoscopic lobectomy at Beijing Chest Hospital between June 2019 and December 2020. The inclusion criteria were (1) patients with American Society of Anesthesiologists (ASA) physical status I–III undergoing thoracoscopic lobectomy; (2) conscious and able to independently describe and evaluate pain after explanations; (3) 55–75 years old. Exclusion criteria included (1) serious cardiopulmonary diseases; (2) serious coagulation/hepatorenal function disorders; (3) history of alcohol or drug abuse; and (4) body mass index (BMI) $\geq$ 40 kg/m^2; (5) preoperative narcotic analgesic use history, (6) with acute or chronic pain or oral analgesics before surgery; and (7) mental disorders or cognitive impairment [the score assessed by Montreal Cognitive Assessment (MoCA) is less than 26 points] (19).

Randomization

Eligible participants were randomly assigned into two groups at a 1:1 ratio *via* a computer-generated random number table randomization system for clinical research. All peri-operative assessments and data collection were accomplished by the nurses.

Interventions

l Thoracic paravertebral blocks and ICNBs were performed in a lateral position under real-time ultrasound-guided out-of-plane technique. A Philips ultrasound machine (Philips, CX-50, Holland) with a high-frequency linear transducer (L12-3) was utilized. In the TPVB group, the ultrasonic transducer was positioned to the long axis of the thoracic spine which was approximately 2–3 cm lateral to the spinous process. Then, the ultrasound transducer was moved until the tip of the transverse process was visible. In this position, the thoracic PVS was visualized between two transverse processes and parietal pleura. The parasagittal out-of-plane technique of needle insertion that was initially introduced into anesthesia by Hara (20) was applied in our study. The position of needle

insertion was located and marked. After skin infiltration with 2% lidocaine (1–3 ml), and a 22-gauge insulated regional block needle (Stimuplex D, B. Braun, Germany) was inserted out-of-plane from lateral to medial direction. Hydrolocation with sterile saline was utilized to identify the needle tip until anterior pleural deflection was visualized on ultrasound, indicating that the needle tip was located in the PVS. Patients in the TPVB group received 2 injections of the PVB at the T3-4 and T6-7 (T means thoracic vertebrae; 3–4 and 6–7 means entry points on thoracic vertebrae of the needle tip) PVS with 7.5 ml of 0.75% ropivacaine and 2.5 ml of 2% lidocaine. Fifteen minutes after the block administration, the pinprick method at the midclavicular line was used to assess the extent of the dermatomal blockade.

Patients in the ICNB group received intercostal nerve blocks depending on the locations of skin incisions (the fourth intercostal space in the anterior axillary line) and chest tube placement (the seventh intercostal space in the midaxillary line). Ultrasound was used to identify anatomic landmarks. Ribs were identified as hyperechoic streaks and the pleura appeared as hyperechoic lines between and below the ribs. A mixture of 7.5 ml of 0.75% ropivacaine and 2.5 ml of 2% lidocaine was injected at the level of incision using a 22-gauge nerve block needle in an out-of-plane fashion. The needle was advanced until the distal tip was immediately adjacent to the pleura. A tissue plane between the internal and innermost intercostal muscles was delineated as the local anesthetic agent.

All nerve blocks were administered by the same experienced anesthesiologists, and the same total dose of ropivacaine and lidocaine was administrated to patients in both groups. All complications were recorded, including pneumothorax, local anesthetic intoxication, and total spinal anesthesia. TPVB failure was diagnosed as two unblocked adjacent dermatomes during pinprick assessment.

Standard anesthesia monitoring was performed after patients entered the operation room, including pulse oxygen saturation, electrocardiogram, bispectral index (BIS) monitor, and invasive blood pressure in the radial artery.

No patient received any premedication. Anesthesia was induced with midazolam (0.05 mg/kg), sufentanil (0.1–0.2 mcg/kg), plasma target-controlled infusion (TCI) Marsh model (TCI propofol) (3.0–3.5 mcg/mL); and cisatracurium (0.3 mg/kg). Left or right double-lumen tube was used to intubate and ventilate mechanically with 100% oxygen. The flow was set at 3 L/min, respiratory rate at 12 breaths per min, I:E ratio of 1:1.5, and tidal volume at 6–8 ml/kg. Intermittent administration of sufentanil and TCI propofol 1.5–3.5 mcg/mL was used to keep the BIS between 40 and 60, and the systolic arterial pressure and heart rate (HR) within ± 20% of baseline values during the procedure. Cisatracurium was administered for muscle relaxation as required. The neuromuscular blockade was reversed and the patient was extubated if awake. After extubation, patients had intravenous patient-controlled analgesia (PCA) *via* an infusion pump to deliver oxycodone at an infusion rate of (16–18) mcg/kg/h and a bolus dose of 1.5 mg with a lockout time of 15 min during the first 48 h postoperatively.

Outcomes

The primary outcome was the occurrence of EA which was evaluated using Aono's four-point scale (AFPS) score. Patients' status was divided into four stages by AFPS score (2, 21): stage 1, calm; stage 2, not calm but could be easily calmed; stage 3, not easily calmed, moderately agitated or restless; stage 4, combative, excited, or disoriented. EA was defined as an AFPS score ≥ 3 from "time zero" to 2 min after extubation.

$$EA\ occurrence = \frac{Number\ of\ patients\ (stage3 + stage4)}{Total\ number\ of\ patients} \times 100\%$$

The secondary outcomes included intraoperative mean arterial pressure (MAP) and HR at different time points after extubation; blood loss; duration of anesthesia; duration of surgery; duration of one-lung ventilation (OLV); emergence time; extubation time; sufentanil consumption; and propofol consumption; and post-operative pain intensity was measured by visual analogue scale (VAS), Ramsay sedation score (RSS), and PCA demand times at different time points after extubation.

Emergence time was defined as the time between propofol termination and first eye opening. Extubation time was defined as the time between propofol termination and extubation. The MAP and HR was recorded at the end of surgery just before extubation, and at 5, 10, 30, and 60 min after extubation. VAS pain scores, RSS, and PCA demand times were recorded at 60 min, 240 min, 24 h, and 48 h after extubation.

Statistical Analysis

The sample size was calculated based on a preliminary pre-experimental study using PASS 15.0 software (NCSS, Kaysville, UT, United States). The incidence of EA (RSS $\geq$ 1) in thoracoscopic lobectomy in our hospital was 45%. Assuming that at a significance level of 5%, the incidence in the TPVB group was reduced to 20%, the trial power at 80%, and the dropout rate is at 10–15%, the study required a minimum of 47 patients per group. This study expanded the sample size to 50 patients per group.

Statistical analyses were performed using SPSS software version 15 (SPSS, Inc., Chicago, IL, United States). The primary efficacy data on the occurrence of EA were examined using intention-to-treat analysis. The normality of distribution was assessed with a Q-Q plot and the Shapiro–Wilk test. Data conforming to normal distribution were described as mean ± standard deviation (SD) and non-normal distribution of data was shown as median (IQR). The normally distributed variables, including demographic characteristics data, intraoperative and recovery data, were assessed by independent *t*-test. Non-parametric data were analyzed using the Mann–Whitney U-test and descriptive variables were evaluated using the Chi-square test or Fisher's exact test. Hemodynamic data were compared by repeated measurement analysis of variance. Multivariable logistic regression analysis was applied to measure the relative risk of TPVB vs. ICNB on EA. P-value < 0.05 was considered statistically significant.

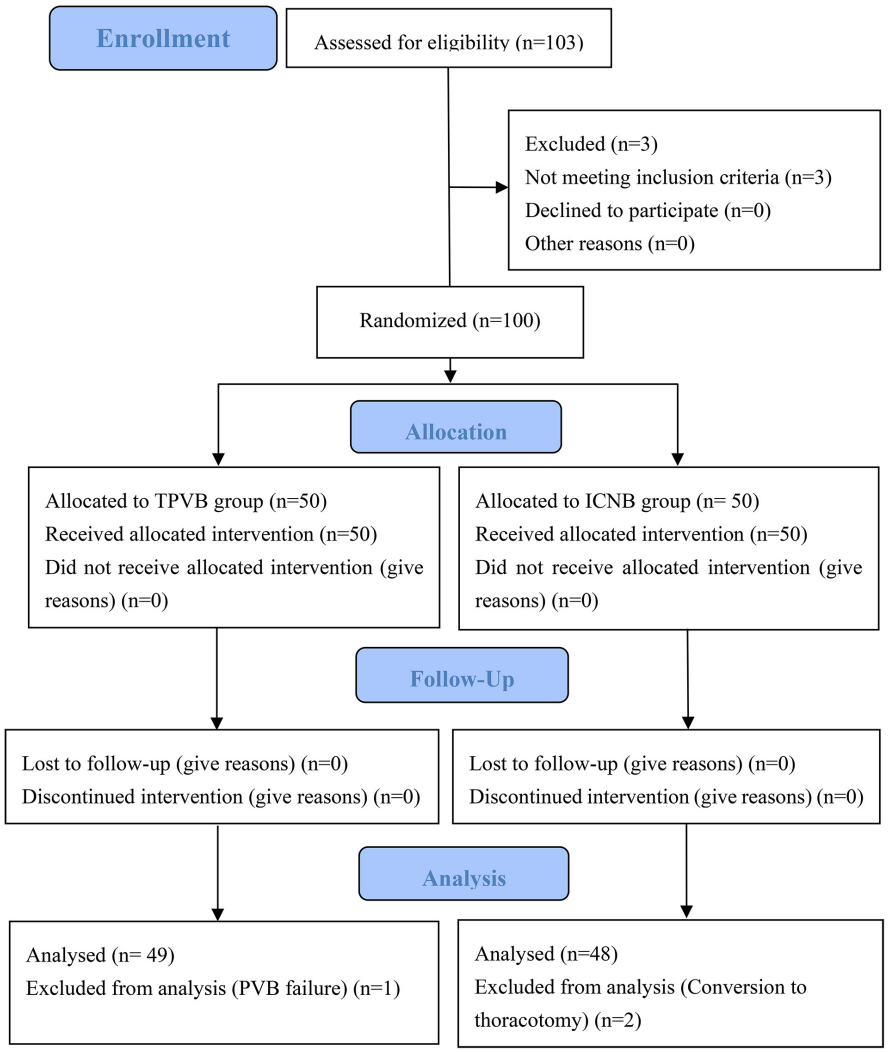

FIGURE 1 | CONSORT flow diagram. TPVB indicates thoracic paravertebral blocks, and ICNB indicates intercoastal nerve blocks.

RESULTS

A total of 103 patients were assessed for eligibility. Among them, 3 patients did not meet the eligibility criteria and another 3 patients withdrew from the final analysis because of either conversion to thoracotomy or TPVB failure. Thus, 97 patients were included in the final analysis (**Figure 1**). There were no significant differences between the two groups in terms of age, gender, BMI, ASA classification, MoCA, lung function, preoperative forced expiratory volume in the first second (FEV1), preoperative forced vital capacity (FVC), preoperative FVC/FEV1 ratio and preoperative comorbidities (all $P > 0.05$) (**Table 1**).

The occurrence rates of EA during tracheal extubation in the TPVB group (12.2%, 6/49) were significantly less than in the ICNB group (31.3%, 15/48). Furthermore, multivariable logistic regression analysis suggested that preoperative TPVB (relative risk = 1.276, 95% CI: 1.020–1.600, $P = 0.028$) was associated with lower occurrence of EA (**Table 2**). However, the results of hemodynamics showed that the MAP and HR did not change significantly before extubation in both groups ($P > 0.05$), but were significantly lower in the TPVB group at 5, 10, and 30 min after extubation than those in the ICNB group ($P < 0.05$, **Table 3**). The emergence time (12.8 ± 7.2 vs. 16.1 ± 6.7, $P = 0.023$) and extubation time (14.4 ± 7.5 vs. 17.6 ± 6.9, $P = 0.031$) in TPVB group were significantly shorter than those in the ICNB group. Moreover, patients in the TPVB group showed less intraoperative consumption of sufentanil (26.1 ± 5.5 mcg vs. 29.2 ± 8.1 mcg, $P = 0.028$) than those in the ICNB group (**Table 3**).

Further analysis showed that the post-operative pain was well controlled in both groups from 1 to 48 h after surgery (mean VAS pain scores less than 3). There were significantly lower VAS pain scores in the TPVB group at rest or coughing at each time point than those in the ICNB group ($P < 0.05$). Additionally, the RSS in the TPVB group at 60 and 240 min after extubation was significantly lower than those of the patients in the ICNB group ($P < 0.05$, **Table 3**). There were 5 cases of post-operative nausea

TABLE 1 | Clinical characteristics of the patients.

	TPVB group (*n* = 49)	ICNB group (*n* = 48)	*P*-value
Age (year)	62.4 ± 7.6	63.8 ± 7.6	0.360
Gender (male/female)	25/24	23/25	0.760
BMI (kg/m^2)	25.1 ± 3.5	25.5 ± 3.7	0.528
ASA (I/II/III)	11/36/2	8/39/1	0.750
Montreal Cognitive Assessment	28.7 ± 1.4	28.9 ± 1.3	0.442
Lung Function			
Preoperative FEV_1 (L)	2.33 ± 0.48	2.36 ± 0.54	0.816
Preoperative FVC (L)	3.01 ± 0.59	2.93 ± 0.75	0.545
Preoperative FEV_1/FVC	78.06 ± 8.74	76.34 ± 10.18	0.375
Preoperative comorbidities			
Hypertension, *n*	21	22	0.768
Diabetes, *n*	10	10	0.959
Coronary heart disease, *n*	4	4	0.976

BMI, body mass index; ASA (I/II/III), American Society of Anesthesiologists physical status I–III; FEV1, forced vital capacity rate of one second; FVC, forced vital capacity.

TABLE 2 | Comparison of Aono's four-point scale between the two groups.

	AFPS stage ≥ 3	Relative Risk (95% CI)	*P*-value
TPVB group	6/49	1.276, (1.020 ∼ 1.600)	0.028
ICNB group	15/48	Ref.	Ref.

in the TPVB group and 3 cases in the ICB group ($P = 1.000$) and there was no vomiting in either group.

DISCUSSION

This study showed that preoperative TPVB significantly decreased the occurrence of EA during tracheal extubation and the changes in hemodynamic instability after tracheal extubation in patients who underwent thoracoscopic lobectomy.

There might be several factors to explain the better efficacy of TPVB when compared to ICNB. First, the two-level injection of local anesthetics (LA) into the PVS at T_{3-4} and T_{6-7} can spread across from T_1 to T_8 (T1–T8 means the anesthetic plane). The two-level injection of LA into the intercostal space could only result in two dermatomal blockades. Second, TPVB might cause unilateral sympathetic and somatic nerve blockade, and preoperative ICNB could only cause segmental somatic nerve blockade. In addition, preoperative TPVB might reduce central sensitization by blocking the transference of nociceptive stimulation to the central nervous system. As a result, TPVB could decrease the occurrence of hyperalgesia and allodynia. The follow-up data also indicate that patients who received preoperative TPVB had lower VAS pain scores at rest and coughing than patients with ICNBs at each time point within 48 h after surgery. Thirdly, less use of sufentanil may avoid or reduce the hyperalgesia effects induced by opioids (22). Taken together, TPVB might reduce the occurrence of EA possibly by alleviating the acute post-operative pain. Previous studies showed that regional nerve blockade not only enhances post-operative analgesia but also produces a higher quality of recovery after surgery (23–25). This study found that patients receiving TPVB had a shorter emergence and extubation time than those with ICNBs. Furthermore, patients in the TPVB group presented a lower RSS within 4 h postoperatively than that in the ICNB group. Additionally, TPVB could reduce the general anesthetic dosage of sufentanil during operation. At the end of the surgery,

TABLE 3 | Comparison of secondary outcomes between the two groups.

	TPVB group (*n* = 49)	ICNB group (*n* = 48)	*P*-value
Hemodynamics			
MAP (mmHg)			
Before extubation	92.2 ± 9.6	94.7 ± 10.4	0.225
5 min after extubation	96.0 ± 13.6	101.6 ± 12.9	0.041
10 min after extubation	92.3 ± 10.6	97.3 ± 13.1	0.047
30 min after extubation	88.8 ± 9.9	95.3 ± 11.7	0.004
60 min after extubation	88.4 ± 11.0	91.2 ± 9.9	0.194
HR (beats·min^{-1})			
Before extubation	69.9 ± 13.4	71.3 ± 13.8	0.615
5 min after extubation	88.0 ± 11.1	94.1 ± 12.0	0.011
10 min after extubation	84.9 ± 12.4	90.4 ± 11.7	0.026
30 min after extubation	80.0 ± 12.9	85.8 ± 12.2	0.022
60 min after extubation	78.6 ± 14.0	83.0 ± 11.0	0.087
Intraoperative details and recovery characteristics			
Blood loss (ml)	186 ± 156	212 ± 222	0.506
Duration of anesthesia (min)	187 ± 54	187 ± 55	0.995
Duration of surgery (min)	175 ± 55	172 ± 52	0.774
Duration of OLV (min)	165 ± 57	163 ± 52	0.872
Emergence time (min)	12.8 ± 7.2	16.1 ± 6.7	0.023
Extubation time (min)	14.4 ± 7.5	17.6 ± 6.9	0.031
Sufentanil (mcg)	26.1 ± 5.5	29.2 ± 8.1	0.028
Propofol (mg)	800 ± 240	820 ± 293	0.720
Post-operative pain intensity			
VAS score at rest			
60 min	0 (0–1)	1 (0–1)	0.161
240 min	0 (0–1)	0 (0–1.75)	0.001
24 h	1 (0–2)	1.5 (1–2)	0.018
48 h	1 (0–1)	1 (1–2)	0.028
VAS score at coughing			
60 min	1 (0–2)	2 (0–3)	0.039
240 min	1 (0–2)	2 (1–3)	0.014
24 h	2 (2–3)	3 (2–3.75)	0.014
48 h	2 (1–2.5)	2 (2–4)	0.022
RSS scores			
60 min	2 (2–3)	3 (2–3.75)	0.017
240 min	2 (2–2)	2 (2–3)	0.028
24 h	2 (2–2)	2 (2–2)	1.000
48 h	2 (2–2)	2 (2–2)	1.000
PCA demand times			
60 min	0 (0–1)	0 (0–1)	0.460
240 min	0 (0–1)	1 (0–2)	0.381
24 h	1 (1–3)	2 (0–4)	0.526
48 h	2 (1–4.5)	4 (0–6)	0.173

MAP, mean arterial pressure; HR, heart rate; OLV, one-lung ventilation; VAS, visual analogue scale; RSS, Ramsay sedation score, PCA, patient-controlled analgesia.

the residual anesthetics in patients were lower and could be naturally eliminated more quickly, making them transition from the anesthesia state to a normal waking state.

EA can increase sympathetic nerve excitability, induce hemodynamic changes including hypertension and tachycardia, and may lead to cerebral vascular events. Patients undergoing lobectomy are usually older and complicated with multiple comorbidities, such as cardiovascular diseases, hypertension, and diabetes. Although there were no cardio-cerebral vascular events in either group, patients in the TPVB group maintained better hemodynamic stability when compared to the ICNB group during tracheal extubation. The hemodynamic stability in the TPVB group might be from the blockade of the cardio-accelerator nerves (T_1–T_4) with this block.

Vishal et al. (26) showed that the ultrasound-guided single-injection TPVB provided equivalent dermatomal spread and duration of analgesia when compared with the multiple-injection TPVB. The reason we chose two-level thoracic PVS injection was that thoracoscopic surgery is usually performed through two access ports in our hospital (27). The procedure port (4-cm incision) and the scope port (1.5-cm incision) were chosen at the level of the 3rd or 4th intercostal space in the anterior axillary line and the 7th or 8th intercostal space along the post-axillary line respectively, so the block area needs to cover T_3–T_8 unilaterally. Cowie et al. (28) showed that 20 ml of contrast dye could spread 4.5 segments after a single paravertebral injection and could spread to 6 segments with a two-level paravertebral injection in a cadaveric study. In addition, Kasimahanti et al. (13) reported that patients receiving two-level TPVB showed better analgesic effects than those with single-level TPVB. Copik (29) and Coopey (30) found that the ultrasound-guided TPVB failure rate in adults ranged from 3.9 to 7.4%. In this study, the failure rate was 2.00% (1/50) as one patient developed sensory blockade in less than 3 adjacent segments. The main cause of failure block might be the difficulty of clearly defining the transverse process (TP) with ultrasound due to excessive tissues.

There are some limitations to our study. First, the sample size was small and there might be a type 2 error. Second, previous studies indicated that the preoperative anxiety state was related to agitation and this study did not evaluate the preoperative anxiety state of these patients.

In conclusion, preoperative TPVB was associated with less EA during tracheal extubation when compared with ICNB in patients undergoing thoracoscopic lobectomy.

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.

ETHICS STATEMENT

The present study was approved by the Institutional Review Board of Beijing Chest Hospital [ID: (2018) Ethical Review of Clinical Trial Recommended Project No. 03-01]. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

WL: study design, data analysis, manuscript revision, and critical content editing. TJL: statistical review and manuscript revision. FW: data collection and manuscript preparation. DZ: data collection and manuscript revision. TL: data verification and manuscript revision. JH: study design and data analysis. SX: study design, data analysis, and critical content editing. All authors have read and agreed to the published version of the manuscript.

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Postoperative Nausea and Vomiting in Female Patients Undergoing Breast and Gynecological Surgery: A Narrative Review of Risk Factors and Prophylaxis

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Postoperative nausea and vomiting (PONV) have been widely studied as a multifactorial entity, being of female gender the strongest risk factor. Reported PONV incidence in female surgical populations is extremely variable among randomized clinical trials. In this narrative review, we intend to summarize the incidence, independent predictors, pharmacological and non-pharmacological interventions for PONV reported in recently published clinical trials carried out in female patients undergoing breast and gynecologic surgery, as well as the implications of the anesthetic agents on the incidence of PONV. A literature search of manuscripts describing PONV management in female surgical populations (breast surgery and gynecologic surgery) was carried out in PubMed, MEDLINE, and Embase databases. Postoperative nausea and vomiting incidence were highly variable in patients receiving placebo or no prophylaxis among RCTs whereas consistent results were observed in patients receiving 1 or 2 prophylactic interventions for PONV. Despite efforts made, a considerable number of female patients still experienced significant PONV. It is critical for the anesthesia provider to be aware that the coexistence of independent risk factors such as the level of sex hormones (pre- and postmenopausal), preoperative anxiety or depression, pharmacogenomic pleomorphisms, and ethnicity further enhances the probability of experiencing PONV in female patients. Future RCTs should closely assess the overall risk of PONV in female patients considering patient- and surgery-related factors, and the level of compliance with current guidelines for prevention and management of PONV.

Keywords: postoperative nausea and vomiting, female gender, gynecological surgery, breast surgery, randomized clinical trial ERAS (Enhance Recovery After Surgery)

INTRODUCTION

Postoperative nausea and vomiting (PONV) are one of the main distressing symptoms commonly reported after surgery and prompt patients at risk to serious complications, such as gastric aspiration, psychological distress, wound dehiscence, deferred recovery, and prolonged discharge times. Female gender is considered an independent predictor of PONV, being a determinant factor when assessing its preoperative risk (1–3). The Society for Ambulatory Anesthesia (SAMBA) Guidelines for PONV management recommend a multimodal approach or combination therapy consisting of two or more interventions in patients with moderate and high risk of PONV, respectively (4, 5). Although the pathophysiology of PONV is multifactorial, PONV is more insidious in female surgical patients than in male, including elderly patients (6). Women also show a higher susceptibility to motion sickness during air, water, and terrestrial travel, which further increases their risk of PONV (1–3). Several studies have demonstrated an association between hormonal changes and PONV in females at a reproductive age (7–10). Nevertheless, current reports on the frequency of PONV during pre-ovulatory (proliferative) and post-ovulatory (luteal) phases of the menstrual cycle are controversial (7, 9–11).

Current literature describing PONV in female patients undergoing breast and/or gynecological surgery is highly variable in terms of incidence, predictors, risk stratification and management. Several reviews, protocols and guidelines have attempted to summarize PONV management in the general population,. We reviewed the most recent evidence on the impact of PONV occurrence after breast and gynecological surgery to summarize the reported specific considerations about the incidence, independent predictors, and perioperative management (pharmacological and non-pharmacological). Furthermore, we consider that this extensive review of the literature that we have carried out can provide us with a more precise view of some aspects of the clinical spectrum of PONV in female surgical patients that should require a systematic review and meta-analysis.

Objectives of the Review

To determine the incidence of PONV in female patients undergoing breast and/ or gynecological surgery.

- To identify independent predictors and risk factors for PONV in this subset of patients, although they apply to the female surgical population
- To evaluate the pharmacological and non-pharmacological strategies most currently used for the prophylactic and therapeutic management of PONV.
- To assess the influence of anesthetic agents on PONV occurrence and clarify the optimal anesthetic technique.
- To evaluate the efficacy of the most widely used risk-scoring systems in the risk stratification for PONV in the female surgical population.

Aims

To Provide updated knowledge to anesthesia providers about key elements that allow them to optimize the perioperative management of PONV in the female population.

Abbreviations: ERAS, Enhance Recovery After Surgery; GA, general anesthesia; NIH, National Institutes of Health; PONV, postoperative nausea and vomiting; PON, postoperative nausea; POV, postoperative vomiting; TIVA, Total Intravenous Anesthesia.

METHODS

The research question was formulated according to the PICO methodology. P = Women undergoing breast or gynecological surgery; I = Prevention and treatment of PONV; C = Premenopausal and postmenopausal adult female surgical patients; O = independent predictors and risk factors, risk stratification, available therapeutic strategies, anesthetic management in high-risk patients for PONV.

We performed an extensive literature search in PubMed, MEDLINE, and Embase databases of articles describing PONV management in female surgical populations (i.e., breast surgery and gynecologic surgery) published between January 1, 2011, and June 30, 2021, following the Preferred Reporting Items for Systematic Reviews and meta-Analysis (PRISMA) guidelines (**Figure 1**) (12). Initially, we use the following keywords and Medical Subject Headings (MeSH) terms: "postoperative nausea and vomiting," "PONV," "female gender," "gynecological surgery," "breast surgery" and their combinations were used. Thereafter, the following systematic search strategy was used: (PONV OR postoperative nausea and vomiting OR nausea and vomiting, postoperative OR postoperative vomiting OR vomiting, postoperative OR nausea, postoperative OR emesis, postoperative, postoperative, OR postoperative emesis OR postoperative nausea OR antiemetic effect OR complete response) AND (gynecological procedure OR gynecological surgery OR breast surgery OR mastectomy OR mammaplasty) AND (female OR woman). With the results of the initial electronic search, two authors hand-screened several to confirm the following eligibility criteria: Articles published in English language between January 1, 2011, and June 30, 2021, reporting PONV as a primary outcome and describing PONV management in female patients undergoing either breast or gynecologic surgery were included. In addition, our literature search included retrospective studies, systematic reviews, meta-analyses, and review articles from a cited reference search. We excluded conference abstracts and posters, reviews of non-primary research, case reports, series of case reports and articles published in other language other than English. All authors conducted the final review of all databases in July 2021.

RESULTS

Our database search identified a total of 3,299 articles. After 1,320 duplicated articles were removed, 1,979 articles underwent title and abstract screening. Following this, we selected around 89 publications as reliable articles addressing exclusively PONV in females and screened for eligibility (**Figure 1**). Among these

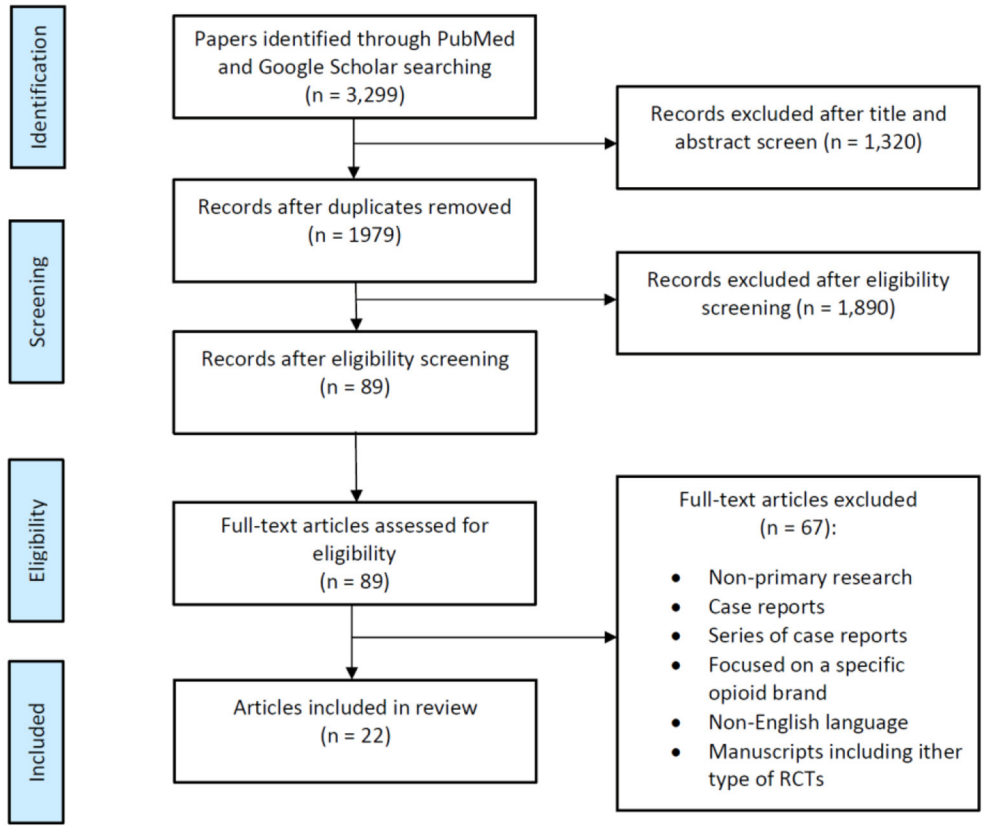

FIGURE 1 | Flow diagram summarizing the selection of randomized clinical trials (RCTs) describing postoperative nausea and vomiting (PONV) in female surgical population.

89 articles, 67 were excluded for various reasons as shown in **Figure 1**, and we finally identified a total of 22 eligible publications with a significant number of patients and relevant compilation of demographic and clinical outcomes (**Table 1**). This is a narrative review; therefore no statistical analysis was performed.

DISCUSSION

Incidence of PONV in Patients Undergoing Breast and Gynecological Surgery

There is sufficient documentation showing that women undergoing breast and gynecological surgery have a reported incidence of postoperative nausea and vomiting up to 80% to 95% within the first 24 h after surgery when they received insufficient or no prophylactic antiemetic therapy (34–36). Conversely, the occurrence of PONV in this subset of surgical patients can dramatically decrease after the systematic implementations of PONV guidelines (37).

Breast cancer surgery constitutes an additional risk factor for PONV in female surgical patients with a reported incidence of up to 30% to 68% within the first 24 h postoperatively in patients that received intraoperative prophylactic antiemetics (38–40), whereas in non-treated patients PONV frequency increases to 70%-80% of patients (41–43).

Gynecological surgery involves patients who are at high risk for PONV is associated with a higher incidence of PONV (female sex, non-smoking status, and requirement for postoperative opioids) (34). The incidence of PONV in the obstetric and gynecological surgical patients has ranged between 40–80%, especially in laparoscopic surgery (28, 44–46).

Specific Risk Factors for Postoperative Nausea and Vomiting in Female Surgical Populations

The multifactorial etiology of PONV has been widely studied with the subsequent identification of several independent predictors such as emetogenic factors (e.g., perioperative use of opioids, inhaled or balanced anesthesia, length of anesthesia) and patient-related risk factors (e.g., smoking status, female gender) (2). Being a female patient is the strongest predictor of PONV, followed by the antecedent of episodes of PONV and motion sickness (2, 3, 5). Other known PONV predictors in women are preoperative history of nausea and vomiting during pregnancy, female neonate, and premenstrual syndrome (2, 4). However, it is very important for the anesthesia providers to recognize the presence of other lesser known independent risk factors

TABLE 1 | Randomized clinical trials and postoperative nausea and vomiting outcomes.

References	Surgery type	Anesthesia type	N/Groups	Dose active/Control	PONV incidence
D'souza et al. (13)	Lap. Gyn	Inhaled	31/31/31	Dexamethasone 4 mg / dexamethasone 8 mg / ondansetron 4 mg	29% / 43% / 61% of PONV at 24 h, $p = 0.16$
Ekinci et al. (14)	Lap/open Gyn	Inhaled	20/20/20/20 /20	Droperidol 2.5 mg / metoclopramide 10 mg / tropisetron 2.5 mg / ondansetron 4 mg / control	20% / 40% / 25% / 15% / 60% at 24 h; drop. vs. control $p < 0.009$; Trop. vs. control $p < 0.02$; Ond. vs. control $p < 0.003$
Park and Cho, (15)	Lap. Gyn	Both	50/50	Palonosetron 0.075 mg + Inhaled / Palonosetron 0.075 mg + TIVA	48% / 50% at 24 h, $p > 0.05$
Park and Cho, (16)	Lap. Gyn	Inhaled	45/45	Palonosetron 0.075 mg / ondansetron 8 mg	42.2% / 66.7% at 24 h, $p < 0.05$
Kasagi et al. (17)	Lap. Gyn	TIVA	30/30/30/30	Fentanyl 20 $\mu g.kg^{-1}$ / fentanyl 20 $\mu g.kg^{-1}$ + droperidol 2 mg / fentanyl 20 $\mu g.kg^{-1}$ + naloxone 0.1 mg / fentanyl 20 $\mu g.kg^{-1}$ + droperidol 2 mg + naloxone 0.1 mg	43% / 43% / 70% / 17% at 24 h, $p < 0.001$
Kawano et al. (18)	Lap. Gyn.	Both	42/42/42	Sevoflurane / propofol 4-8 $mg.kg^{-1}.h$ / propofol 2 $mg.kg^{-1}.h$ + sevoflurane	62% / 29% / 21% at 24 h, $p < 0.0005$
Soga et al. (19)	Open Gyn.	Inhaled	24/20	Fosaprepitant 150 mg / ondansetron 4 mg	71% / 55% at 24 h, $p > 0.05$
Joo et al. (20)	Lap. Gyn.	Inhaled	50/49/50	IV saline / haloperidol 1 mg / haloperidol 2 mg	42% / 22% / 20% at 24 h, $p = 0.03$
Yang et al. (21)	Lap. Gyn.	Inhaled	50/53/50	Acu+ dexamethasone 10 mg / Tropisetron 5 mg + dexamethasone 10 mg / dexamethasone 10 mg	28% / 26% / 50% at 24 h, $p = 0.048$
Bang et al. (22)	Lap. Gyn.	TIVA	50/50	Palonosetron 0.075 / saline 1.5ml	34% / 58%, $p = 0.027$
Dewinter et al. (23)	Lap. Gyn.	Inhaled	196/196/123	Alizapride 100 mg / Ondansetron 4 mg / Saline 4ml	32.1% / 28.6% / 34.1% in PACU (RR 1.13, 90% CI 0.87–1.45); 36.8%/31.5%/39.3% at 24h (RR 1.17, 90% CI 0.91−1.50)
Geng et al. (24)	Lap. Gyn.	TIVA	65/65	Dexmedetomidine 0.5 $\mu g.kg^{-1}$ over 10 mins loading, 0.1 $\mu g.kg^{-1}.h$ maintenance / equal volume of saline	5% /14% at 2 h. $p = 0.069$; 38.5% / 43.1% at 24h. $p = 0.592$
Soga et al.Lee (19)	Lap. Gyn.	Inhaled	55/55	Aprepitan 80 mg + ondansetron 4 mg stat + 12 mg into PCA / ondansetron 4 mg stat + 12 mg into PCA	62% / 84% at 24h. $p = 0.011$; 67% / 84% at 48 h. $p = 0.05$.
Lee et al. (25)	Lap. Gyn.	Inhaled	45/44	Ramosetron 0.3 mg EOS + 0.3 mg 4 h postop/ramosetron 0.3 mg EOS + saline 4 h postop	42.2% / 25% at 24h. $p = 0.086$
Kim et al. (26)	Lap. Gyn.	Inhaled	44/44/44/44	Ramosetron 0.3 mg stat + 0.6 mg into PCA / Ramosetron 0.3 mg stat / Palonosetron 0.075 mg / normal saline	8/27/22/33 patients had PONV at 24h; 4/19/17/22 at 48 h; 0/13/14/12 at 72h after discharge from PACU, $p < 0.05$;
Oh et al. (27)	Lap. Gyn.	Inhaled	47/47	Nefopam PCA / fentanyl PCA; rescue ondansetron 4 mg	31.9% / 57.4% at 24 h. $p = 0.022$
Bhakta et al. (28)	Lap. Gyn.	Both	30/30	Propofol + nitrous oxide / Propofol infusion + Isoflurane + nitrous oxide	36.6% / 76.6%, $p < 0.01$
Khan et al. (29)	Lap. Gyn.	Inhaled	70/70	Gabapentin 600 mg /oral placebo 2h. before surgery	32.9% / 64.3% at 24h $p = 0.001$
Seki et al. (30)	Lap. Gyn.	GA / GA + epidural	45/45	12–15 ml 0.5% Ropivacaine + GA / GA with remifentanil infusion + intermittent fentanyl boluses	44.4% / 60% (RR 0.53, 95% CI 0.23–1.23), $p = 0.14$

(Continued)

TABLE 1 | Continued

References	Surgery type	Anesthesia type	N/Groups	Dose active/Control	PONV incidence
Omran and Nasr (31)	Mastectomy	Inhaled	40/40	Mirtazapine 30 mg / Ondansetron 16 mg	25% / 35% at 24 h (RR 0.7143, 95 % CI 0.3607–1.414)
Voigt et al. (32)	Elective breast surgery	Both	80/80/80/79 /80/81	Haloperidol 1.25 mg + Tropisetron 2 mg + TIVA / Haloperidol + Tropisetron + Volatile / Dimenhydrinate 31 mg + Dexamethasone 4 mg + TIVA / Dimenhydrinate + Dexamethasone + Volatile / Placebo + TIVA / Placebo + Volatile	25% /17.5% / 15% / 11.4% / 43.8% / 48.1%; halo. + trop. reduced PONV 3.4 x more than placebo (OR 0.30, CI 0.18–0.50, $p > 0.0001$); dimen. + dexa. reduced PONV 5.9 x more than placebo (OR 0.17, CI 0.09–0.30, $p < 0.0001$)
Olanders et al. (33)	Partial mastectomy	Inhaled	37/38	Betamethasone 8 mg / control	57% / 68%, $p = 0.27$

N, number of patients; PONV, postoperative nausea and vomiting; Drop, droperidol; Trop, tropisetron; Ond, ondansetron; TIVA, total intravenous anesthesia; IV, intravenous; Acu, acustimulation; PACU, post-anesthesia care unit; RR, relative risk; CI, confidence interval; PCA, patient controlled analgesia; EOS, end of surgery; Postop, postoperatively; GA, general anesthesia; TIVA, Total Intravenous Anesthesia; Halo, haloperidol; Dimen, dimenhydrinate; Dexa, dexamethasone.

that enhance the frequency of PONV such as sex hormones levels, psychosocial factors, pharmacogenomic pleomorphism, and ethnicity.

Hormonal Status According to the Menstrual Cycle

Anecdotally, the incidence trend of emetic episodes increases after menarche and decreases through the menopausal transition (10, 47). Moreover, increased estrogen and progesterone levels during pregnancy have been associated with a prolonged gastrointestinal transit time and a reduction in the esophageal sphincter pressure (10). These facts suggest that cyclic variations in reproductive hormones in females may influence their susceptibility to nausea and motion sickness and therefore, to PONV (4, 6). Previous reports in women revealed that their hormonal status could play an important role in the occurrence of PONV within the first 5 days of the menstrual cycle (48, 49). Based on these assertions, a female patient undergoing major surgery under balanced or inhaled anesthesia, in which postoperative opioid use is expected (e.g., breast cancer surgery or laparoscopic gynecological surgery), is considered at high risk of PONV regardless of her age, smoking status or history of PONV and a multimodal prophylactic approach for PONV (>2 interventions) is highly recommended (5).

The correlation between the menstrual cycle phases and the frequency of PONV has been assessed by several authors, however, there is no firm evidence linking any specific phase of the cycle with a higher propensity for PONV. Nevertheless, an increased incidence of early PONV in women in the follicular and ovulatory stage, when levels of estrogen (estradiol) are higher, compared to those who were in the luteal phase has been reported by several studies (8, 9). Other researchers found a significant association between the ovulatory phase of the menstrual cycle and a higher incidence of early and late PONV when compared to the follicular and luteal phases. In addition, in the study of Zou et al., after multivariate logistic regression analysis showed that the phase of the menstrual cycle was an independent risk factor for early and late PONV (50). Conversely, other studies have concluded that changes in female hormones during the different stages of the menstrual cycle were not associated with an increased incidence of PONV (7, 51). The higher incidence of PONV in premenopausal women has been associated to high plasma levels of estrogen hormones, and to greater requirements of opioids (52, 53). The study conducted by *Kudach et al.* showed an equivalent rate of PONV in female patients up to $\geq$ 70 years, when the incidence of PONV was significantly lower (52). Therefore, we should consider these variables in female patients undergoing major surgery when assessing the PONV risk factors as described in the current consensus guidelines (4).

PONV Associated With Tumor Receptor Status in Breast Cancer Surgery

Estrogen and progesterone receptors in the breast tissue are affected by the level of sex hormones and are actively involved in the development of breast cancer; with the endogenous estrogen and progesterone binding specifically to estrogen receptors (ER) or progesterone-receptor (PR), and influencing tumor growth (54). In addition, elevated estrogen levels are also known to increase emesis, suggesting a potential interaction of the estrogen receptor (49). The higher incidence of PONV in premenopausal patients has been linked to elevated estrogen levels (estrone, estradiol, and dehydroepiandrosterone), hence, the higher frequency of PONV observed in postmenopausal women (>50 years) and positive-ER breast cancer also correlates with high estrogen levels (55) (**Table 2**).

Preoperative Psychosocial Factors Affecting Women Undergoing Breast and Gynecological Surgery

Preoperative psychological factors such as anxiety and distress may be associated with increased severity of PONV in women

TABLE 2 | Physiologic changes associated with an increased risk of postoperative nausea and vomiting in the female population (Independent risk factors).

Preoperative history of severe nausea and vomiting during pregnancy, female neonate, premenstrual syndrome (2, 4)
Follicular and proliferative phase of menstrual cycle (7, 8, 9, 11, 30, 31, 32, 33, 34).
Age ≥ 50 years, previous chemotherapy, and estrogen-positive breast tumor (30, 35, 36).
Preoperative anxiety and stress (36, 38, 39, 40, 41).
Pharmacogenomic pleomorphism (28, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52).
Ethnicity (lower incidence in Black-Africans) (53, 54, 55).

with breast cancer (56). Even conservative minor procedures, such as excisional breast biopsy and conservative lumpectomy can be very stressful for women. The onset of preoperative stress in these patients was associated to a variety of factors such as exposure to surgery and anesthesia, experiencing postoperative pain, appearance, scarring, and cancer diagnosis and prognosis (57). Response expectancies based on previous personal or vicarious experiences, have shown to determine immediate postoperative outcomes regarding pain, PONV and fatigue (56, 58–60). In addition, *Montgomery et al.* reported that anxiety and stress, as part of response expectancies, may have an important influence on late post-discharge nausea and vomiting occurrence (59).

Genomic Pleomorphisms and Ethnicity

Recent studies have demonstrat that previous history of chemotherapy-induced nausea and vomiting (CINV) may contribute to increase the risk of PONV (61). Conversely, there is also evidence showing that patients who have not presented PONV after general anesthesia do not experience CINV either because of different mechanisms including genetic predisposition (47, 61–65).

For instance, polymorphisms in the serotonin transport genes are associated with increased PONV in women with breast cancer, even before receiving chemotherapy (47), while there is a tendency for individuals categorized as CYP2D6 poor metabolizers to experience PONV (66). Moreover, polymorphisms in the serotonin receptor genes HTR3A and DRD3 are linked to a decrease rate of PONV, while on the contrary, HTR3B receptor gene polymorphism may contribute to an increase PONV (67–69). Therefore, pharmacogenomic variability in serotonin transport genes may explain the erratic incidence of PONV and the irregular response to antiemetic medication observed in around 30% of patients undergoing breast cancer surgery (69). Individual carriers of alleles to COMT, DRD3 and TPH genes show a tendency to low PONV frequency (69). Women presenting some genotypes such as Val/Val may experience higher pain intensity, and opioid requirements contributing to increase the occurrence of PONV (especially nausea), when compared with patients with heterozygous V/Met polymorphism (69). The Met/Met genotype has been related with an elevated density of mu receptors, which may explain the reduced levels of pain and opioid consumption observed in those patients (70, 71).

Several studies have demonstrated that ethnicity can be an independent risk factor for PONV, whose incidence shows variations in different ethnic groups, which have so far been more noticeable in Black patients. The effect of ethnicity on PONV could be influenced by pharmacogenomic and cultural factors (72–74). However, although more studies are lacking in various ethnic groups, the existing evidence would raise a question about the validity of the scoring systems derived predominantly from the ethnically Caucasian population and if ethnicity could be used to improve the predictability of PONV in the female surgical population.

PHARMACOLOGICAL INTERVENTIONS FOR POSTOPERATIVE NAUSEA AND VOMITING IN FEMALE SURGICAL POPULATIONS

Postoperative nausea and vomiting persist as one of the commonest complications even though the use of many aggressive antiemetic prophylactic strategies has increased over the last twenty years (75). The growing implementation of the Enhance Recovery After Surgery (ERAS) protocols in most surgical procedures have allowed to tailor the pharmacologic treatment to the patient's risk level of PONV determined by the currently validated risk-scoring system and treatment guidelines (2, 4, 41).

Regarding the pharmacological management of PONV/PDNV, dexamethasone and 5-hydroxytryptamine-3 (5-HT_3) receptor antagonists are the most common PONV prophylactic medications used among trials. Other pharmacological interventions can be used such as dopamine receptors antagonists, neurokinin-1 (NK-1) receptor antagonists, total intravenous anesthesia (TIVA), gabapentin, nefopam, midazolam, intranasal nicotine, and naloxone were also reported (4, 76). Moreover, there is limited data on non-pharmacological interventions such as the use of transcutaneous acupoint stimulation in female surgical populations (4).

Dexamethasone

The prophylactic effect of dexamethasone on PONV may vary based on dose administered and population-specific risk. Dexamethasone has proven its effectiveness at dosage of 4–12 mg IV usually combined with other antiemetics (13, 17, 20, 21, 32, 77). *D'Souza et al.* reported a significant reduction in PONV incidence at 3 and 24 h after the prophylactic administration of intravenous (IV) dexamethasone (4 mg) in comparison with IV ondansetron (4 mg) in patients undergoing laparoscopic gynecological surgery under inhaled anesthesia (22.6% vs. 51.6%, $p = 0.03$ and 29% vs. 61%, respectively; $p = 0.02$). Of note, authors excluded patients with past medical history of motion sickness from this trial (13). However, a higher dexamethasone dose (8 mg) was not associated with a significant reduction on PONV occurrence, being this outcome consistent with other published reports in similar surgical populations (13, 17, 20, 21).

In an interesting design, *Kasagi et al.* reported an important reduction in PONV incidence with the combination of droperidol, dexamethasone and naloxone in patients undergoing laparoscopic gynecological surgery under total intravenous anesthesia (TIVA) and who received patient-controlled analgesia (PCA) with fentanyl IV for the management of postoperative pain. Based on Apfel's score (34), more than a half of the patients included in this trial were at high risk of PONV. Then patients were randomly assigned to either one of four groups: droperidol (Dr), dexamethasone (Dx), naloxone (Nx) and combined therapy (Cm).There was a significant reduction in PONV occurrence in the group treated with combined therapy (Cm) (17).

A combination of prophylactic IV dexamethasone and IV haloperidol is also associated with a significant reduction of PONV incidence when compared to placebo in patients at high risk undergoing laparoscopic gynecological surgery under inhaled anesthesia ($p = 0.003$) (25). Likewise, Voigt *et al.* reported a 5.9 times reduction of PONV risk in patients undergoing elective breast surgery who received a prophylactic combination of dimenhydrinate and dexamethasone when compared to a control group (OR 0.17, CI 0.09–0.30; $p < 0.0001$) (32). Other dexamethasone combinations such as dexamethasone + IV tropisetron and dexamethasone + acupoint stimulation have been also associated with a significant reduction in PONV occurrence when compared to dexamethasone alone ($p = 0.021$) (21).

5-Hydroxytryptamine-3 (5-HT$_3$) Receptor Antagonists

5-HT3 receptor antagonists have proved its effectiveness in PONV/PDNV prophylaxis and are the most recommended first-line prophylactic treatment for PONV (4, 5, 76, 78, 79). Recent clinical trials showed the efficacy of newer 5-HT3 receptor antagonist in reducing the incidence of PONV in gynecological and breast surgery (15, 16, 22, 80–82). In a prospective controlled trial comparing the effect of prophylactic palonosetron on PONV after gynecological laparoscopic procedures, *Bang et al.* reported a substantial reduction on PONV occurrence when compared to placebo (22). Moreover, *Park et al.* compared the PONV prophylactic effect of IV palonosetron (0.075 mg) with IV Ondansetron (8 mg) in patients with Apfel's score $\geq$2 finding a significant decrease in PONV incidence at 24 h in the palonosetron group when compared to ondansetron (42.2% vs. 66.7%, respectively; $p < 0.05$), although there were no significant differences between groups within the first 6 postoperative hours (15). The longer half-life of palonosetron compared to ondansetron could have influenced these outcomes (83). To our knowledge, no studies have been published describing the PONV incidence after postoperative day 1 in female patients receiving palonosetron or assessing cost-benefit of palonosetron administration on surgical patients at high-risk of PONV. Additionally, the effect of a prophylactic dose of palonosetron on the incidence of PONV is comparable to the results obtained with the administration of TIVA in this patient setting (16). In a recent report, *Hong et al.* compared the effectiveness of palonosetron (P) with the combination of midazolam-palonosetron (MP) in 104 patients undergoing breast cancer surgery. From 0 to 24 h after surgery with no intergroup statistical significance (42.3% and 48.1%) (81).

Ramosetron was also compared to palonosetron in female patients undergoing gynecological laparoscopic surgery in a study conducted by *Kim et al.* (26). They reported no significant differences on PONV occurrence in patients receiving one prophylactic IV dose of ramosetron (0.3 mg) when compared to 2 doses, one prophylactic and another dose 4 h after gynecological laparoscopic surgery (80).

Neurokinin-1 (NK-1) Receptor Antagonists

Aprepitant and fosaprepitant are the NK-1 receptor antagonists with long elimination half-life most studied as preventive treatment for PONV (84). An early study carried out by *Gesztesi et al.* revealed that NK-receptor antagonist CP-122,721 (200 mg PO), was more effective than ondansetron lowering the frequency of PONV in the first 24 following gynecological surgery (85). In a prospective study, *Soga et al.* compared the efficacy of fosaprepitant (150 mg IV) to ondansetron (4 mg) in 44 patients undergoing gynecological laparoscopic surgery under balanced general anesthesia and receiving epidural fentanyl in PCA pump for postoperative pain management. Even though complete response was similar between groups, there were no vomiting episodes reported in patients receiving fosaprepitant, whereas 4 patients experienced vomiting in the ondansetron group (0% vs. 20% respectively, $p < 0.05$) (19).

Moreover, the efficacy of oral aprepitant combined with IV ondansetron compared with ondansetron alone for PONV prophylaxis was studied by *Ham et al.* in patients with $\geq$2 risk factors for PONV and undergoing laparoscopic gynecological surgery (86). The occurrence of PONV at 24 h was significantly lower in the aprepitant +ondansetron group when compared to ondansetron group (62% vs. 84%, respectively; $p = 0.011$). However, this difference was not maintained at 48 h.

Dopamine Receptor Antagonists

Dopamine receptor antagonists (e.g., butyrophenones) have successfully been used for prevention and treatment of PONV in female surgical populations. However, effective doses are commonly linked to side effects such as sedation and extrapyramidal symptoms, hence limiting their perioperative use. Joo *et al.* randomized 150 female patients considered at high-risk of PONV and undergoing gynecological laparoscopic surgery into 3 groups: normal saline (Group H0), haloperidol 1 mg (H1), or haloperidol 2 mg (H2). The authors reported a significant reduction in PONV occurrence in both haloperidol groups when compared to normal saline (H1 = 29%, H2 = 24% and H0 = 54%, $p = 0.001$), although higher levels of sedation occurred in patients receiving 2 mg of haloperidol (H2 group) (20). *Ekinci et al.* compared the incidence of severe PONV in patients undergoing gynecologic procedures and receiving different prophylactic medications such as droperidol (2.5 mg), metoclopramide (10 mg), tropisetron (2.5 mg), ondansetron (4 mg), or saline (control group). The overall PONV incidence was 48%, being the lowest incidence of severe emesis observed in the ondansetron group compared to droperidol, metoclopramide, tropisetron, and

saline (15%, 20%, 40%, 25%, and 60% respectively) (14). This finding correlates with previous reports describing the lack of efficacy of low metoclopramide doses for PONV prophylaxis (5).

To our knowledge, only one study has described the PONV incidence in patients receiving alizapride, another dopamine antagonist commonly used in oncology. *Dewinter et al.* found no significant differences in PONV occurrence after the administration of alizapride in patients at high risk of PONV undergoing laparoscopic gynecological surgery when compared to ondansetron (23).

Other Pharmacological Interventions

The impact of a single prophylactic dose of betamethasone on PONV in patients undergoing breast surgery was assessed by *Olanders et al.* Patients were randomized to receive IV betamethasone or no prophylaxis before surgery. The authors reported no significant intergroup differences in the overall PONV incidence. Nevertheless, severity of nausea between postoperative hours 4–12 was significantly lower in the group of patients receiving betamethasone (23% vs. 50%, $p<0.05$) (33).

Considering that preoperative anxiety may play an important role in the onset of PONV, *Omran et al.* compared the PONV prophylactic effect of oral mirtazapine (30 mg), an antidepressant, to oral ondansetron (16 mg) in 80 patients undergoing mastectomy. Even though patients in the mirtazapine group experienced significantly lower preoperative anxiety levels, no differences were found in overall PONV incidence between groups (31).

In contrast, the short-acting benzodiazepine midazolam may be effective in diminishing PONV, especially when used combined with other antiemetics or as part of a multimodal antiemetic therapy in breast and other cancer-related surgeries (81, 82, 87, 88). A meta-analysis conducted by Grant *et al.* determined that midazolam was associated with a significant decrease in overall PONV rates as well as when used as rescue antiemetic medication (89). Similarly, *Ahn et al.* reported that patients medicated with midazolam presented lower incidence of PON, POV, and PONV (RR, 0.45; 95% CI, 0.36–0.57; $I^2 = 31\%$; NNT = 3; $n = 7$) (90). Although the exact mechanism for the antiemetic action of midazolam remains unknown, it has been proposed that midazolam may decrease dopamine synthesis and release by direct action on the chemoreceptor zone or by blocking adenosine reuptake (91). Although anxiolysis may contribute to the antiemetic effects of midazolam, binding to the Gamma-Aminobutyric Acid (GABA)-benzodiazepine complex reduces 5-HT_3 release and dopaminergic neuronal activity (18, 92, 93).

Kamali et al. conducted a double blind randomized clinical trial to compare the effectiveness of ginger 1 mg (before and after anesthesia) with dexmedetomidine 25 mg (before surgery) in preventing PONV after hysterectomy (94). The group of patients treated with ginger showed a lower incidence of nausea ($p = 0.02$) and vomiting ($p = 0.03$) than the dexmedetomidine group within the first 2 h postoperatively. Beyond this timepoint, there were no differences between groups (94).

NON-PHARMACOLOGICAL INTERVENTIONS FOR POSTOPERATIVE NAUSEA AND VOMITING IN FEMALE SURGICAL POPULATIONS

There are reports describing the use of acupoint electrical stimulation to reduce the incidence of PONV after breast surgery. However, its efficacy remains controversial (95–98). *Küçük et al.* studied the effect of acupressure on PONV occurrence after gynecological surgery (99). Patients were randomly allocated into three groups: to acupoint point P6 (both wrists) 1 h before surgery, to K-K9 point (both hands) 30 min before the end of surgery, and a control group (routine care). At 24 hours after surgery, patients in the K-K9 group experienced less nausea than the control group ($p < 0.05$), and less retching than patients in the P6 group ($p < 0.05$) (99). The results of a recent meta-analysis conducted by *Sun et al.* showed that non-needle acupoints stimulation also reduced the incidence of PONV in patients at moderate risk of PONV. However, the low quality and limited number of studies included in this meta-analysis did not allow for definite conclusions and recommendations (97).

ANESTHETIC MANAGEMENT AND POSTOPERATIVE NAUSEA AND VOMITING IN FEMALE SURGICAL POPULATIONS

Even though female gender, non-smoking status, past medical history of PONV (or motion sickness) and postoperative use of opioids are recognized as the main risk factors for PONV (34), other secondary variables (e.g., age <50 years, gynecological surgery, laparoscopic surgery) should be considered when determining the overall individual PONV risk (5).

There is a weak association between intraoperative use of opioids and PONV occurrence. However, inhaled anesthesia (i.e., volatile anesthetics and/or nitrous oxide) is considered the main predictor of PONV related to the anesthetic management (level of evidence A1) (5). Inhaled general anesthesia is associated with increased incidence of early PONV (0–2 h after surgery) but has no impact in delayed PONV (2, 100).

Propofol infusion is widely known to improve PONV outcomes in female surgical patients when compared to balanced anesthesia (18, 28). *Kawano et al.* studied the incidence of PONV at 0–2 h and 0–24 h after gynecological laparoscopic surgery in 126 women. Patients were randomly assigned to receive general anesthesia with either sevoflurane (Group S), propofol (Group P), or a combination of propofol and sevoflurane (Group PS) (18). Immediately after surgery (0–2 h) and up to 24 h a significantly greater number of patients in

the P and PS groups experienced a complete response when compared to group S ($p = 0.001$ and $p < 0.0005$ respectively). Nausea was also more frequent in the Group S than in the other two groups (Group S = 62%, Group P = 29% and Group PS = 21%; $p < 0.0005$) (18). Likewise, *Bhakta et al.* reported a significant reduction in postoperative emesis with the use of propofol infusion when compared to isoflurane anesthesia in patients undergoing gynecological laparoscopic surgery (28).

The use of inhalation anesthetic agents is associated with a dose-dependent rise in PONV prevalence (2, 100). In a retrospective study, *Morita et al.* reviewed 928 patients undergoing breast cancer surgery under inhalation anesthesia (101). Their results showed that the use of desflurane and the duration of anesthesia were independent risks factors for early PONV, whereas Apfel score and duration of anesthesia were considered by the authors independent risks factors for delayed PONV (101).

Dexmedetomidine as part of a TIVA approach or in combination with dexamethasone may improve PONV outcomes in female surgical populations (24, 102). In a randomized, controlled, double-blind trial, *Kwak et al.* demonstrated the efficacy of dexmedetomidine alone and in combination with dexamethasone to prevent PONV when compared to placebo after breast surgery (102). The incidence of PONV was significantly higher in the placebo group compared with the dexmedetomidine group and the dual group during both, at PACU stay (12%, 4%, and 3%, respectively) and within the first 24 h after surgery (70%, 20% and 12%, respectively). They concluded that dexmedetomidine alone or in combination with dexamethasone was equally effective in decreasing the occurrence of PONV in this subset of patients (102).

The antiemetic effect of dexmedetomidine may be mediated by a modulatory action on the post-synaptic α_{2A} receptors acting as heteroreceptors, and reducing the release of 5-HT in the dorsal and median raphe nucleus located in cerebellum and mid-brain pons respectively (103). Other proposed antiemetic mechanisms of dexmedetomidine are the modulatory effect on dopamine release in the nucleus recumbens (104) and the suppression of histamine-mediated production of pro-inflammatory interleukine-6 (IL-6) (105).

The incidence of PONV was studied in patients undergoing laparoscopic gynecological surgery under an opioid-sparing anesthesia technique by *Seki et al.* They randomly assigned 90 patients to receive either general anesthesia alone (group G) or a combination of general anesthesia and epidural block with ropivacaine (group GE). All patients received PONV prophylaxis with dexamethasone and anesthesia maintenance with sevoflurane. Even though patients in the group G received more intra- and postoperative opioids, the authors found no significant difference when comparing PONV incidence among groups (RR:0.53, 95% CI: 0.23–1.23, $p = 0.14$) (30).

Other opioid-sparing analgesic approaches are the administration of nefopam, a centrally acting analgesic mostly used for neuropathic pain management, and gabapentin. *Chung-Sik Oh et al.* randomized 94 patients to receive either nefopam- or fentanyl-based PCA for pain management after gynecological laparoscopic surgery under total intravenous anesthesia (TIVA). The use of nefopam was associated with a significant decrease in PONV occurrence when compared to fentanyl (31.9% vs. 57.4% respectively, $p = 0.022$) (27). Likewise, *Khan et al.* reported a significant decreased PONV incidence after oral gabapentin (600 mg) compared to placebo in patients undergoing diagnostic gynecological laparoscopy surgery (32.9% vs. 64.3% respectively, $p < 0.001$) (29).

The development of Enhance Recovery After Surgery (ERAS) pathways for different surgical specialties, including cancer breast surgery, has led to a reduction in the prevalence of PONV, although the number of studies remains limited (106, 107). The growing use of multimodal perioperative analgesia strategies in ERAS protocols contributes to an effective management of postoperative pain with a considerable reduction in the amount of perioperative opioid use through the combination of non-opioid pharmacological management and regional anesthesia techniques, which consequently, decreased the prevalence of PONV (106, 108, 109). A recent retrospective study by *Chiu et al.* clearly showed a drastic reduction in PONV occurrence after the initiation of ERAS pathways for total mastectomy compared with a non-ERAS cohort (28% vs. 50%, respectively; $p<0.001$) (107). The use of regional nerve blocks (e.g., pectoral blocks or PECS, paravertebral, erector spinae plane block, and interfascial plane block) as a central component of multimodal opioid-free perioperative analgesia has had a significant impact on the frequency of PONV after breast surgery (110–114).

CONCLUSIONS AND FUTURE DIRECTIONS

Despite the efforts made by health care providers and researchers to reduce the occurrence of PONV in female patients at high risk, breast and gynecological surgery constitute additional risks factors for PONV, with an incidence that reaches 30–68% in the first 24 postoperative hours even in patients who have received prophylactic antiemetic treatment. Even though published data is limited, other variables such as sex hormone levels (especially estrogens) in pre and post-menopausal women, preoperative psychosocial status, pharmacogenomic pleomorphisms, and ethnicity, which can be considered independent risk factors must be considered when assessing the risk of PONV in female surgical populations.

Overall risk stratification and increasing compliance with the consensus for PONV management may positively influence clinical outcomes. While novel drugs are continuously under research, future randomized clinical trials should aim to identify both pharmacological and

non-pharmacological alternatives that could potentially decrease the current threshold of PONV incidence in female surgical patients.

AUTHOR CONTRIBUTIONS

ME-V performed literature search, worked on the structural design and methodology, and wrote and authored the manuscript. JF-D and AU collaborated equally in developing the methodology, collecting the data, and writing the manuscript. SB provided the publication concept, editorial advice, and supervised the production. All authors reviewed the final manuscript before submission. All authors contributed to the article and approved the submitted version.

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Have we forgotten something when caring for patients for surgery?

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Introduction

An astonishing number of patients will have surgery each year in the USA and the world. Among them, 20 to 40% of patients will suffer from cognitive dysfunction during the hospitalization and about 10% of elderly patients will have cognitive dysfunction months later (1, 2). Similarly, 10 to 60% of elderly patients will develop postoperative delirium (3). Patients suffering from postoperative delirium or cognitive dysfunction have a poor outcome including longer hospitalization and a higher rate of mortality and leaving the job market (1, 2). Thus, postoperative delirium and cognitive dysfunction are very significant issues.

Undoubtedly, a cognition uncompromised patient for surgery will be anxious during the perioperative period. Over-anxiety and other unhealthy neuropsychological activities may negatively affect the outcome of patients. For example, patients with depression symptoms have a higher incidence of postoperative delirium (4). Also, patients with postoperative cognitive dysfunction tend to have higher Beck depression inventory scores ($P = 0.089$) (2). However, the neuropsychological status of patients is not evaluated before the surgery in current practice. This evaluation is not performed in the majority of studies aiming to determine the outcome of surgical patients. Understandably, measures to improve neuropsychological status during the perioperative period have not been routinely applied to patients. However, the importance of the pre-surgery screening for postoperative delirium and cognitive dysfunction has been emphasized by an expert panel from the American Society of Anesthesiologists. The interventions recommended by this panel are general measures including reducing the use of medications that may contribute to the development of these postoperative cognitive disorders and providing a familiar environment as much as possible (5). These efforts are the initial steps to improve perioperative brain health for patients with surgery. In addition, a checklist targeting 8 areas before surgery has been proposed by the "Strong for Surgery" program that is now sponsored by the American College of Surgeons. Among the 8 areas, two areas, screening the risk for delirium and prehabilitation, are important elements for perioperative brain health.

Potential effects on the relatives of patients with surgery

Obviously, patients for surgery are not in isolation. They have family members and friends. The consequences of surgery on the family members and close friends of surgery patients have been largely unknown. Neurobiologically, behaviors and feelings can be "contagious." Itch and pain sensation can be transmitted to observers (6, 7). Stress responses are transmitted to subjects that are not exposed to the initial stress stimuli (8). Familiarity is an important factor for the transmission of the behaviors and feelings (7, 8). Interestingly, consolation, a behavior to comfort the injured or distressed individual, occurs in animals. This behavior toward distressed subjects is oxytocin-dependent and involves anterior cingulate cortex in prairie vole (8). The distress was caused by separation, loud tone and foot shocks in that study. Our recent study has shown that consolation occurs from cage-mates toward individuals with surgery in mice. This behavior reduces the anxiety of surgery mice. The interaction between surgery mice and non-surgery mice increases the anxiety of non-surgery mice. The orexin signaling in the paraventricular thalamic nucleus may play a critical role in the consolation and anxious behaviors of non-surgery mice (9). These basic science studies have shown the transmission of behaviors and anxiety among animals.

Humans are highly social and have a much more complex system for communication and interaction. Undoubtedly, family members, especially the close family members of patients for surgery, will be anxious, particularly when the patients will have a major surgery (10). Consolation and care of the family members toward the patients with surgery will likely have a positive effect on the recovery of the patients. Anxiety induces physiological responses and has a detrimental effect on patients with various diseases (11). However, the effects of anxiety and other negative psycho-behaviors of family members on their health are rarely studied. The influence of potential negative interaction between patients and family members in the health of both parties and surgery outcome is not known. Interestingly, non-surgery cage-mates of mice with surgery develop learning and memory impairment, similar to the presentation of mice with surgery. Surgery mice and their non-surgery cage-mates have increased inflammatory cytokines in their brain (12). Although the mechanisms for the impaired learning and memory in the non-surgery cage-mates are not known, neuroinflammation is known to impair learning and memory and is a major pathological process for postoperative delirium and cognitive dysfunction (2, 13). Similarly, a population-based study has shown that spousal caregivers of a patient with incident dementia have a six-fold increase in the hazard for incident dementia later in life compared to others whose spouses are not demented (14). Also, spousal caregivers of patients with dementia have a greater cognitive decline than spouse caregivers of non-dementia patients (15). Anxiety and stress may be contributing factors for the findings in the spouses (14, 15). Thus, reducing anxiety and stress is a possible approach to improve the brain health of these spouses. These studies illustrate an important and largely untouched field in perioperative medicine, the health of patients' family members and close friends, and the effects of their interaction with patients on the outcome of patients after surgery. In supporting the potential of these effects, a recent study has shown that the quality of life of patients with stem cell transplantation is correlated with the anxiety and depression of their family caregivers (16).

Current practice to reduce anxiety of patients with surgery and their family members

Effective communication and frequent updates on surgery progress are good practices to reduce the anxiety and stress of patients with surgery and their relatives. Excellent support from the social community including friends may prepare the patients for better recovery and family members for less stress. Many of these practices are in place for patients with surgery. Advanced training for perioperative care providers on effective communications and consolation skills will be important elements to improve the wellbeing of the patients for surgery and their family members.

TABLE 1 Proposed changes in evaluating and preparing patients for surgery.

Present model
Patient is evaluated before surgery to optimize cardiac and pulmonary functions for surgery.
Patient may be evaluated by acute pain service for pain management.
New model
Patient is evaluated before surgery to optimize cardiac and pulmonary functions for surgery.
Patient is evaluated by PEBS to optimize brain health of patients and family members for surgery.
Patient may be evaluated by acute pain service for pain management.
Patient will be followed up by PEBS for neuropsychological management.
Perioperative care providers have additional training on effective communications and consolation

Proposed measures to improve the outcome of patients with surgery and their family members and relevant discussion

Additional work can be done to better prepare the patients and their family for surgery. It is important to evaluate the patients and family members to identify factors that increase anxiety and stress and to mitigate these factors. Consolation toward the patients with surgery and their family members should be part of the practice of health care providers. More importantly, applying appropriate interventions and programs to improve the neuropsychological status should be incorporated into the perioperative care. Measures to improve brain functions, such as environmental enrichment, should be applied. A multidisciplinary team focusing on reducing anxiety, distress and other negative psycho-behaviors and improving brain functions should be formed for patients with surgery, especially for those at high risks for postoperative neurocognitive disorders. The team members should include the anesthesiologist, surgeon, neuropsychological specialist, and social worker. The team can be named perioperative enhancing brain-health service (PEBS) (Table 1). This practice will be similar to that of the acute pain service that was not provided routinely 30 years ago. Finally, close follow-up of surgery patients and their family conditions after surgery should be performed by PEBS. To achieve the goals of PEBS, PEBS consultation for those patients who will require significant care from the family members after surgery or are at a high risk for developing postoperative neurocognitive disorders should be requested immediately after the decision for surgery has been made to give PEBS enough time to work with the patients and their family members. Preoperative screening, preparations and interventions can be performed in the form of family-based neurocognitive prehabilitation to increase the resiliency of patients and family members to harmful effects on the brain during the perioperative period. A neuropsychological specialist may lead these activities but a close working relationship among the members of PEBS is needed to provide a timely and effective program for patients and family members throughout the perioperative period. These practices are different from the commonly referred prehabilitation that emphasizes interventions for patients before surgery. The success of PEBS service can be measured by not only the decrease in the rates of postoperative delirium and cognitive dysfunction, length of hospitalization, and number of patients returning to work force but also the wellbeing of their family members, such as anxiety and depression levels, number of missing work days and percentage of them returning to their jobs. Considering that more than 50 million patients have surgery annually in the USA, there are more family members who will benefit from these practices. Let us work together to make the perioperative period a less fearful and anxious time for the patients and family members. These practices will maximize the benefit of surgery to the patients, their family members and ultimately to our society.

Author contributions

The author confirms being the sole contributor of this work and has approved it for publication.

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Peripheral interleukin-6-associated microglial QUIN elevation in basolateral amygdala contributed to cognitive dysfunction in a mouse model of postoperative delirium

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Background: Developing effective approaches for postoperative delirium has been hampered due to the lack of a pathophysiologically similar animal model to offer insights into the pathogenesis. The study, therefore, aimed to develop a delirium-like mouse model and explore the underlying mechanism.

Methods: The three cycles of 10-min clamp following 5-min reopening of the superior mesenteric artery (SMA) were performed in adult male C57BL/6 mice to induce a delirium-like phenotype. Composite Z score calculated based on the results of Open Field, Y Maze and Buried Food Tests was employed to assess the delirium phenotype in mice. Microglia activities were monitored by immunofluorescence staining and comprehensive morphological analysis. Systemic administration of minocycline (MINO), IL-6 antibody or IL-6 neutralizing antibody, was applied to manipulate microglia. The expressions of Indoleamine 2,3-dioxygenase-1 (IDO-1) and quinolinic acid (QUIN) were examined by RT-PCR and High-Performance Liquid Chromatography/Mass Spectrometry, respectively. Cytokines were measured using fluorescence activated cell sorting method.

Results: The repeated ischemia/reperfusion (I/R) surgery caused significant anxiety ($P < 0.05$) and cognition decline in working memory and orientation ($P < 0.05$) in mice at postoperative 24 h. The composite Z score, indicating an overall disturbance of brain function, fluctuated over 24 h after I/R surgery ($P < 0.001$). Immunofluorescent staining showed that the percentage of microglia in the basolateral amygdala (BLA) ($P < 0.05$) was reactivated after I/R surgery and was negatively correlated with dwell time at Y maze ($R = -0.759$,

$P = 0.035$). Inhibiting microglia activities by MINO reduced QUIN productions ($P < 0.01$) that improved cognitive deficits ($P < 0.05$). The peripheral IL-6 might cause IL-6 elevation in the BLA. Systemic administration of IL-6 antibodies suppressed I/R-induced IL-6 elevations ($P < 0.05$), microglial reactivations ($P < 0.05$), IDO-1 expressions ($P < 0.01$), and neuroactive metabolite QUIN productions ($P < 0.05$) in the BLA, resulting in a recovery of cognitive deficits ($P < 0.05$). Injection of IL-6 exerted opposite effects.

Conclusion: The repeated intestinal I/R surgery-induced mouse model is a simple and reproducible one of postoperative delirium. Peripheral IL-6-associated microglial QUIN elevations in the BLA contributed to cognitive dysfunction in the model of postoperative delirium.

KEYWORDS

delirium, repeated intestinal I/R, IL-6, microglia, BLA, QUIN

Introduction

Postoperative delirium has been reported to be associated with cognitive decline, higher mortality, and lower quality of life (1, 2). Risk factors for postoperative delirium include acute systemic inflammation, medications (e.g., anticholinergic drugs), and aging-associated neurological abnormalities, such as impaired neuronal network, dysfunction of blood brain barrier (BBB), and reactivation of microglia cells (3).

Resting microglia dynamically surveil the central nervous system (CNS) niches and can be rapidly reactivated when sensing abnormal signals. In this way, microglia play an important role in neuroinflammation, neuropathy, and synaptic strength (4). Reactivated microglia are also known to secrete various bioactive molecules, including inflammatory mediators and neuroactive metabolites (5, 6). The association between microglia and delirium has been demonstrated in both human and animal studies (5, 7, 8). For example, patients with delirium were found to have higher levels of microglia-derived soluble triggering receptor expressed on myeloid cells 2 (TREM2) in cerebrospinal fluid (8). In postmortem tissue sections, it was shown that microglial markers of Human Leukocyte Antigen-DR isotype (HLA-DR) and CD68 were higher in patients with delirium than in age-matched controls (7). In animal studies, microglia reactivation was observed in the hippocampus that dominated neuroinflammation postoperatively. Inhibition of microglial proliferation reversed hippocampal inflammatory mediators, leukocyte invasiveness, and postoperative cognitive decline (5). Despite all these findings, the mediators leading to microglia reactivation and microglia-derived neuroactive substances remain elusive and deserve further exploration in the new studies.

The development of effective treatments for postoperative delirium has been blocked in part due to the lack of a pathophysiologically similar animal model that offers insights into its pathogenesis. Several animal models of delirium have been developed, but there are limitations with these models. Systemic LPS administration is a popular approach to induce behavioral disturbances in animals to mimic a delirium-like state (9–11). However, LPS challenge is not a clinically established factor for delirium, in addition, most of these studies used a single behavioral test to assess such a complicated disease. Small intestine I/R-induced animal model could alter brain function from the short to long term (12–14). However, the models involve long-time ischemic attack (usually 60–90 min), resulting in high immediately postoperative mortality and prolonged neurological abnormalities that are inconsistent with features of clinical postoperative delirium. Recently, Peng et al. (15) reported that a simple laparotomy induced delirium-related behaviors. Furthermore, they developed a scoring tool analogous to Confusion Assessment Method (CAM) algorithm (diagnosis tool for clinical delirium) (16) to assess the delirium-like phenotypes in rodents based on the outcomes of all behavior tests. This model included a simple midline abdominal incision under isoflurane anesthesia without affecting any intra-abdominal organs.

In this study, we attempt to improve the mouse model of postoperative delirium by applying laparotomy and attacks through three cycles of transient ischemia (10 min) and reperfusion (5 min). This repeated protocol was devised from the recognition that intermittent ischemia potentiates intestinal reperfusion injury (17). To comprehensively assess the delirium-like phenotype, composite Z scores were calculated based on a battery of behavior tests, namely Open Field Test, Y Maze Test, and Buried Food Test. Finally, microglia reactivation induced by peripheral IL-6 in the associated brain region, and neuroactive molecule of QUIN were found and studied using this new mouse model of postoperative delirium.

Materials and methods

Animals

All animal procedures were approved by the Animal Experiment and Welfare Committee of Nanfang Hospital, Southern Medical University (Guangzhou, China). Male C57BL/6 mouse (male, 8 weeks old, 20–22 g) were obtained from SPF Biotechnology (Beijing, China). Mice were housed in a controlled environment (temperature 20–22°C; humidity of 50 ± 10%; 12 h of light/dark on a reversed cycle) with *ad libitum* access to food and water. All mice were acclimated to the environment for 7 days before performing behavioral tests between 12:00 PM and 5:00 PM on the experimental day. Researchers who were blinded to the grouping conducted behavioral experiments and data collection.

Surgery and experimental protocol

The intestinal ischemia and reperfusion surgery was performed as described previously (12). Animals were fasted 12 h before surgery. Under isoflurane anesthesia, the small intestine was exteriorized through a 1-cm midline abdominal incision. The SMA was clamped for 10 min using a microvascular clip (18055-02, 85 g, F.T.S., CA, United States) following revascularization for 5 min. This cycle was repeated three times before closing the wound. Cream containing 2.5% lidocaine was applied immediately and every 8 h to treat incisional pain. Animals at sham group underwent all procedures except for SAM clamping and revascularization.

The postoperative delirium-like phenotypes of mice were assessed according to previous methods developed by Peng et al. (15) with minor modifications (**Table 1**). Briefly, all mice were evaluated in a battery of neurological tests, namely Open Field Test, Y Maze Test, and Buried Food Test 7 days before surgery (baseline) and 6, 9, 24 h after operation. Latency to eat (Buried Food Test), time spent in the center (Open Field Test), latency to the center (Open Field Test), freeze time (Open Field Test), number of entries in novel arm (Y Maze Test), duration in novel arm (Y Maze Test), and first choice of novel arm (Y Maze Test) were then extracted to compare changes in neurological activities between groups and used to calculate composite Z scores to monitor delirium-like manifestation between treatment or over time.

The experimental protocol is illustrated in **Figure 1A**. Initial microglia assessment across whole brain was detected at 6, 9, 24 h after surgery as well. Histologic examination of small intestine was performed at immediate time and the severest brain disturbance time after surgery. Pro-inflammatory cytokines of IL-1β, IL-6, and TNF-α, suggested by results of clinical trials for delirium (18), were measured along the intestine-brain axis at the severest disturbance time.

TABLE 1 The tool to assess postoperative delirium for mice.

1. Acute onset and fluctuating course: Mean composite Z score fluctuates during postoperative 24 h
2. Inattention: Buried food test/open field test/Y maze
3. Disorganized thinking: Buried food test/open field test/Y maze
4. Altered level of consciousness: Buried food test/open field test/Y maze
1 + 2/3/4 abnormity: Delirium-like phenotype

We explored underlying mechanism for core symptom of cognitive dysfunction, detected by Y maze, because it is a such complicated disease with a constellation of symptoms.

Intervention

Minocycline (MINO, Sigma-Aldrich M9511, St. Louis, MO, United States) was employed to inhibit microglia activation. MINO was dissolved in normal saline and injected intraperitoneally at 50 mg/kg 1.5 h before behavioral experiments (19). Recombinant IL-6 (PeproTech 200-06, Cranbury, NJ, United States) and mouse IL-6 neutralizing antibody (R&D Systems, Minneapolis, MN, United States) were given to study the role that peripheral IL-6 played in this model. IL-6 of 50 μg/kg were i.p injected at immediate, 6 and 12 h (20, 21). Anti-IL-6 antibody of 0.1 μg/mouse was injected via tail vein at postoperative 6 h when the first behavioral testing was performed (13). The large size of IL-6 antibody and its complex with IL-6 (> 150 kD) makes them impossible to cross the blood-brain barrier to affect the brain directly (22, 23).

Open Field Test

Open Field Test was performed as previous studies (13, 15). Mice were moved into the experimental room 1 h prior to the testing. A mouse was then gently placed in the center of an open field and allowed to freely explore the chamber for a period of 10 min. Total distance, rearing time, and duration at the border and in the center were recorded by VersaMax (v3.02-125, Omnitech Electronics, Columbus, OH, United States).

Y Maze Test

Y Maze Test was used to assess cognition-associated spatial memory and orientation (24). The maze is comprised of three arms (8 × 30 × 15 cm, width × length × height), with an angle of 120 degrees between each arm. In the study, the recognition memory protocol was implemented including two trials (15, 24). During the first training trial, one arm of the Y maze was blocked, and a mouse was allowed to freely explore the starting arm and the other arm for 10 min. After 1 h at

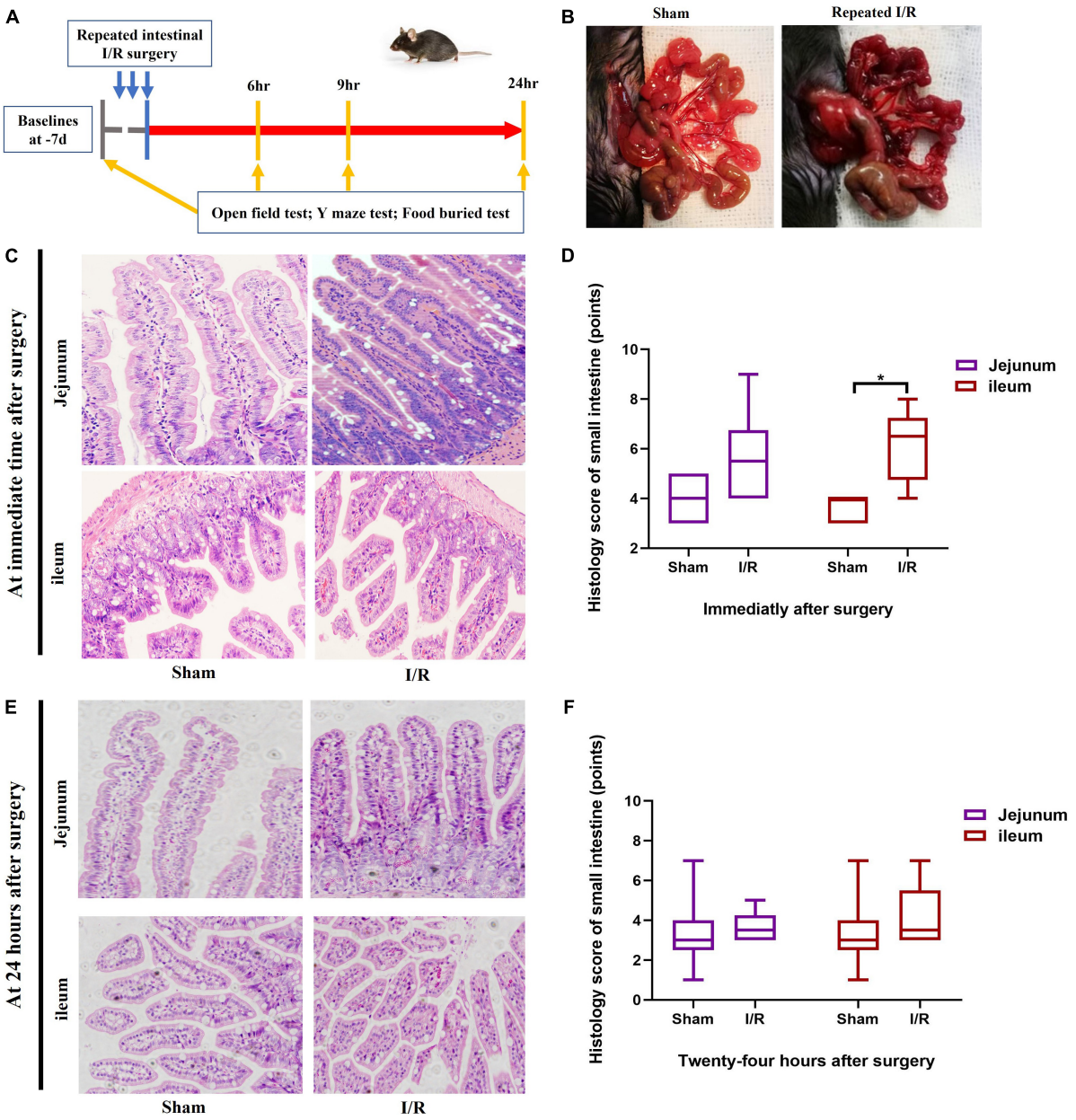

FIGURE 1
Experimental protocol and histological assessment on small intestine. **(A)** Experimental protocol. **(B)** Small intestine changed due to I/R or sham operation. **(C,D)** Histological assessment on small intestine immediately after surgery. **(E,F)** Histological assessment on small intestine at postoperative 24 h. *N* = 10 per group for behavioral testing, *N* = 8 per group for histological assessment, **P* < 0.05. I/R: ischemia and reperfusion, d: days, hr: hours.

the second trial with all three arms accessible, the mouse was returned to the maze for a 5-min exploration to test the memory recognition. The starting arm and the other arm had been randomly set to avoid potential bias. A video camera linked to EthoVision (v7.0, Noldus, Wageningen, Netherlands) was installed 60 centimeters above the maze to monitor and analyze number of arm entries, the time spent in each arm, and the first choice of the arm.

Buried Food Test

Buried Food Test was performed to examine the latency to forage food buried in the cage bedding (15, 25). Mice were familiarized with cereals for 2 days before the experiments. On the experimental day, the mice were acclimated to the testing room for an hour prior. A cereal pellet was buried 0.5 centimeters below surface of bedding (3 cm high) and was

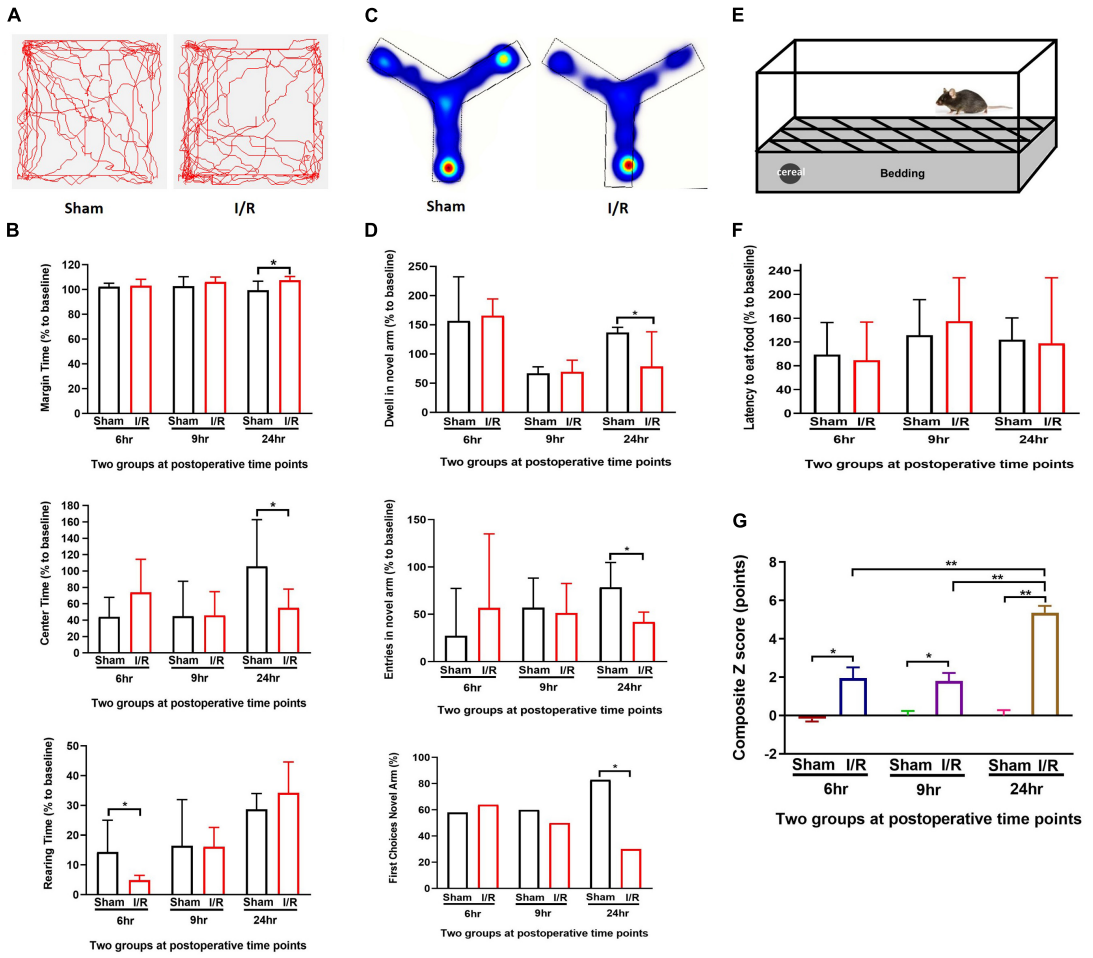

FIGURE 2
Repeated I/R surgery of small intestine disturbed the behaviors in mice at postoperative 6, 9, and 24 h which had higher composite Z scores. **(A)** Open Field Test. **(B)** Y Maze Test. **(C)** Buried Food Test. **(D)** Track map of Open Field Test. **(E)** Heating map of Y Maze Test. **(F)** Composite Z score of each mouse. **(G)** Summary of composite Z scores. The percentage data were presented as median (IQR). Composite Z score was presented as Mean ± SD. Larger values of composite Z score suggest severer impairment. $N = 10$ per group, $^{*}P < 0.05$, $^{**}P < 0.01$. I/R: ischemia and reperfusion, hr: hours.

located randomly at each time. A mouse was placed in the center of the testing cage and allowed to search for the cereal pellet for 5 min. When the mouse finding out the food and grasping it with forepaws and/or teeth, we recorded the time latency and stopped the experiment. If a mouse failed to find the food over a period of 5 min, the latency was recorded as 300 s. The clean cage, fresh bedding, new gloves, and new pellet of cereal were used for each mouse to prevent transmission of olfactory cues.

Hematoxylin and eosin staining and scoring

Jejunum and ileum were harvested and stained with H&E for histologic examination. The histologic scoring scale (26) was applied to assess the tissue injury caused by ischemia and reperfusion. The scoring system includes three categories relating to mucosal damage, inflammation, and hyperemia/hemorrhage, each with 0–5 points (normal to severe) (**Supplementary Table 1**).

Immunofluorescence and microglial analysis

The animals were transcardially perfused with 4% paraformaldehyde. The brains were taken and fixed in paraformaldehyde for 4–6 h, followed by cryoprotection with 30% sucrose and the organs were cut into 40 μm sections. For microglial detection, the sections were incubated with rabbit-anti IBA-1 (1:500; Wako Pure Chemicals, Osaka, Japan) and further with fluorescein

isothiocyanate-conjugated secondary antibody (1:500; goat anti-rabbit, Invitrogen, Waltham, MA, United States). Images of brain were acquired using LSM880 confocal microscope (Carl Zeiss, Oberkochen, Germany) controlled by Zen2010 software (Carl Zeiss, Jena, Germany). Regions of plaques were pictured at 400 × magnifications. Images were sampled at a resolution of 1024*1024 pixels. A multi-plane Z mode allowed to capture 20 images (2 μm thick) in 40 μm depth of the tissue section, which were later combined to obtain a single high-quality confocal image.

Microglia activation was initially assessed by phenotypic characterization of stages one to five cells (4, 27). Microglia at stages from three to five with cell body increasing and processes shrinking, were considered reactivation (4, 27). All Iba-1 positive cells were graded twice in an area of 0.09 mm^2 using image analysis software (Image J, v1.52a, NIH, United States). The percentage of reactivated microglia was measured in the basolateral amygdala (BLA) (28), medial prefrontal cortex (PFC) Zilles cg1, Cornu Ammonis (CA1), Cornu Ammonia 3 (CA3), Dentate Gyrus inner blade (DGib), and striatum (STR), which are well recognized to be associated with emotions and cognition (29–31). In the mechanism studies, a comprehensive analysis of microglia was performed on 3D images without projection. Imaris (v9.0.1, Bit plane, Belfast, United Kingdom) was applied to create surface and trace filaments of microglia, followed by quantification of cell number, cell volume, cumulative process length, and number of branch points in these images. The process included the following steps: (1) segment microglia from background and mark the cells with somas, processes, and branch points, and use the same Gama value for all images, (2) create a skeleton to represent the 3D structure of cell body and processes, (3) quantify the microglia (32, 33).

Quantification of pro-inflammatory cytokines

The concentrations of IL-1β, IL-6, and TNF-α were determined using the BD Mouse/Rat Soluble Protein Master Buffer Kit (558266, BD Biosciences, San Jose, CA, United States) in conjunction with the BD CBA Flex Sets for the specific detection of mouse IL-1β (560232), IL-6 (558301), and TNF-α (558299). The assays were conducted and analyzed according to the manufacturer's instructions. Briefly, 50 μl of serially diluted standards or test samples were incubated with 50 μl of capture beads and then with 50 μl of PE detection reagent, followed by quantification of cytokine concentrations using the BD LSRFortessa^{TM} X-20 flow cytometer (BD Bioscience) and FCAP array software (version 3.0, BD Biosciences).

RT-PCR for IDO-1 mRNA in basolateral amygdala

Mouse was transcardially perfused with normal saline to wash out blood. The brain was quickly removed from the skull and was chilled on ice for 10 min. Bilateral dissections of the BLA regions were performed according to a previous report (34). Coronal sections between Bregma −1 and Bregma −2.75 were isolated and verified under microscope. The sections were placed caudal side up. Cuts were then made in the lower-left and lower-right corners while avoiding any hippocampal tissue. Isolated BLA tissues were placed in the tube containing TRIzol reagent (Invitrogen, New York, NY, United States) and homogenized for 120 s. Total RNA was then extracted using chloroform and precipitated with isopropanol, followed by conversion to complementary DNA (cDNA) using SYBR Green kit (TOYOBO, Tokyo, Japan). The following primers were used: forward 5′-TGCCTCCTATTCTGTCTTATGC-3′ and reverse 5′-CTTTCAGGTCTTGACGCTCTAC-3′. PCR was performed using the ABI Q5 Real-Time PCR System (Applied Biosystems, Foster City, CA, United States). The relative IDO-1 gene expression was determined by normalization to the housekeeping gene (β-actin) and the IDO-1 gene in the control group using the $2-\Delta\Delta$ CT method.

Quantification of QUIN using high-performance liquid chromatography/mass spectrometry

Standards were dissolved in caffeic acid (Macklin, Shanghai, China) solution. Internal standards (IS) were added to each standard and sample for a final concentration of 10 ng/ml to correct for sample and instrument variability. Tissue homogenizations (50 μl) were diluted 12-fold (w/v) by adding 10 μl IS, 500 μl water and 140 μl acetonitrile. Diluted samples were then filtered through Amicon Ultrafilter (Millipore, Billerica, MA, United States) by centrifugation at 15,000 *g* for 10 min at 4°C. Quantifications of QUIN were determined by HPLC (Waters, Milford, MA, United States) with tandem mass spectrometry (MS/MS) (Thermo Scientific, Waltham, MA, United States). Samples were run in positive ionization mode optimized for QUIN detection. Resultant acquisitions were directly injected into the Waters, equipped with an C18 (waters T3, 2.1 × 100 mm, 1.7 μm) column. The mobile phase consisted of an aqueous component (A: 10 mM ammonium acetate + 0.1% formic acid in ultrapure water) and an organic component (B: 0.1% formic acid in acetonitrile). The elution gradient was used as follows: 100% A for 30 s and 90% B for 6 min. The flow rate was set at 0.25 ml/min and the run time for each sample was 13 min. The concentration of QUIN in each sample was quantified by comparison to the standard curve.

Statistical analysis

Variables were presented as mean (standard deviation, SD) or median (interquartile range, IQR). The behavior parameters at postoperative 6, 9, and 24 h were presented as percentages compared to their baselines. An independent Student's *t*-test or Mann–Whitney *U* test was used to compare results where appropriate. Fisher's exact test chi-square was used to test first choice of the novel arm at Y maze. Z score was calculated using formula described by Moller et al. (35) and Peng et al. (15). $Z = \Delta X\text{-I/R} - \text{MEAN}(\Delta X\text{-sham})/\text{SD}(\Delta X\text{-sham})$. ΔX-sham was the change score of mice in sham group at 6, 9, and 24 h after operation minus the baseline score; ΔX-I/R was the change score of mice in I/R group at 6, 9, and 24 h minus corresponding baseline score; MEAN (ΔX-sham) was the mean of ΔX-sham; SD (ΔX-sham) was the standard deviation of ΔX-sham. The composite Z score was calculated as sum of six Z scores (latency to eat food, time spent in the center, latency to the center, rearing time, entries in novel arm, and duration in novel arm) normalized with SD for that sum. Spearman's rank correlation was used to analyze correlation analysis between the cognitive outcomes of Y Maze Test and the percentages of reactivated microglia in each brain region. The one-way analysis of variance or the Kruskal–Wallis test was used for comparing three groups depending on the nature of data. Statistical analysis was performed in SPSS (version 23.0; SPSS for Windows, Chicago, IL, United States) and Graph Pad Prism 8.0 (GraphPad Software Inc., United States). A two-tailed $P < 0.05$ was set as statistical significance.

Results

Repeated I/R insults in the small intestine of mice mimicked the transient and reversible I/R injury and delirium associated with abdominal surgery

The timeline of the experimental design was shown in Figure 1A. I/R injury was introduced by performing three cycles of 10-min clamping and 5-min reopening of the SMA. The small intestine of I/R mice turned from red to dark purple and became distended after completing surgery (Figure 1B). The jejunum and ileum were collected to assess histological injury using H&E staining. The histological score of ileum, representing severities of inflammation and hyperemia, was higher in I/R mice than the score of sham mice at immediate time after surgery ($P = 0.020$, Figures 1C,D). There was no difference in jejunal score between groups ($P = 0.097$, Figures 1C,D). At 24 h postoperatively, the histological scores of both ileum and jejunum were similar between the two groups ($P > 0.05$ for both, Figures 1E,F). This indicated that the injuries caused by this repeated I/R interventions were transient and reversible, similar to the nature of I/R injury during abdominal surgery and the associated delirium. There was no death occurred during the experimental period.

Repeated I/R insult in the small intestine resulted in a delirium-like manifestation in the mouse

We investigated whether mice could develop delirium-like manifestation by assessing behavioral changes in Open Feld test, Y Maze Test, and Buried Food test. At Open Feld test, I/R insult increased the marginal time while decreased the center time in the mice compared to those of the sham at 24 h postoperatively (marginal time: 107.50 vs. 99.39%, $P = 0.022$; center time: 55.11 vs. 105.80%, $P = 0.020$, Figures 2A,B), The results suggested anxiety induced by the intestinal I/R surgery. The I/R mice spent shorter rearing time than the sham at 6 h (4.86 vs. 14.31%, $P = 0.007$, Figure 2B), but not 9 and 24 h postoperatively (both $P > 0.05$, Figure 2B), indicating I/R injury suppress the willingness to explore in the early time. The I/R surgery did not alter the total distance between the two groups at any time point (Supplementary Table 2). At Y maze testing, I/R insult reduced duration and number of entries in the novel arm as compared to the sham at postoperative 24 h (durations: 75 vs. 101%, $P = 0.036$, entries: 41.88 vs. 78.53%, $P = 0.002$, Figures 2C,D), indicating the impaired working memory and spatial orientation in mice with intestinal I/R injury. Consistent with this result, fewer percent of I/R-injured mice initially chose the novel arm for entry than the sham-operated mice at the same time point (30 vs. 83%, $P = 0.027$, Figure 2D), indicating that the I/R surgery reduced interest in exploration in those mice. We did not find any difference in the arm visits between the two groups either (Supplementary Table 3). At Buried Food testing, the repeated I/R insult did not change the latency to eat the food ($P > 0.05$, Figures 2E,F). Composite Z score for each mouse was calculated based on the three behavioral tests (Table 2 and Figure 2G). A higher score indicates worse performance. We noted that the composite Z score of I/R mice fluctuated over 24 h after surgery and peaked at 24 h (5.36 vs. 1.96, 5.36 vs. 1.80, both $P < 0.001$, Table 2 and Figure 2G). In addition, mice undergoing I/R surgery were graded the higher Z scores than the sham at all assessed time points (6 h: 1.96 vs. −0.17, $P = 0.004$; 9 h: 1.80 vs. 0.000, $P = 0.001$; 24 h: 5.36 vs. 0.000, $P < 0.001$, Table 2 and Figure 2G). These results showed that repeated I/R insults in the small intestine could successfully develop a manifestation with the feature of postoperative delirium, which shows an acute and fluctuating change in mental level.

TABLE 2 Summary of composite Z scores in sham and I/R mice.

	Z scores at each time point		
Mouse	**6 h**	**9 h**	**24 h**
Sham 1	−0.47	−0.32	0.90
Sham 2	−0.60	−0.39	−0.10
Sham 3	0.24	0.45	−1.58
Sham 4	0.26	−0.87	1.40
Sham 5	0.22	−0.88	−0.11
Sham 6	−0.77	1.13	−0.63
Sham 7	0.24	0.89	−0.23
Sham 8	0.21	−0.22	−0.41
Sham 9	−0.21	−0.64	−0.20
Sham 10	−0.81	0.85	0.96
Sham mean	−0.17	0.00	0.00
Sham SD	0.14	0.25	0.28
Comparison of the scores at the three time points			>0.05
I/R 1	2.11	2.59	3.55
I/R 2	0.90	2.74	3.37
I/R 3	0.18	3.57	7.07
I/R 4	2.91	2.10	5.36
I/R 5	−1.10	−1.28	6.08
I/R 6	2.72	2.28	5.52
I/R 7	1.31	1.04	5.28
I/R 8	5.33	1.56	6.08
I/R 9	2.50	1.31	5.21
I/R 10	2.69	2.12	6.10
I/R mean	1.96	1.80	5.36
I/R SD	0.56	0.41	0.36
Comparison of the scores at the three time points			<0.001**
Comparison of the scores between sham and I/R mice at each time point	0.004**	0.001**	<0.001**

**$P < 0.01$. I/R, ischemia and reperfusion; hr: hours.

Transient intestinal I/R injury-induced microglial reactivation in the basolateral amygdala that was negatively correlated with delirium-associated cognitive dysfunction and the expressions of cytokines

Microglia can sense and rapidly adapt to locally environmental changes. We examined microglia reactivation in different brain regions associated with delirium (Figures 3A–E). For BLA and CA3, it was observed that the percentage of microglia activated was higher in I/R mice than that of the sham at 6 h (BLA: 40.00 vs. 18.62%, $P < 0.01$; CA3: 14.67 vs. 0%, $P < 0.01$, Figures 3A,B), 9 h (BLA: 29.41 vs. 6.45%, $P = 0.029$; CA3: 15.79 vs. 0%, $P < 0.01$, Figures 3A,B), and 24 h (BLA: 53.57 vs. 18.33%, $P < 0.01$; CA3: 31.31 vs. 0%, $P < 0.01$, Figures 3A,B). For DGib of hippocampus, the percentage of microglia activated was greater in I/R mice at 6 h (42.06 vs. 0%, $P < 0.01$, Figure 3C) and 24 h (22.22 vs. 0%, $P = 0.026$, Figure 3C), but not at 9 h ($P = 0.111$, Figure 3C). In PFC, we only found the higher value in I/R mice at 24 h (23.08 vs. 0%, $P = 0.016$, Figure 3D), while in STR we observed significant microglia activation only at postoperative 9 h (30.77 vs. 0%, $P < 0.01$, Figure 3E). There were no microglia activated found in CA1 of hippocampus (data not shown).

Cognitive dysfunction underpins postoperative delirium. We further examined the brain regions involved in cognitive dysfunction 24 h after surgery by performing correlation analyses between behavioral changes in the Y Maze Test and the percentage of activated microglia in each brain region. It was only found that a negative correlation between dwell time in the novel arm and the percentage of activated microglia in BLA in I/R mice ($R = -0.759$, $P = 0.035$, Table 3), suggesting that abnormal microglia activation in BLA may play a role in postoperative delirium. We thus chose brain BLA region to initially investigate the underlying mechanism for such a complicated brain disorder.

The up-regulation of IL-1β, IL-6, and TNF-α in the postoperative period have been reported by extensive studies. In this model, expression of IL-6 was elevated remarkably in all three samples compared with those of the sham ($P < 0.01$, Figure 3F). Production of IL-1β of I/R mice was increased in the small intestine and plasma but not in the BLA compared with the sham (both $P < 0.01$, $P > 0.05$, Figure 3F). Production of TNF-α was only higher in the small intestine of I/R mice than the sham ($P < 0.01$, Figure 3F). The results indicated that proinflammatory IL-6 persisted highly in the small intestine, blood, and BLA in I/R-induce delirium-like mice.

Inhibition of microglial activation and associated IDO-1/QUIN in basolateral amygdala by minocycline led to cognitive improvement in I/R-induced mice

To further assess microglial involvement, the widely used microglia inhibitor MINO was administered to the I/R-injured mice. At postoperative 24 h, microglia activation in BLA was found to be attenuated in MINO-injected mice, as reflected in smaller microglia volumes ($P = 0.031$, Figures 4A,B), longer process lengths ($P = 0.029$, Figures 4A,B), and more branch points ($P = 0.021$, Figures 4A,B) compared to vehicle administration, although the number of microglia was not affected ($P > 0.05$, Figure 4B). We then assessed the expressions of IDO-1 mRNA (the rate-limiting metabolic enzyme of the kynurenine pathway) Ana QUIN (endogenous neuroexcitatory

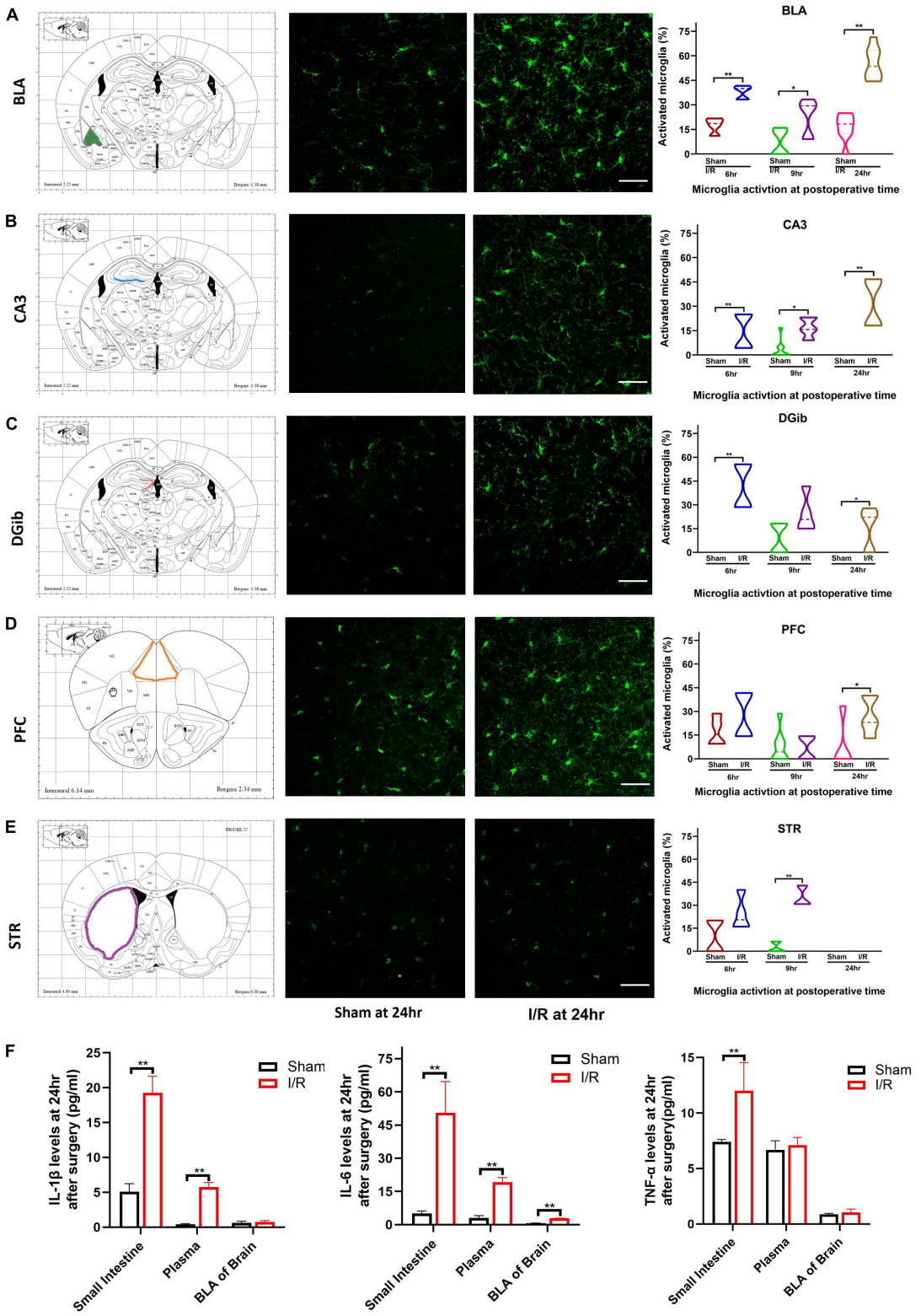

FIGURE 3
Microglia reactivation in different brain regions and levels of proinflammatory cytokines at 24 h after surgery. **(A)** BLA. **(B)** CA3. **(C)** DGib. **(D)** PFC. **(E)** STR. **(F)** Levels of IL-1β, IL-6, TNF-α in intestine, plasma, and BLA. The percentage data were expressed as median (IQR). $N = 8$ per group, $^{*}P < 0.05$, $^{**}P < 0.01$. I/R, ischemia and reperfusion; hr, hours; BLA, basolateral amygdala; CA3, Cornu Ammonis; DGib, dentate gyrus inner blade; PFC, medial prefrontal cortex; STR, striatum.

TABLE 3 The correlation between the microglia activation and quantitative outcomes of Y maze at 24 h in the I/R mice.

Brain regions Outcomes	BLA	CA3	DGib	PFC	STR
Dwell in novel arm	−0.759*	−0.433	−0.546	−0.609	nil
Entries in novel arm	−0.633	−0.636	−0.403	−0.685	nil

*$P < 0.05$. I/R, ischemia and reperfusion; BLA, basolateral amygdala; CA3, Cornu Ammonis; DGib, dentate gyrus inner blade; PFC, medial prefrontal cortex; STR, striatum; nil, non-existent.

metabolite of kynurenine pathway) in the BLA. IDO-1 mRNA amplifications and QUIN levels were lower in MINO-injected mice than vehicle-injected mice ($P < 0.01$, Figures 4C,D). Consistent with the improvements in biochemistries, MINO also rescued the cognitive impairment caused by I/R insult, indicated by longer dwell time ($P = 0.025$, Figures 4E,F), more entries in the novel arm ($P = 0.027$, Figures 4E,F) at Y maze testing, and propensity to choose the novel arm for the first entry ($P > 0.05$, Figure 4F).

Peripheral IL-6 promoted microglial QUIN production in basolateral amygdala and exacerbated cognitive impairment in I/R-injured mice

As shown above, intestinal I/R injury resulted in dramatic up-regulation of IL-6 in the intestine and blood. We next examined whether manipulation of peripheral IL-6 affected injury-related microglial reactivation and cognitive impairment. Compared with vehicle group, intravenous injection of IL-6 antibody inhibited microglia activation in the BLA in I/R mice, indicated by smaller microglia volumes ($P = 0.021$, Figures 5A,B), longer process lengths ($P = 0.028$, Figures 5A,B), and fewer branch points ($P = 0.022$, Figures 5A,B), but numbers of cells did not change ($P > 0.05$, Figures 5A,B). In parallel, the IDO-1 mRNA syntheses and QUIN productions in the BLA were also reduced in I/R mice after IL-6 antibody administration ($P = 0.029$ for I/R vs. I/R + IL-6 antibody; $P < 0.01$ for the rest, Figures 5C,D). At 24 h after surgery, IL-6 neutralizing antibody did not affect IL-6 expressions in the intestine ($P > 0.05$, Figure 5E), but increased the plasma levels of IL-6 and IL-6 antibody complex ($P < 0.01$, Figure 5E). As a result of treatment, IL-6 neutralizing antibody significantly decreased IL-6 levels in BLA ($P = 0.033$, Figure 5E). The performances of IL-6 antibody-injected I/R mice at Y maze testing were improved in dwelling time and entries in the novel arm they never explored before ($P = 0.031$, $P = 0.033$, Figures 5F,G).

To examine the role of elevated IL-6, we injected IL-6 or vehicle three times after I/R surgery via intraperitoneal injection. Additional IL-6 did not promote microglia proliferation in I/R mice ($P > 0.05$, Figures 6A,B). Compared to vehicle, IL-6 protein further activated microglia, as evidenced by increased microglia volumes ($P < 0.01$ Figures 6A,B), decreased process lengths ($P < 0.001$, Figures 6A,B), and fewer branch points ($P = 0.020$, Figures 6A,B). Microglia cells were not proliferated by extra peripheral IL-6 at postoperative 24 h ($P > 0.05$, Figure 6B). In the meantime, I/R injury-induced upregulation of IDO-1 mRNA and QUIN in BLA were significantly increased by IL-6 treatment ($P < 0.01$, Figures 6C,D). The blood and BLA pure IL-6 levels were significantly elevated at 24 h ($P < 0.01$, $P = 0.020$, Figure 6E) but not in intestine ($P > 0.05$, Figure 6E). As a result of elevated peripheral IL-6, the mice performed worst at Y maze indicated by the shortest stay and least enters in the novel arm ($P = 0.014$, $P = 0.031$, Figures 6F,G). Overall, the results suggested that peripheral IL-6 contributed to CNS neuroinflammation and cognition impairment in delirium.

QUIN levels of basolateral amygdala were negatively correlated with dwell time at Y maze in the I/R mice

Analysis was conducted using the I/R mice which both measured QUIN and performed Y maze testing ($n = 24$). Results showed that higher QUIN levels of BLA were correlated with longer dwell time in the novel arm at Y maze ($R = -0.617$, $P = 0.001$, Figure 7A). The analysis supported the QUIN levels associated with on delirious cognition in the model. In summary, as illustrated in Figure 7B, peripheral IL-6 mediating microglia activation in the BLA of brain, which promoted IDO-1 mRNA amplification and its catabolite QUIN production, eventually introduced the delirium-like state in I/R mice.

Discussion

The current study reported a simple and reproducible mouse model of postoperative delirium by introducing three cycles of transient I/R attacks into the SMA. The model rapidly developed delirium-associated symptoms, including anxiety and cognitive impairment, within 24 h after surgery, mimicking the manifestation of postoperative delirium in clinical practice. Using this model, we reported that rapid BLA modulation may be implicated in postoperative delirium. We found that microglia reactivation accompanied by upregulation of IDO-1 mRNA and its neuroexcitatory metabolite QUIN in BLA was associated with postoperative cognitive impairment. Furthermore, we revealed that elevated peripheral IL-6 contributed to upregulated levels of IL-6, reactivated microglia, and microglial IDO-1/QUIN in BLA after surgery. Our study provided new insights into the

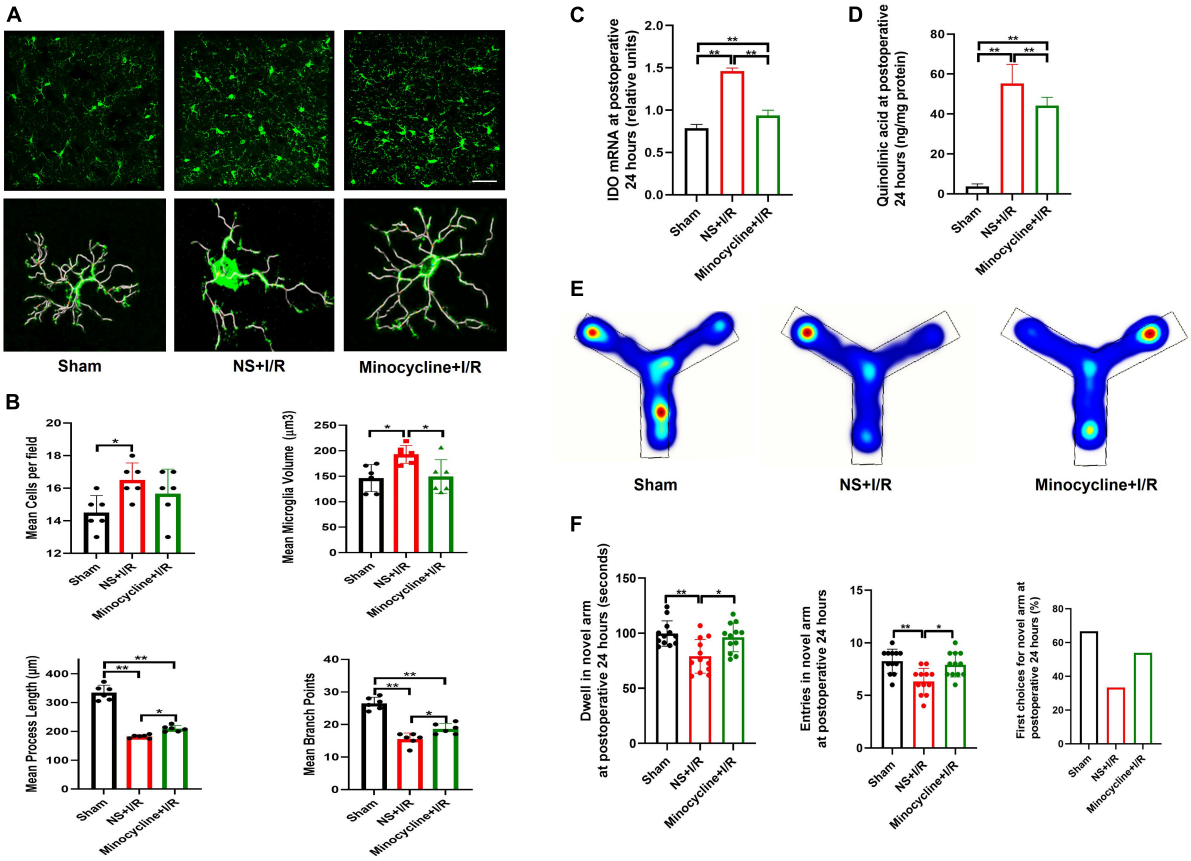

FIGURE 4
Microglia reactivation and IDO-1/QUIN in BLA inhibited by MINO improved the cognition in the model mice. **(A)** Immunofluorescence staining and skeleton of microglia. **(B)** Analysis of microglia reactivation. **(C)** IDO-1 mRNA expression in BLA. **(D)** QUIN levels in BLA. **(E)** Heating map of Y Maze Test. **(F)** Results of Y Maze Test. N = 10–12 per group for Y maze testing, N = 8 for others, $^{*}P < 0.05$, $^{**}P < 0.01$. I/R, ischemia and reperfusion; BLA, basolateral amygdala; NS, normal saline; MINO, minocycline.

neurological basis of postoperative delirium and highlighted Il-6, microglia, and QUIN as targets for the treatment of postoperative delirium.

Abdominal aortic aneurysm open repair (AAA) is a surgical procedure that involves occlusion of mesenteric arteries and mesenteric revascularization. The incidence of delirium after this surgery was estimated as high as 33% (36). We speculated that I/R attacks during surgery might serve as a risk factor for clinical postoperative delirium. Previous rat model acquiring ischemic attacks by clamping SMA for 90 min (12) resulted in high immediate mortality. Based on the evidence that intermittent ischemia exaggerated reperfusion injury in the small intestines (17), we improved the I/R protocol by applying repeated (three cycles) and transient (10/5 min for one I/R cycle) I/R procedures. The current model successfully developed behavioral changes associated with postoperative delirium, including anxiety and impaired cognition, while avoiding animal deaths during the experiments.

Regarding the specific behavioral tests, we found that intestinal I/R surgery disturbed the mice mainly in the Open Field and Y Maze tests, but not in the Buried Food Test. Compared to the sham mice, the I/R-injured mice showing less rearing time and less time spent in center region postoperatively indicated increased anxiety after surgery. These results capitulated the features of delirious patients who were agitated or restless after abdominal surgery. Meanwhile, the I/R-injured mice also showed the cognitive dysfunction at postoperative 24 h as evidenced in the Y Maze Test. This phenotype is consistent with the cognitive deficits in working memory and orientation observed in patients with delirium. I/R injury did not cause any significant changes in the Food Buried Test. The test was adopted according to Peng's report (15) that can be used to assess postoperative delirium. However, in most cases the test was used to evaluate olfactory dysfunction, which was not a typical symptom associated surgery, and only to a lesser extent with delirium related inattention. Other behavior tests should be considered to comprehensively

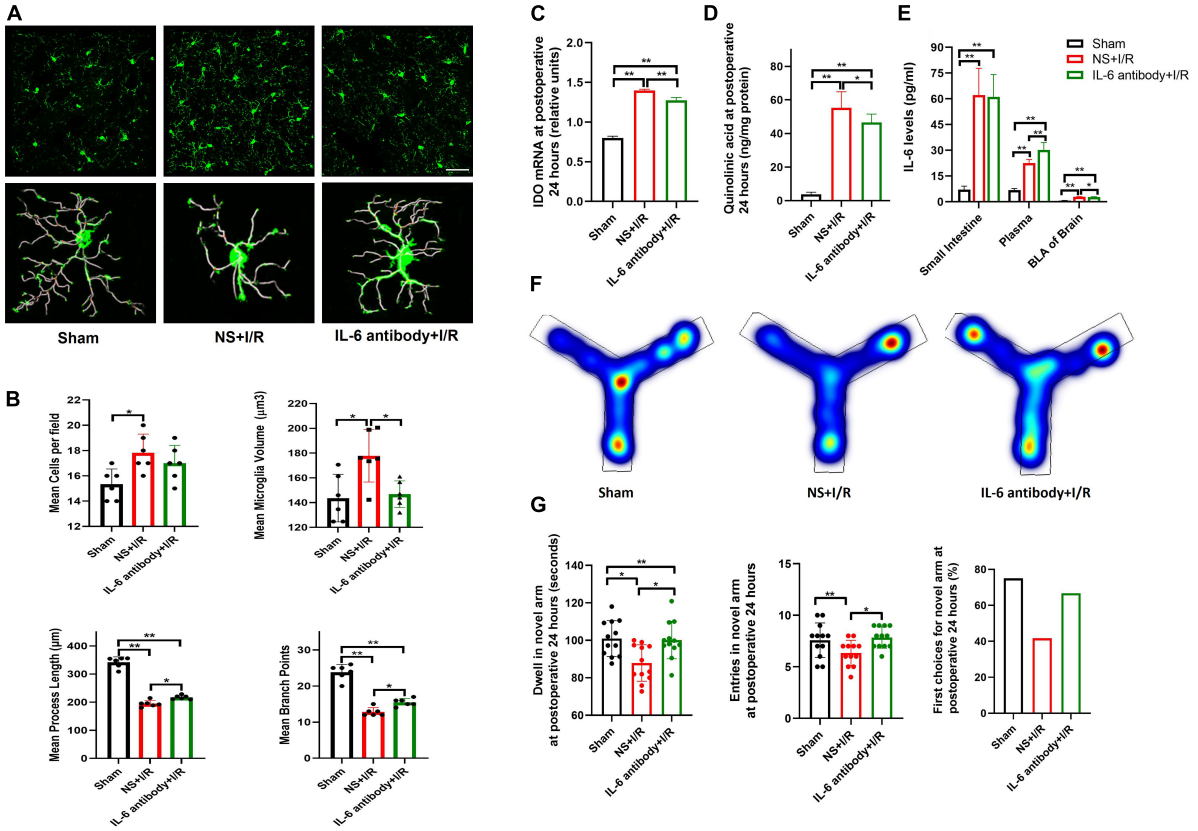

FIGURE 5
Neutralizing peripheral IL-6 reduced microglia reactivation and IDO-1/QUIN in BLA that improved the cognition in the model mice. **(A)** Immunofluorescence staining and skeleton of microglia. **(B)** Analysis of microglia reactivation. **(C)** IDO-1 mRNA expression in BLA. **(D)** QUIN levels in BLA. **(E)** IL-6 levels in intestine, plasma and BLA. **(F)** Heating map of Y Maze Test. **(G)** Results of Y Maze Test. N = 10–12 per group for Y maze testing, N = 8 for others, $^{*}P < 0.05$, $^{**}P < 0.01$. I/R, ischemia and reperfusion; BLA, basolateral amygdala; NS, normal saline; IL-6 antibody, Interleukin 6 antibody.

assess delirium-like phenotypes in the rodent models. Finally, given the multiple manifestations of delirium-like phenotype, the composite score encompassing different aspects of the assessment can serve as a comprehensive and comparable parameter to evaluate delirium among different animal groups. We adopted Peng's tool (15), which calculates composite Z score based on a battery of behavior tests and is analogous to the formulation of CAM/CAM-ICU and CAM-Severity (37). We found that the current model caused ascending composite Z scores over 24 h after surgery, mimicking the natural course of clinical delirium. The current model thus represents a simple and clinically relevant mouse model of postoperative delirium.

One of the major findings of the current study is that postoperatively abnormal BLA activities may underpin the pathogenesis of the delirious phenotype. Microglia can respond rapidly to environmental changes and then adapt/maladapt to such changes by modulating neuronal activities with various microglia-derived molecules (4). Indeed, after I/R surgery, microglia were rapidly reactivated in various brain regions involved in emotion and cognition. Two regions, namely BLA and CA3, showed sustained microglia reactivation over 24 h. Remarkably, BLA was the only region in which the percentage of reactivated microglia was negatively correlated with cognitive deficits. We then applied MINO, recombinant IL-6 protein and IL-6 neutralizing antibody to manipulate microglia activities and found that microglia modulation in BLA was associated with changes in I/R-induced cognitive impairment, further supporting the BLA involvement. Previous studies identified IDO-1 as a critical modulator of depression- and anxiety-like behaviors induced by systemic inflammation (38, 39). IDO-1 is a rate-limiting metabolic enzyme of the kynurenine pathway composed of several neuroactive metabolites including QUIN, an endogenous *N*-methyl-D-aspartate receptor (NMDAR) agonist implicated in depression and cognitive deficits (6, 40). Although IDO-1 is expressed in different types of glial cells, microglia dominate the production of the neuroexcitatory metabolite QUIN in response to inflammatory mediators (41). These studies suggest that microglial IDO-1 could produce QUIN to modulate neural

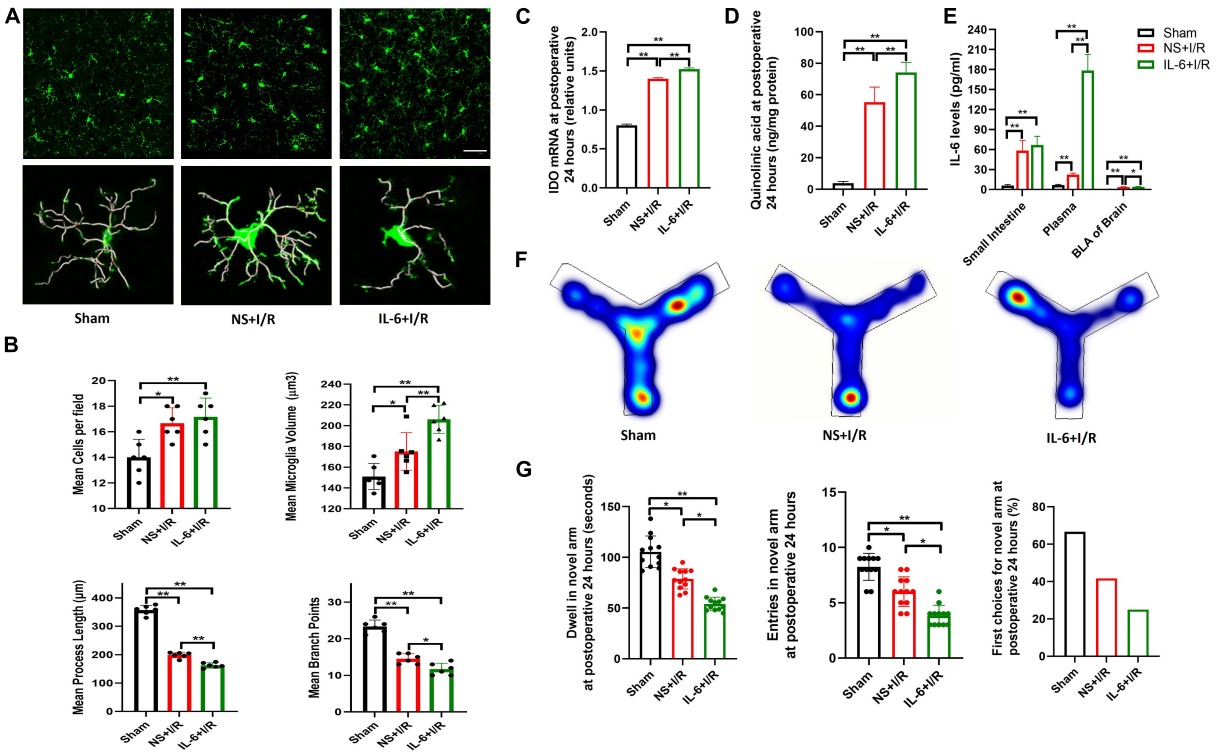

FIGURE 6
Microglia reactivation and productions of IDO-1/QUIN in BLA triggered by extra peripheral IL-6 worsened the cognition in model mice. **(A)** Immunofluorescence staining and skeleton of microglia. **(B)** Analysis of microglia reactivation. **(C)** IDO-1 mRNA expression in BLA. **(D)** QUIN levels in BLA. **(E)** IL-6 levels in intestine, plasma and BLA. **(F)** Heating map of Y Maze Test. **(G)** Results of Y Maze Test. *N* = 10–12 per group for Y maze testing, *N* = 8 for others, **P* < 0.05, ***P* < 0.01. I/R, ischemia and reperfusion; BLA, basolateral amygdala; NS, normal saline; IL-6, Interleukin 6.

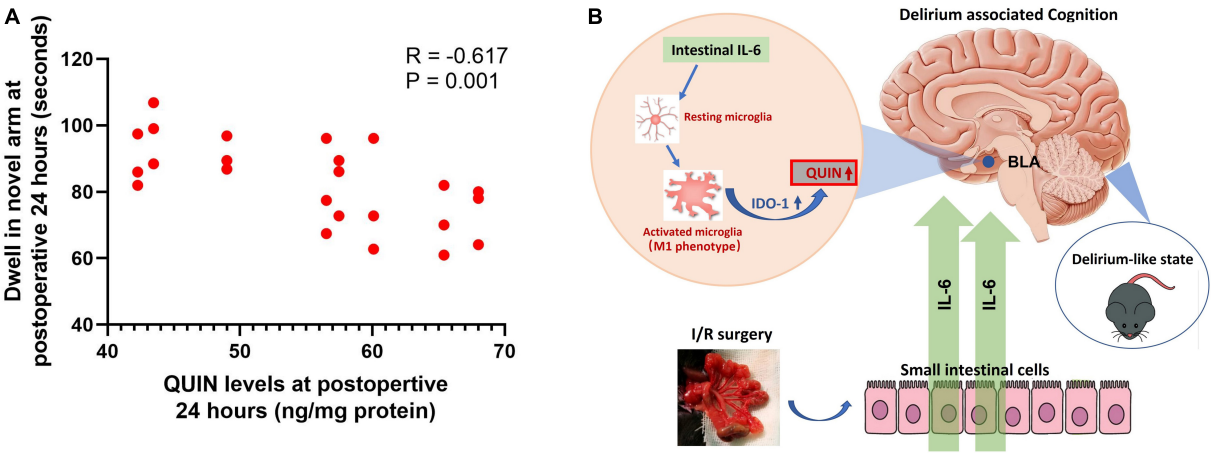

FIGURE 7
Correlation analysis between QUIN and dwell time at Y maze and illustration of the pathway mediated the delirium-associated cognition in the model. **(A)** Correlation analysis in the I/R mice model, *N* = 24 per group. **(B)** Illustration of the pathway.

activities in the CNS. In this study, we found that IDO-1 and QUIN levels were significantly increased along with microglia reactivation in BLA after I/R surgery, while these changes were reduced by MINO administration, suggesting that abnormal microglia activation can lead to excessive QUIN in BLA, bringing about cognitive impairment after surgery. Previous studies have reported hippocampus or cortex were two activated regions after intestinal I/R injury (12–14). For example, Zhou et al. (12) reported activated microglia in the cortex and CA1 of hippocampus in rats after 1-h ischemia and 48-h perfusion of small intestine surgery. Hovens et al. (13, 14) screened the brain regions tagged with reactivated microglia after intestinal I/R surgery, including cortex, hippocampus, and BLA. However, since those results were obtained 1 week after surgery, the models should relate to delayed neurocognitive recovery rather than delirium. The finding in our study that abnormalities in the BLA started early in the disease deserves close attention. BLA is responsible for promoting the fear response and consolidating the cued fear memory (29). In a systematic review summarizing the qualitative findings of patients' experiences of delirium, fear was an overarching feeling reported by the vast majority of patients (42). The results of our animal model were consistent with this clinical manifestation that implied alleviating patient's fear as potentially effective therapies to reduce postoperative delirium.

I/R attacks induced a dramatic increase in IL-6, IL -1β, and TNF-α in the small intestines. However, along the gut-blood-brain axis only IL-6 was increased, but not IL-1β or TNF-α. Previous study showed that peripheral IL-6 can cross BBB (43). The findings that systemic administration of recombinant IL-6 protein and anti-IL-6 antibody increased and decreased IL-6 levels in BLA, respectively, supported the direct penetration of IL-6 after I/R attacks. A recent study using a similar rat model of intestinal I/R reported that plasma IL-6 was elevated over 24 h after surgery (13). In addition, two large clinical cohort studies reported that plasma IL-6 were increased in delirious patients shortly after surgery (44, 45) and IL-6 levels were significantly associated with an increased risk of postoperative delirium. However, the mechanism of how peripheral IL-6 mediated the brain disorder was not studied in these studies. In our study, microglia were considered as target cells of increased IL-6 since the IL-6 receptor is mainly detected in microglia in the CNS (46). Furthermore, IL-6 manipulation can enhance or reverse intestinal I/R-induced microglia reactivation supports microglia as potential targets of IL-6. In the meantime, it has been reported that IDO-1 expression could be upregulated by IL-6 in the brain (47, 48). We found that administration of IL-6 antibodies caused decreased IL-6 levels in the BLA accompanied by suppression of IDO-1/QUIN (41) which improved the cognitive function, while injection of IL-6 protein had opposite effects. These results provided evidence that intestinal I/R-induced IL-6 might penetrate BBB and derived the pathogenesis of postoperative delirium through activation of microglial IDO-1/QUIN metabolic pathway in the BLA. Our results together with previous evidence can serve as a pre-clinical justification for IL-6 modulation as a strategy to alleviate delirium associated cognitive impairment.

The current study had several limitations. First, younger adult mice were used in the study which did not represent the older people who have postoperative delirium more commonly. However, a great number of younger adult patients also develop postoperative delirium at an incidence from 5 to 13.9% (49). We expected the older mice would present grave delirium-like phenotype due to the high-risk factor of advanced age for delirium. Second, we did not evaluate the model in female mice, which did not reflect the same incidence of delirium in male and female patients. Future comparative studies need to be conducted to explore the difference in pathology between different age groups or sexes. Finally, the connection between microglial QUIN and BLA neuron activities was not thoroughly explored in the current study. The selective interference of microglial IDO-1 or neuronal NMDAR to validate the implication of the IDO-1/QUIN/NMDAR axis-dependent microglia-neuron interaction in the pathogenesis of postoperative delirium will be investigated to consolidate the findings of current study.

In conclusion, the repeated I/R insults on the SMA capitulated certain features of postoperative delirium. The core symptom of cognition decline was explained by peripheral IL-6-mediated microglial reactivation followed by IDO-1/QUIN production in the BLA. The model is a useful tool for delineating the mechanisms of delirium after abdominal surgery.

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.

Ethics statement

The animal study was reviewed and approved by the Animal Experiment and Welfare Committee of Nanfang Hospital, Southern Medical University.

Author contributions

J-LM, X-DL, and K-XL conceived and designed the study and prepared the manuscript, with editing and revision by all authors. J-LM, Y-HD, S-DQ, Y-YF, and FZ performed

the experiments. J-LM, Y-HD, and Y-YF analyzed the data. 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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.998397/full#supplementary-material

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Analgesic efficacy and risk of low-to-medium dose intrathecal morphine in patients undergoing cardiac surgery: An updated meta-analysis

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Background: To evaluate the analgesic efficacy and risk of low-to-medium dose intrathecal morphine (ITM) (i.e., ≤0.5 mg) following cardiac surgery.

Methods: Medline, Cochrane Library, Google scholar and EMBASE databases were searched from inception to February 2022. The primary outcome was pain intensity at postoperative 24 h, while the secondary outcomes included intravenous morphine consumption (IMC), extubation time, hospital/intensive care unit (ICU) length of stay (LOS), and ITM-associated side effects (e.g., respiratory depression). Subgroup analysis was performed on ITM dosage (low: <0.3 mg vs. medium: 0.3–0.5 mg).

Results: Fifteen RCTs involving 683 patients published from 1988 to 2021 were included. Pooled results showed significantly lower postoperative 24-h pain scores [mean difference (MD) = −1.61, 95% confidence interval: −1.98 to −1.24, $p < 0.00001$; trial sequential analysis: sufficient evidence; certainty of evidence: moderate] in the ITM group compared to the controls. Similar positive findings were noted at 12 (MD = −2.1) and 48 h (MD = −1.88). Use of ITM was also associated with lower IMC at 24 and 48 h (MD: −13.69 and −14.57 mg, respectively; all $p < 0.05$) and early tracheal extubation (i.e., 48.08 min). No difference was noted in hospital/ICU LOS, and nausea/vomiting in both groups, but patients receiving ITM had higher risk of pruritus (relative risk = 2.88, $p = 0.008$). There was no subgroup difference in IMC except a lower pain score with 0.3–0.5 mg than <0.3 mg at postoperative 24 h. Respiratory depression events were not noted in the ITM group.

Conclusion: Our results validated the analgesic efficacy of low-to-medium dose ITM for patients receiving cardiac surgery without increasing the risk of respiratory depression.

KEYWORDS

analgesia, cardiac surgery, intrathecal morphine, tracheal extubation, respiratory depression

Introduction

Cardiac surgery, which is traditionally performed *via* median sternotomy and involves extensive tissue retraction and dissection, can be associated with severe pain within postoperative 2 days (1, 2). Not only does uncontrolled pain activate the sympathetic nervous system and increase myocardial oxygen demand by triggering tachycardia, increased cardiac contractility, and hypertension (3), but it could also increase the risks of pulmonary infections and other complications through restricting respiratory capacity, hampering breathing mechanism, and impairing clearance of respiratory secretions (4). Notwithstanding the analgesic effectiveness of high-dose opioid, the associations with potential adverse side effects including prolonged mechanical ventilation, postoperative respiratory complications, and lengthened intensive care unit (ICU) stay have precluded its incorporation into the standard care protocol for patients undergoing cardiac surgery (5, 6). To address this issue, previous studies have shown that central neuraxial blocks (i.e., epidural and intrathecal analgesia) combined with general anesthesia (GA) could attenuate the severity of pain and adrenergic stress response as well as analgesic consumption more effectively compared to parenteral analgesia (7, 8). Indeed, intrathecal analgesia has been gaining popularity for pain control among patients receiving cardiac surgery to alleviate stress response and enhance postoperative recovery (9–11).

Intrathecal morphine (ITM), which enables rapid action of morphine on the central nervous system by enhancing its access to the cerebrospinal fluid, is being increasingly used in a variety of surgeries to provide effective analgesia and decrease opioid consumption (12–15). In addition to its analgesic advantages, other beneficial effects may include a potentially reduced hospital length of stay (LOS) and enhanced recovery after surgery (15–17). However, its use may be associated with side effects such as nausea, vomiting, itching, and even respiratory depression (12–15). Although ITM has been used for decades in patients undergoing cardiac surgery, its possible association with respiratory depression as reported in a previous meta-analysis (i.e., odds ratio of 7.86) has raised a clinical concern that may restrict its application in this patient population (18). On the other hand, pooled evidence has revealed that ITM-associated adverse events are dose-dependent (15, 19). In that meta-analysis involving patients undergoing cardiac and non-cardiac surgeries, a relatively high dosage of ITM (e.g., >0.5 mg or >7 μg/kg) was adopted in over 40% of the included studies (i.e., 11 out of 27 trials) (18). In contrast, focusing on patients undergoing abdominal surgeries, a meta-analysis suggested that ITM with a dose less than 0.5 mg would not increase the risk of respiratory depression (15).

Although ITM has been reported to be a promising analgesic approach for non-cardiac surgery (15), the analgesic efficacy and associated risks of a relatively low-dose ITM remain unclear in those receiving cardiac procedures. As previous meta-analyses have reported an association of an ITM dose of less than 0.5 mg with a prompt extubation without increasing the risk of respiratory depression (8, 14), we investigated the analgesic efficacy and safety of ITM dosage of ≤0.5 mg or ≤7 μg/kg (i.e., based on a total dose ≤0.5 mg for an average adult with a body weight of 70 kg). In the current meta-analysis, a low-dose ITM was defined as that of <0.3 mg as previously reported (20), while we defined a medium-dose ITM as 0.3–0.5 mg. By hypothesizing that low-to-medium dose ITM (i.e., ≤0.5 mg) may provide favorable analgesic efficacy without increasing the risk of respiratory depression in patients undergoing cardiac surgery, this updated meta-analysis attempted to provide updated evidence for clinical guidance through reviewing the currently available clinical trials.

Methods

This meta-analysis was conducted in accordance with the recommendations of the PRISMA statement and registered with the International Prospective Register of Systematic Reviews (CRD42022310647).

Data sources and searches

We searched the Cochrane Library, Embase, Google scholar, and Medline databases from inception to February 11, 2022 using the following search terms: ["coronary artery bypass surger*" or "cardiopulmonary bypass surger*" or

"cardiovascular surger*" or "cardiac surger*" or "CABG" or "off-pump coronary artery surger*" or "coronary artery bypass graft surger*" or "Heart Surger*" or "Cardiac Surgical Procedure*" or "(Aortic or Mitral or Heart Valve Prosthesis Implantation or Aortic Valve or Mitral Valve) adj4 (procedure* or operation* or surger*)"] and [("Spinal" or "intraspinal" or "intradural" or "lumbar*" or "theca*" or "intrathecal" or "subarachnoid*" or "sub arachnoid*" or "regional") adj4 (puncture* or inject* or anesth* or anaesth* or needle*)] limited to randomized controlled trials (RCTs). No restriction was placed on gender, language, study location, and sample size during literature search. The search strategies for one of these databases are demonstrated in **Supplementary Table 1**. Additional records identified by scrutinizing the reference lists of the retrieved studies were also reviewed for eligibility of being included in the current study.

Inclusion criteria

To identify articles eligible for the present meta-analysis, we adopted the following criteria: (a) Population: adult patients (age $\geq$18 years) undergoing a variety of cardiac surgeries with or without cardiopulmonary bypass, (b) Intervention: the use of a low-to-medium dose ITM with or without adjuncts (e.g., local anesthetics or short-acting opioids) as the intervention approach., (c) Comparison: ITM was not administered for postoperative pain control, (d) Outcomes: pain score, intravenous morphine consumption, length of hospital/ICU stay, extubation time, and ITM-associated side effects. We only included RCTs for analysis and contacted the authors of the included articles in which necessary information was missing in an attempt to access the original data.

Exclusion criteria

Exclusion criteria were: (1) studies which adopted a relatively high-dose ITM (i.e., >0.5 mg or 7 μg/kg); (2) those without a control group; (3) those in which information regarding outcomes was unavailable, and (4) RCTs presented only as letters or abstracts, or (5) those published as reviews, case reports, or other forms instead of original research.

Study selection

Two authors first independently reviewed the titles and abstracts of the retrieved articles for eligibility of being incorporated into the current study. The same two authors then independently scrutinized the full texts of the potentially eligible studies according to the inclusion and exclusion criteria. Discrepancies in opinions about the suitability of inclusion for a particular RCT were settled through consulting a third reviewer.

Data extraction

The following information was retrieved from each study: first author, year of publication, patient characteristics, sample size, dosage of ITM, type of surgery, extubation time, intravenous morphine consumption, postoperative pain score, ITM-related side effects (e.g., pruritus, respiratory depression, nausea/vomiting), hospital LOS, ICU LOS. Disagreements were solved through discussion with a third author.

Outcomes and definitions

The primary outcome was the analgesic efficacy of low-to-medium dose ITM as reflected by the postoperative pain score at postoperative 24 h, while the secondary outcomes included intravenous morphine consumption, extubation time, and hospital/ICU LOS as well as the risks of pruritus, respiratory depression, and nausea/vomiting. The definition of respiratory depression was in accordance with that of each study. If one study did not clearly define this event, we regarded postoperative reintubation or the use of non-invasive ventilation as an indicator of respiratory depression. Subgroup analysis based on the dosage of ITM (i.e., <0.3 mg vs. 0.3–0.5 mg) was also performed to assess possible dose-dependent analgesic efficacy and side effects. Regarding the possible influence of other factors on postoperative 24-h pain score, we conducted subgroup analyses focusing on the impacts of three confounders: (1) the type of surgery [e.g., coronary artery bypass graft surgery (CABG), valve surgery, combined procedures], (2) the use of cardiopulmonary bypass (i.e., yes vs. no), and (3) the use of other intrathecal agents (i.e., ITM alone vs. ITM combined with other agents).

Assessment of risk of bias

Using the Cochrane's tool (RoB 2), two authors independently assessed the risks of different biases of the included RCTs, namely, allocation, performance, attrition, measurement, and reporting biases as well as the overall bias (21). The risk of bias of each RCT was reported as "low," "some concern," or "high." Disagreement between the two authors was settled through arbitration that involved a third reviewer.

Data synthesis and analysis

Cochrane Review Manager (RevMan 5.3; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used for the present meta-analysis. The pooled risk ratios (RRs) and mean difference (MD) with 95%

confidence intervals (CIs) were computed for binary and continuous outcomes, respectively. For the current study, visual analog scale (VAS) 0–10 cm or 0–100 mm, numerical rating scale (NRS) 0–10, and visual numeric scale (VNS) 0–10 were converted into VAS 0–10 cm for pain severity comparison (22). Regarding the comparison of opioid dosage across different studies, we converted all opioid dosages to morphine equivalents as previously described (23). We assessed heterogeneity with I^2 statistics and defined substantial heterogeneity as an I^2 over 50%. Assuming the existence of heterogeneity across the included studies, we adopted *a priori* a random-effects model for outcome evaluation (22, 24). The potential publication bias was assessed by visual inspection of a funnel plot on encountering 10 or more trials sharing a particular outcome. For equivocal findings from funnel plots, Egger's test was conducted to investigate the possibility of bias using Comprehensive Meta-Analysis version 3.3.070 (BioSTAT, United States). Sensitivity analysis was performed with a leave-one-out approach to weigh the potential influence of the data from an individual trial on the overall outcome. The level of significance was set at <0.05 for all outcome analyses.

Robustness of the conclusion and reliability of the pooled evidence were evaluated with trial sequential analysis (TSA) to reduce false-positive or false-negative outcomes from multiple testing and sparse data (25, 26). TSA was conducted with TSA viewer version 0.9.5.10 Beta[1]. We calculated the required information size as well as the trial sequential monitoring boundaries for all outcomes. The variance was obtained from the retrieved data of our included studies.

If the cumulative *Z*-curve crosses the TSA boundary, there is sufficient evidence for the expected intervention effect with no need for support from further studies. In contrast, if the *Z*-curve fails to cross the TSA boundaries or attain the required information size, the level of evidence is inadequate to support a conclusion. Setting a type I error at 5%, a power at 80%, and a relative risk reduction at 20% for dichotomous outcomes, we computed the required information size with two-sided tests (27).

Certainty assessment

The certainty of the evidence from our primary and secondary outcomes was assigned to four grades (i.e., high, moderate, low, and very low) by two independent authors based on the probability of study limitations, publication bias, effect consistency, imprecision, and indirectness as described in GRADE. In case of disagreements about certainty ratings, consensus was reached through discussion.

1 www.ctu.dk/tsa

Results

Study selection and characteristics

The study selection process is shown in **Figure 1**. A total of 740 records were acquired from database search. After removing duplicates and records that did not meet the inclusion criteria, we identified 39 potentially eligible trials for a more detailed review. After analyzing the full text, 24 studies were excluded because of being non-RCTs (review article, $n = 2$), availability only as an abstract ($n = 1$), no control group ($n = 1$), and use of ITM > 0.5 mg or 7 μg/kg ($n = 20$) (**Supplementary Table 2**). Finally, 15 RCTs published between 1988 and 2021 met our inclusion criteria (3, 28–41). The characteristics of the included trials are shown in **Table 1**. The mean or median age ranged from 25.9 to 67.3 years with a male predominance (>70%, 11 trials). CABG and mixed CABG/valve surgery were performed in eight (3, 31, 34–36, 39–41) and four (28, 29, 33, 37) trials, respectively, while the other three trials were focused on minimally invasive cardiac surgery ($n = 2$) (30, 38) and valve surgery ($n = 1$) (32). ITM was administered preoperatively in all studies with a maximum dose of 0.5 mg or 7 μg/kg and a minimum dose of 0.25 mg or 0.4 μg/kg. Intrathecal morphine was used as a single agent in 12 trials (3, 28, 30–34, 36, 38–41) and as a component of a combined regimen in three studies (29, 35, 37). Patients in the control groups received local anesthesia of the back, no treatment, or placebo (e.g., intrathecal normal saline). Analysis of the occurrence of respiratory depression including postoperative reintubation or the use of non-invasive ventilation in the five trials with available information (3, 30–33) showed no such incidence in a total of 234 patients, suggesting the safety of its clinical use. Nevertheless, because of the absence of events indicating respiratory depression in all of the five studies, statistical analysis could not be performed.

Risk of bias assessment

The assessment of the risk of bias is shown in **Figure 2**. The overall risk of bias was considered to be low in 11 studies (3, 28–32, 35–37, 39, 41), and high in four trial (33, 34, 38, 40). High risk of bias was associated with bias arising from the randomization process.

Results of syntheses

Primary outcome: Impact of intrathecal morphine on severity of pain at postoperative 24 h

By adopting a random-effects model, ITM was associated with a lower pain score compared to that in the control group at postoperative 24 h (MD = −1.61, 95% CI: −1.98 to −1.24,

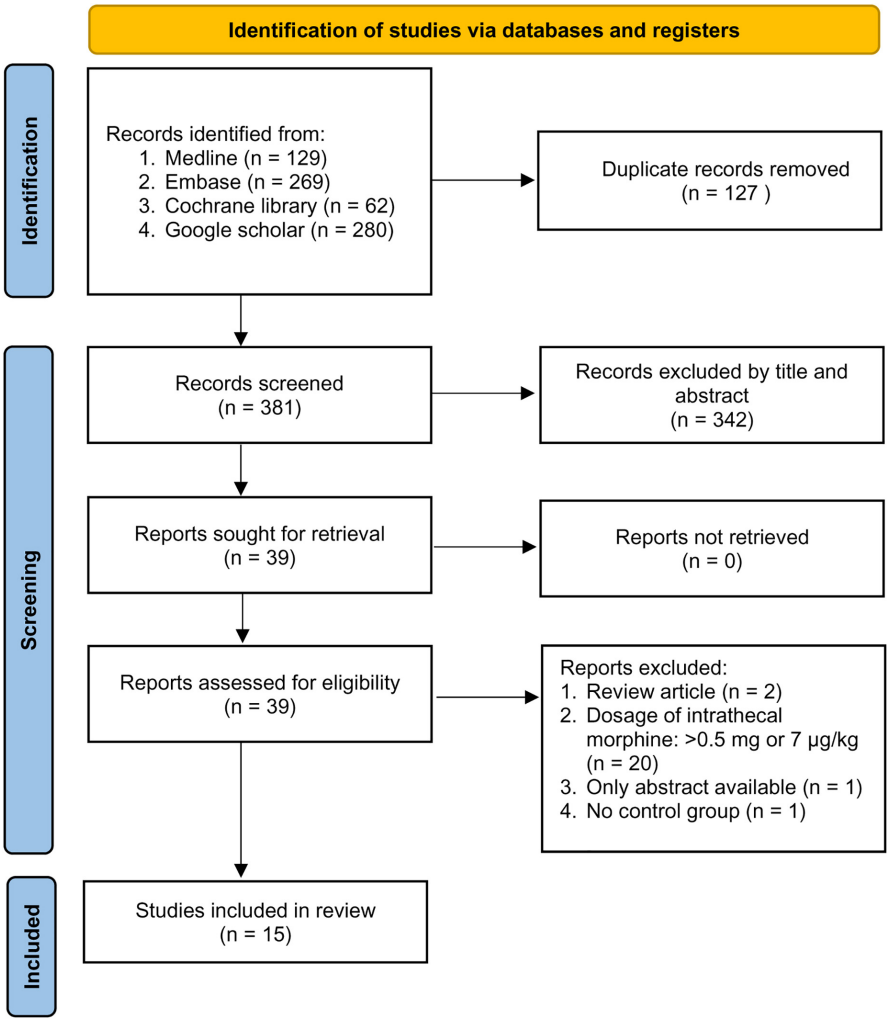

FIGURE 1
PRISMA flow diagram of study selection for the current meta-analysis.

$p < 0.00001$, $I^2 = 90\%$, 11 trials, 578 participants) (Figure 3). There were similar findings at postoperative 12 h (MD = −2.1, 95% CI: −2.83 to −1.36, $p < 0.00001$, $I^2 = 96\%$, 10 trials, 517 participants) and 48 h (MD = −1.88, 95% CI: −2.83 to −0.93, $p = 0.0001$, $I^2 = 80\%$, 4 trials, 259 participants). Subgroup analysis demonstrated a superior analgesic efficacy associated with a dosage of 0.3–0.5 mg compared to that with <0.3 mg ($p = 0.03$) at postoperative 24 h, but not at 12 or 48 h (Supplementary Figures 1, 2).

The results of subgroup analyses based on the type of cardiac surgery, the use of cardiopulmonary bypass, and combination with other intrathecal agents are demonstrated in Figures 4–6, respectively. Despite the absence of notable subgroup variation in 24-h pain score among different types of cardiac surgery ($p = 0.14$) (Figure 4), those not subjected to cardiopulmonary bypass (Figure 5) and those receiving ITM alone instead of a combined regimen (Figure 6) were found to have a more significant reduction in 24-h pain score ($p < 0.00001$ and $p = 0.02$, respectively).

Secondary outcomes: Association of intrathecal morphine with intravenous morphine consumption, early extubation time, and length of stay

Forest plot showed a lower intravenous morphine consumption in the ITM groups than that in the control groups at postoperative 24 h (MD = −13.69, 95% CI: −22.29 to −5.08, $p = 0.002$; I2 = 88%, 355 participants) (Figure 7) and 48 h (MD = −14.57, 95% CI: −26.98 to −2.17, $p = 0.02$; $I^2 = 98\%$, 289 participants) (Supplementary Figure 3). There were no subgroup differences between the doses of 0.3–0.5 mg and <0.3 mg at these two time points.

The extubation time was 41.4–355 and 39.2–396 min in the ITM and control groups, respectively. Merged results

demonstrated a shorter time for tracheal extubation in the ITM group than that in the control group (MD = −48.08 min, 95%: −78.49 to −17.68, p = 0.002, I^2 = 75%, 10 trials, 483 participants) (Figure 8). Subgroup analysis revealed no impact of ITM dosage on extubation time (p = 0.2).

Our results showed no significant beneficial effect of using ITM on shortening ICU LOS (MD = −5.69 h, 95% CI: −11.83 to 0.46, p = 0.07, I^2 = 87%, four trials, 158 participants) (Supplementary Figure 4) or hospital LOS (MD = −0.53 days, 95% CI: −1.16 to 0.1, p = 0.1, I^2 = 0, four trials, 178 participants) (Supplementary Figure 5). Subgroup analysis also demonstrated no dose-related impact of ITM on hospital/ICU LOS.

Secondary outcomes: Impact of intrathecal morphine on risks of nausea/vomiting and pruritus

Merged results demonstrated no association between ITM and the risk of PONV (RR = 1.13, 95% CI: 0.73 to 1.74, p = 0.59, I^2 = 29%, nine trials, 495 participants) (Supplementary Figure 6). Consistently, subgroup analysis showed no impact of ITM on the risk of PONV (p = 0.75).

Forest plot revealed a higher risk of pruritus in patients receiving ITM compared to that in the control group (RR = 2.88, 95% CI: 1.31 to 6.31, p = 0.008, I^2 = 0%, eight trials, 411 participants) (Supplementary Figure 7). Nevertheless, subgroup analysis demonstrated no correlation between ITM dosage and the risk of pruritus (p = 0.92).

Sensitivity analysis and publication bias

Sensitivity analysis confirmed the robustness of most results except three secondary outcomes (i.e., intravenous morphine consumption at postoperative 24 h, ICU LOS, and risk of pruritus). The potential publication bias was assessed by visual inspection of a funnel plot in three outcomes (i.e., pain score at postoperative 12-, 24 h, and extubation time) (Supplementary Figures 8–10). There is a low risk of publication bias on extubation time (Supplementary Figure 10), while there was uncertainty on pain score at postoperative 12 and 24 h (Supplementary Figures 8, 9). Egger's test revealed p-values of 0.68 and 0.086 for pain score at 12 and 24 h, respectively, indicating no publication bias for the two outcomes.

Trial sequence analysis

Trial sequential analysis demonstrated sufficient evidence to support a robust conclusion for pain score at postoperative 24 h (i.e., primary outcome) (Figure 9). In addition, TSA in the current study also suggested a robust conclusion for postoperative pain score (i.e., at 12 and 48 h), intravenous morphine consumption at postoperative 24 h, and extubation time by demonstrating the crossing of cumulative Z-curve through the trial sequential monitoring boundary and reaching the required information size (Supplementary Figures 11–13,15). For intravenous morphine consumption at postoperative 48 h, failure of the cumulative Z-curve to cross the trial sequential monitoring boundary or reach the required

TABLE 1 Characteristics of studies (n = 15).

Study	Age (years)[a]	BMI (kg/m^2) or BW (kg)[a]	N[a]	Male	Procedures	ITM	Time of ITM	Country
Alhashemi (3)	60.4 vs. 64.4	92.6 vs. 90.5	16 vs. 19	34%	CABG	0.25 mg	Preop	Canada
Bettex (28)	53.5 vs. 57.2	76 vs. 81.5	11 vs. 13	92%	CABG/valve surgery	0.5 mg	Preop	Switzerland
Bhat (29)	46 vs. 42	NA	45 vs. 42	43%	CABG/valve surgery	0.25 mg[b]	Preop	India
Dhawan (30)	67.3 vs. 64.5	27.5 vs. 28.6	37 vs. 42	82%	MICS[§]	5 μg/kg	Preop	United States
dos Santos (31)	60.9 vs. 63.8	24.4 vs. 27.1	20 vs. 22	86%	CABG	0.4 mg	Preop	Brazil
Elgendy (32)	26.5 vs. 25.9	56 vs. 64.4	22 vs. 22	48%	AVR	7 μg/kg	Preop	Egypt
Jacobsohn (33)	62 vs. 64	28 vs. 29	22 vs. 21	86%	CABG/valve surgery	6 μg/kg	Preop	United States
Jara (34)	64.4 vs. 64.1	NA	20 vs. 12	78%	CABG[§]	5 μg/kg	Preop	United States
Lena (36)	61 vs. 60	NA	14 vs. 16	77%	CABG	4 μg/kg	Preop	France
Lena (35)	66.4 vs. 66.2	78 vs. 74	20 vs. 20	80%	CABG	4 μg/kg[c]	Preop	France
Lena (37)	66 vs. 66	27 vs. 25	42 vs. 41	80%	CABG/valve surgery	4 μg/kg[d]	Preop	France
Mukherjee (38)	55 vs. 60	25.5 vs. 25.4	30 vs. 31	69%	MICS	1.5 μg/kg	Preop	Germany
Roediger (39)	65.5 vs. 60.7	85 vs. 82.5	15 vs. 15	100%	CABG	0.5 mg	Preop	Belgium
Vanstrum (40)	63.7 vs. 66.8	83.8 vs. 74	16 vs. 14	87%	CABG	0.5 mg	Preop	United States
Yapici (41)	55.3 vs. 59.3	72.8 vs. 62.2	12 vs. 11	70%	CABG	7 μg/kg	Preop	Turkey

AVR, aortic valve replacement; MICS, minimally invasive cardiac surgery; ITM, intrathecal morphine; [a]present as ITM vs. control group; [b]combined with 40 mg Marcaine; [c]combined with clonidine 1 μg/kg; [d]combined with clonidine 2 μg/kg; Preop, pre-operation; BW, body weight; BMI, body mass index; Coronary artery bypass graft surgery (CABG); [§] cardiopulmonary bypass not used.

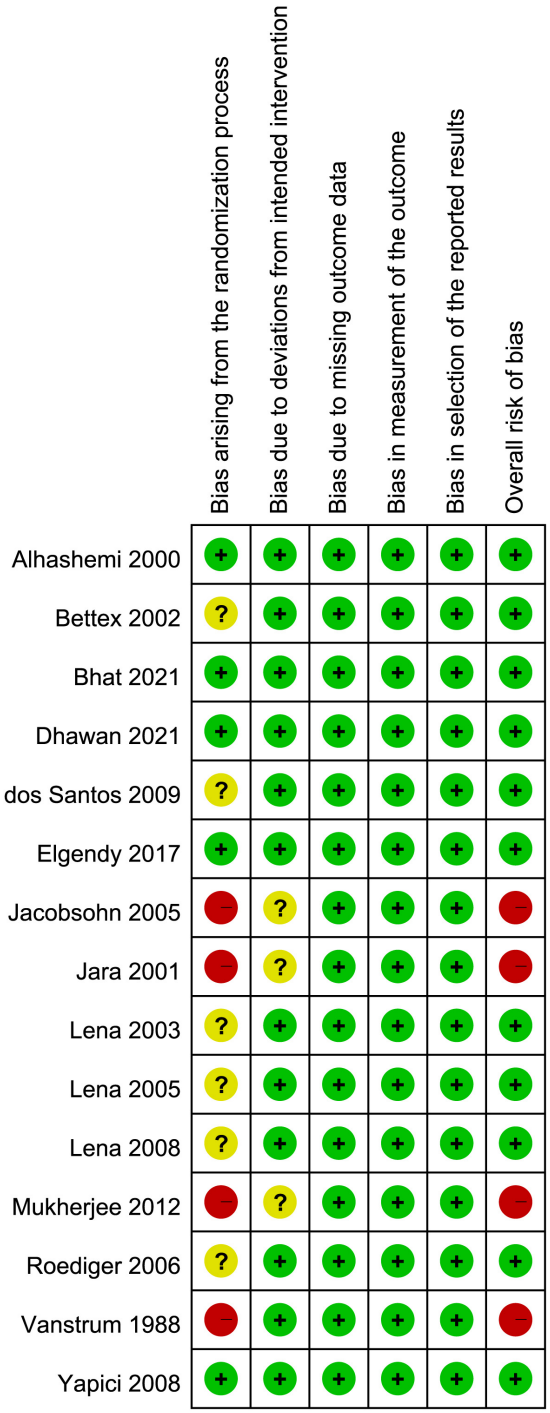

FIGURE 2
Risks of bias of the included studies.

information size on TSA suggested inadequate evidence for this outcome (Supplementary Figure 14). Similarly, the cumulative *Z*-curve did not cross the futility boundary for hospital/ICU LOS and risk of nausea/vomiting, implicating inconclusive evidence for these outcomes (Supplementary Figures 16–18). TSA was not conducted for risk of pruritus due to insufficient information (Supplementary Figure 19).

Certainty of evidence

Table 2 summarizes the quality of evidence for outcome measures in accordance with the GRADE system. The levels of evidence were graded as low, moderate, and high in two (intravenous morphine consumption at 24 and 48 h), five (pain score at 12–48 h, extubation time, ICU stay), and three (hospital stay, risk of nausea/vomiting, risk of pruritus) outcomes, respectively. The level of evidence was downgraded due to a high degree of inconsistency and imprecision.

Discussion

Satisfactory postoperative pain control is essential to patient recovery after cardiothoracic surgery because inadequate analgesia may contribute to prolonged immobilization as well as impaired lung expansion and respiratory function, especially in those undergoing median sternotomy (4, 42–44). Our results demonstrated an association of low-to-medium dose ITM with a lower pain score and intravenous morphine consumption compared to the control group up to postoperative 48 h without increasing the risks of PONV and respiratory depression. Besides, a shorter extubation time (i.e., 48.08 min) was noted in patients receiving low-to-medium dose ITM despite the absence of a positive impact of ITM on ICU/hospital LOS. On the other hand, ITM-associated pruritus was noted regardless of the dosage used in the current meta-analysis.

Although two previous meta-analyses recruiting patients receiving cardiac (8) or cardiac/non-cardiac (18) surgery reported the effectiveness of ITM for reducing pain score and intravenous morphine consumption, most trials in one meta-analysis (i.e., 13 out of 17) (8) and a significant proportion in the other (i.e., 11 out of 27) (18) used a relatively high dose of ITM (i.e., 8 μg/kg–4 mg). Therefore, the relatively high risk of respiratory depression (odds ratio: 7.86) in one of the meta-analyses (18), which may partly be attributed to a high ITM dosage, raises the concern over the possibility of a dose-related increase in the risk of respiratory complications. Similarly, despite focusing on patients receiving CABG, another meta-analysis including mostly trials adopting a high-dose ITM (8) could not reflect the efficacy of low-to-medium dose ITM in the cardiac surgery setting. Accordingly, the present study, which systematically reviewed the evidence from currently available clinical trials, is the first to investigate the impacts of low-to-medium dose ITM on the efficacy of postoperative analgesia as well as the risks of adverse side-effects in patients after cardiac surgery.

In general, surgical pain after cardiac procedures is most intense during the first 2 days, especially in the

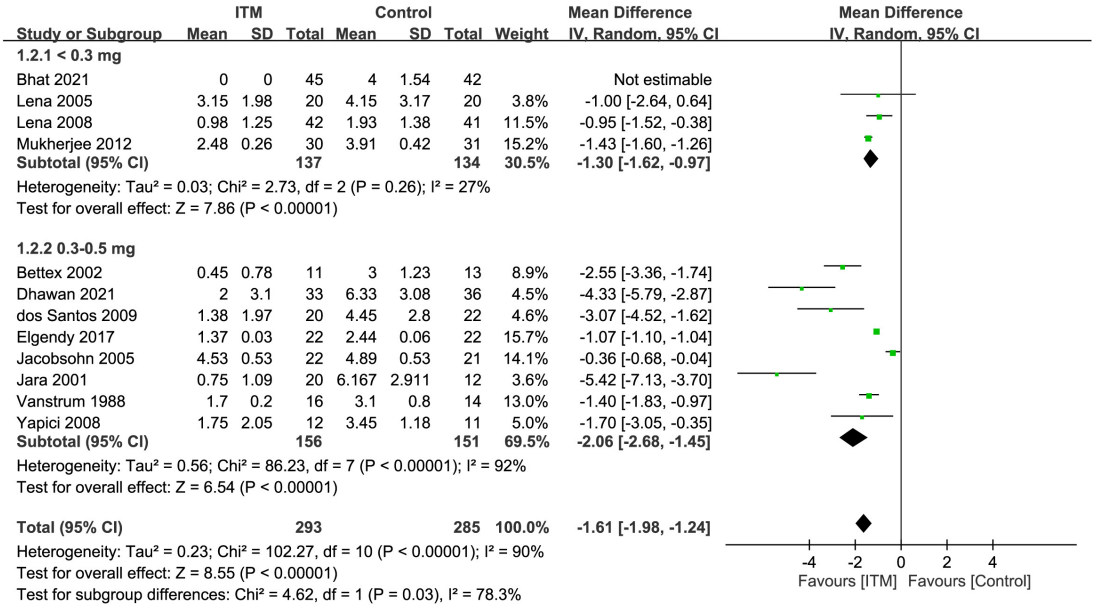

FIGURE 3
Forest plot comparing the pain score at postoperative 24 h between intrathecal morphine (ITM) and control groups. CI, confidence interval; IV, inverse variance; SD, standard deviation.

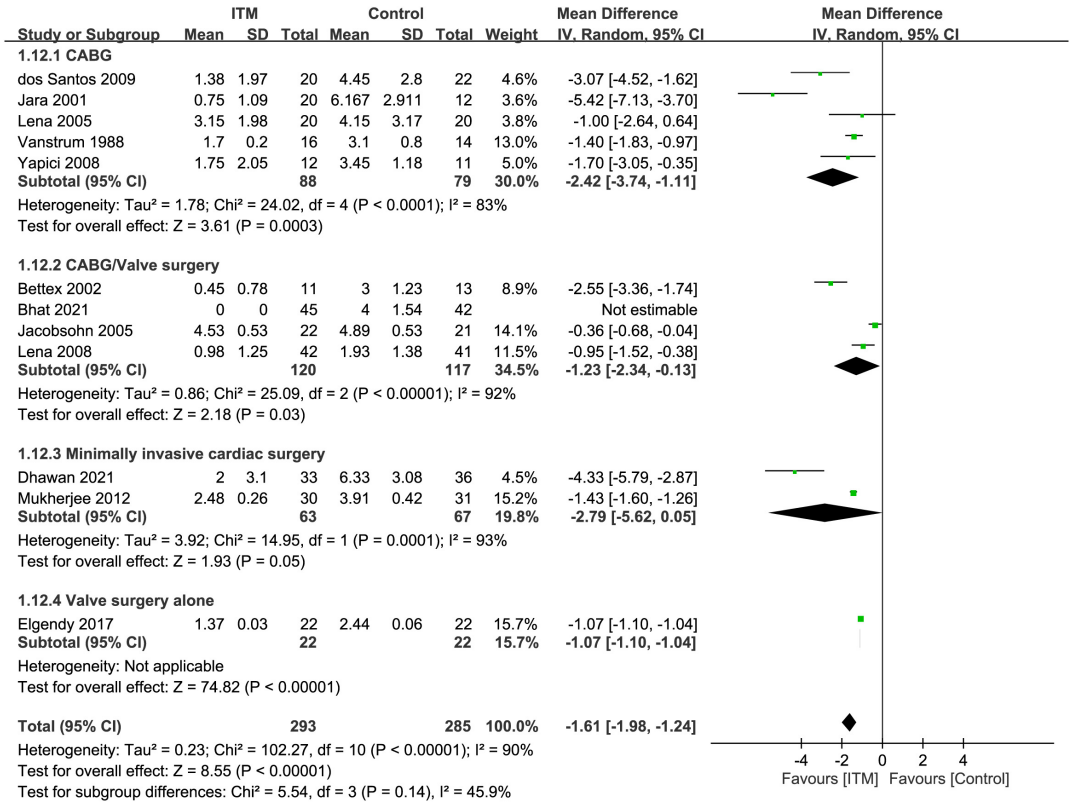

FIGURE 4
Subgroup analysis comparing postoperative 24-h pain score between intrathecal morphine (ITM) and control groups based on type of cardiac surgery. CI, confidence interval; IV, inverse variance; SD, standard deviation.

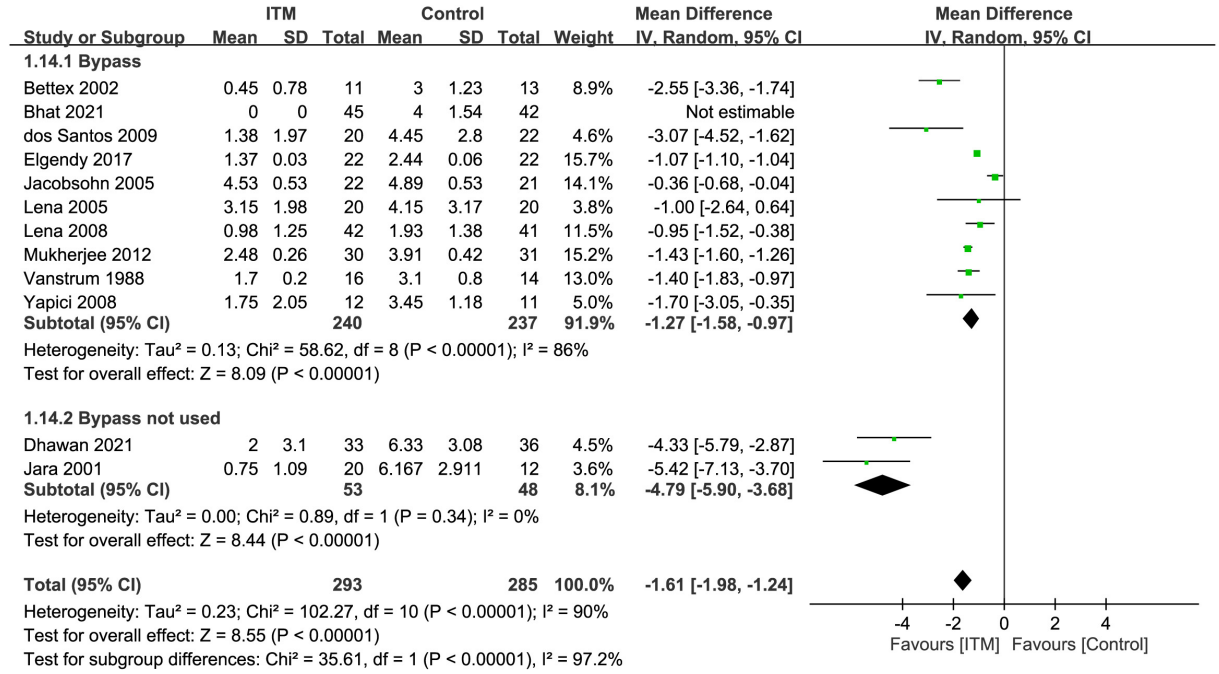

FIGURE 5
Subgroup analysis comparing postoperative 24-h pain score between intrathecal morphine (ITM) and control groups based on the use of cardiopulmonary bypass. CI, confidence interval; IV, inverse variance; SD, standard deviation.

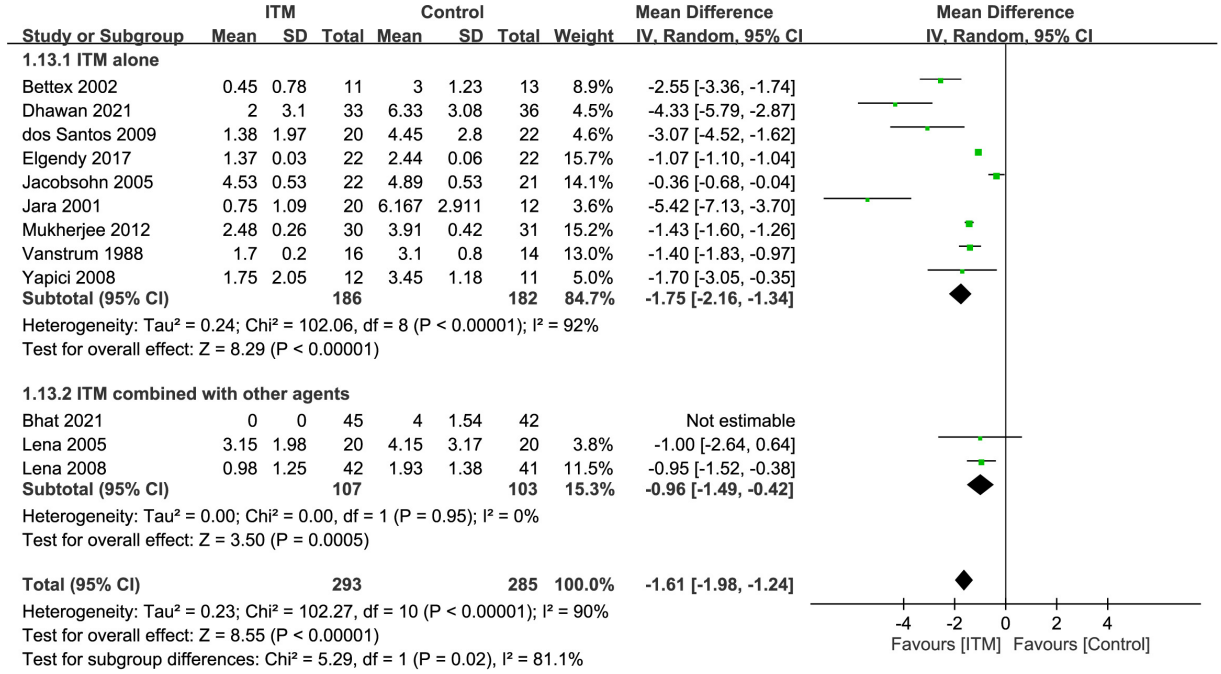

FIGURE 6
Subgroup analysis comparing postoperative 24-h pain score between intrathecal morphine (ITM) and control groups based on the use of intrathecal agents. CI, confidence interval; IV, inverse variance; SD, standard deviation.

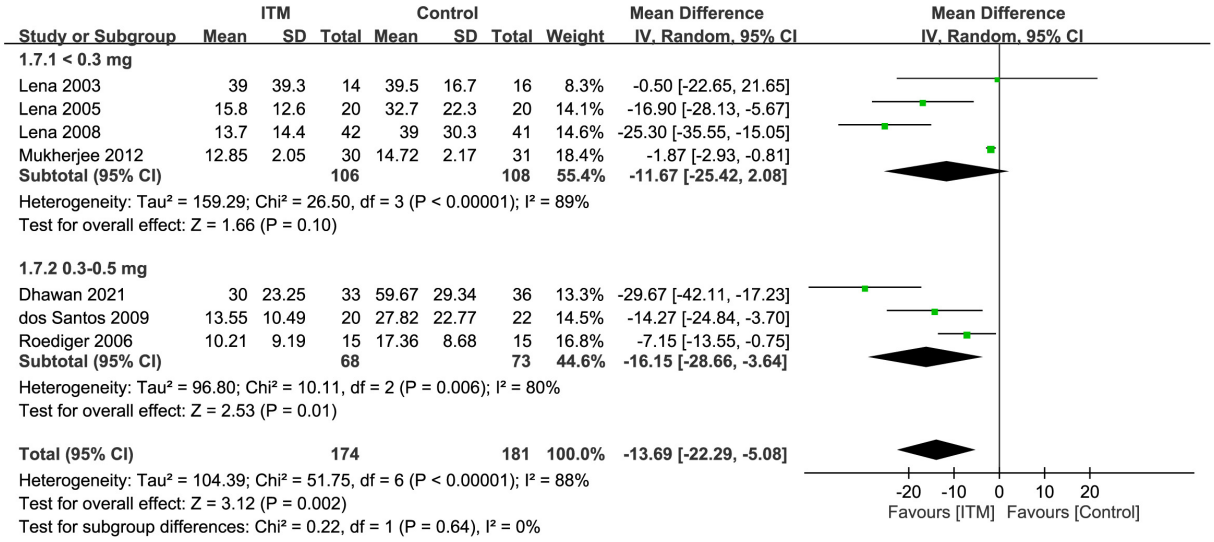

FIGURE 7
Forest plot comparing intravenous morphine consumption at postoperative 24 h between intrathecal morphine (ITM) and control groups. CI, confidence interval; IV, inverse variance; SD, standard deviation.

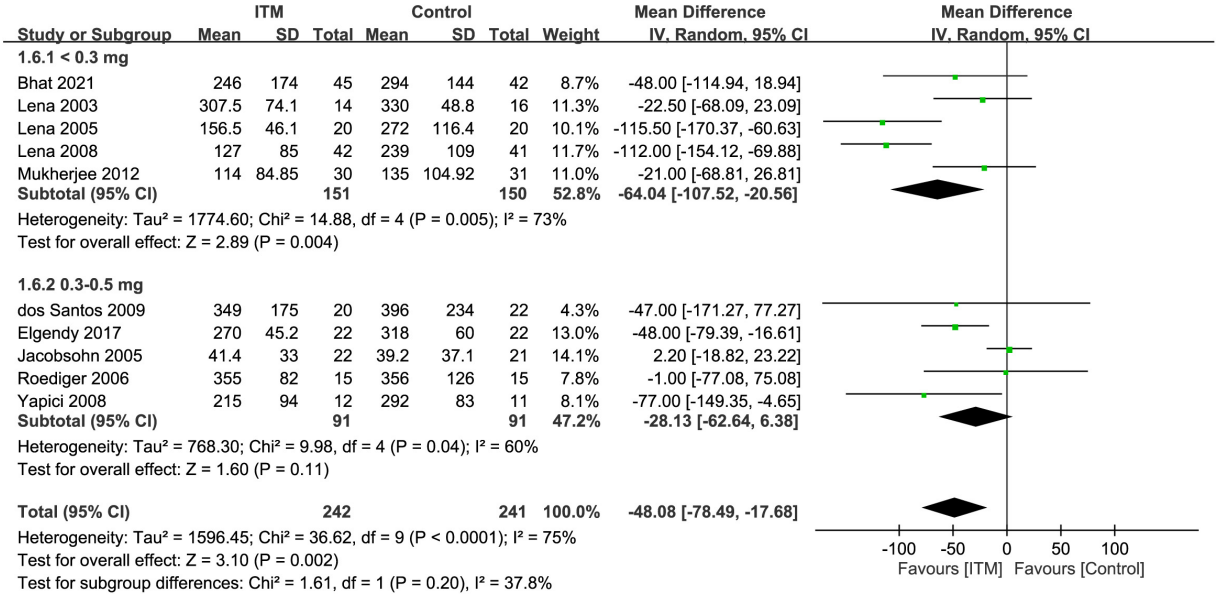

FIGURE 8
Forest plot comparing extubation time between intrathecal morphine (ITM) and control groups. CI, confidence interval; IV, inverse variance; SD, standard deviation.

younger population (1). Compared with previous meta-analyses which did not investigate the analgesic efficacy of ITM at postoperative 48 h (8, 18), our finding of a significant reduction in pain intensity associated with low-to-medium dose ITM at postoperative 12–48 h (range of mean difference: −1.61 to −2.1) highlighted its efficacy during the acute painful period. In addition, subgroup analysis indicated no impact of ITM dosage on analgesic efficacy at postoperative 12 and 48 h, implying the feasibility of adopting a low-dose ITM (i.e., <0.3 mg or 4 μg/kg) in the cardiac operation setting.

Despite the lack of a significant beneficial impact of ITM on mortality or the incidence of myocardial infarction following cardiac surgery from pooled evidence (8, 45), optimization of acute pain management with ITM not only may enhance postoperative recovery and

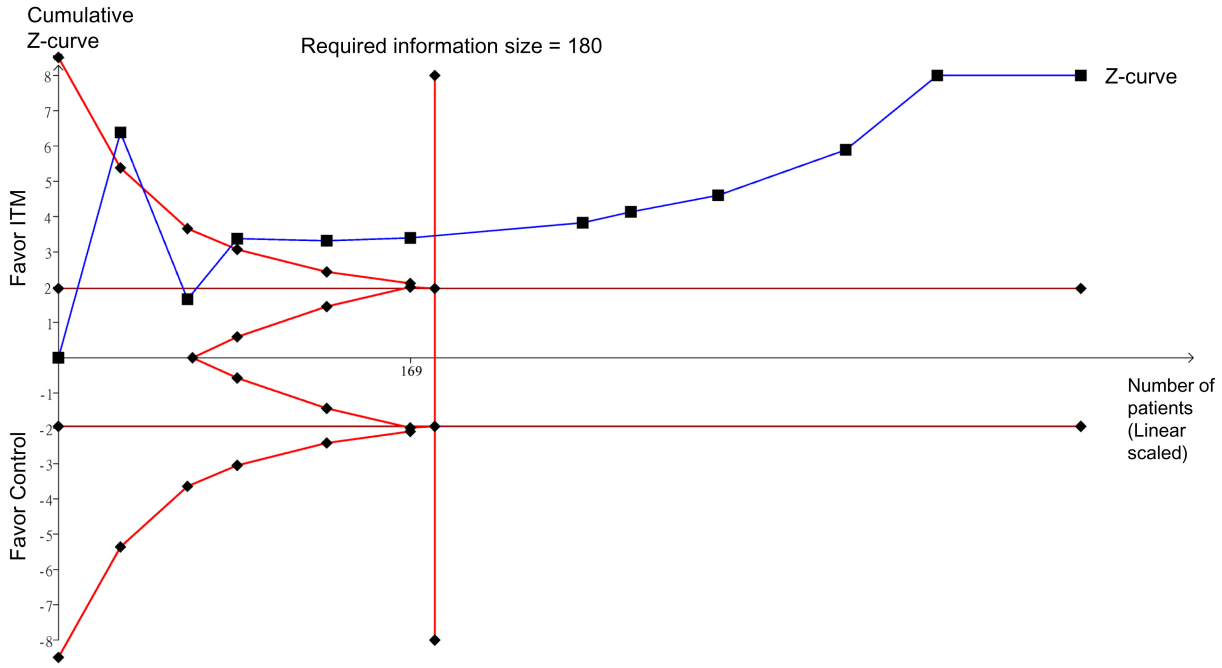

FIGURE 9
Trial sequence analysis for pain score at postoperative 24 h. ITM, intrathecal morphine.

TABLE 2 Summary of findings for the main comparison.

Outcomes	Effect (Risk or mean)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Intervention group	Control group				
Pain score at 12 h	–	–	MD −2.1 (−2.83 to −1.36)	517 (10 RCTs)	⊕⊕⊕◯ Moderate	b
Pain score at 24 h	–	–	MD −1.61 (−1.98 to −1.24)	578 (11 RCTs)	⊕⊕⊕◯ Moderate	b
Pain score at 48 h	–	–	MD −1.88 (−2.83 to −0.93)	259 (4 RCTs)	⊕⊕⊕◯ Moderate	b
Intravenous morphine consumption at 24 h	–	–	MD −13.69 (−22.29 to −5.08)	355 (7 RCTs)	⊕⊕◯◯ Low	a, b
Intravenous morphine consumption at 48 h	–	–	MD −14.57 (−26.98 to −2.17)	289 (5 RCTs)	⊕⊕◯◯ Low	a, b
Extubation time	–	–	MD −48.08 (−78.49 to −17.68)	483 (10 RCTs)	⊕⊕⊕◯ Moderate	b
Intensive care unit (ICU) length of stay	–	–	MD −5.69 (−11.83 to 0.46)	158 (4 RCTs)	⊕⊕⊕◯ Moderate	b
Hospital stays	–	–	MD −0.53 (−1.16 to 0.1)	178 (4 RCTs)	⊕⊕⊕⊕ High	–
Nausea/vomiting	56/251	48/244	RR 1.13 (0.73 to 1.74)	495 (9 RCTs)	⊕⊕⊕⊕ High	–
Pruritis	22/209	6/202	RR 2.88 (1.31 to 6.31)	411 (8 RCTs)	⊕⊕⊕⊕ High	–

[a]Wide 95% CI.
[b]The I square is more than 50%.
GRADE Working Group grades of evidence: High certainty: we are very confident that the true effect lies close to that of the estimate of the effect. Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect. Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

minimize the possibility of persistent chronic pain following cardiac surgery (46, 47) but could also reduce the risk of postoperative delirium, which has been identified as a potential sequela of acute pain (48, 49) possibly associated with long-term cognitive decline (50). Hence, our findings suggested that incorporation of ITM into the standard pain management strategy may be recommended for this patient population.

In the present study, ITM was related to a lower intravenous morphine consumption compared with the control groups at postoperative 24 (MD = −13.69 mg) and 48 (MD = −14.57 mg) hours. Consistent with our findings, a previous meta-analysis in which the majority of included trials used a high-dose ITM (i.e., 8 μg/kg–4 mg) reported that ITM decreased intravenous morphine consumption by 11 mg after cardiac surgery (8). The comparable reductions in intravenous morphine dosage between the present study and the previous meta-analysis (8) suggested similar opioid-sparing effects between high-dose (i.e., 8 μg/kg–4 mg) and low-to-medium dose (i.e., ≤0.5 mg) ITM in the cardiac surgery setting. Furthermore, we also found no impact of ITM dosage on intravenous morphine consumption during subgroup analysis (i.e., <0.3 mg vs. 0.3–0.5 mg), implying the feasibility of using a low-dose ITM in clinical practice. Nevertheless, compared with the control group with a median intravenous morphine consumption of 32.7 mg at postoperative 24 h, our study showed a reduction in intravenous morphine dosage only by only 13.69 mg in those receiving low-to-medium dose ITM. Therefore, our findings implied the need for additional postoperative analgesic strategies in patients after cardiac surgery.

Despite the lack of clinical significance, we revealed a shorter extubation time in the ITM group compared to that in the control group (i.e., MD = −48.08 min). This finding may be attributed to a decreased pain intensity and reduced intravenous morphine consumption in the immediate postoperative period (51). In contrast, the use of a relatively high-dose ITM, which could be associated with respiratory depression (15), may mask the beneficial effect of ITM on early tracheal extubation in a previous meta-analysis (8). Taking into account the recommended practice of early extubation (defined as within postoperative 6 h) after cardiac surgery (52) that was demonstrated in our control group, a further reduction of 48.08 min within such a relatively short period by using ITM as shown in the present study could be of clinical significance. Such a tendency for early tracheal extubation in the current meta-analysis may partially explain the relatively minor shortening in extubation time with low-to-medium dose ITM. As early tracheal extubation has been found to be associated with a decreased risk of infections, stroke, renal failure, and mortality (53–55), our results suggested that adoption of low-to-medium dose ITM in patients with a high risk of delayed extubation [e.g., the elderly (56)] may be recommended.

There are several limitations that need to be addressed in the current meta-analysis. First, the relatively small sample size of each trial included in the present study may potentially bias our results. Second, the recruitment of predominantly males (i.e., ≥70% in 11 out of 15 trials) with a relatively young age (i.e., ≤65 years) in our study may restrict the applicability of our findings to females and the aged population. Third, heterogeneity in study design, procedure, drug dosage, and institute-based practices across the included studies may bias our study outcomes. In fact, our finding of a high heterogeneity in pain score and intravenous morphine consumption implicated a potential adverse effect on the reliability of our results. Fourth, the availability of only five trials that provided information about the absence of respiratory depression warrants further investigations into the potential influence. Fifth, because the analgesic efficacy of ITM may be affected by the use of other adjuncts or cardiopulmonary bypass, further studies are needed to address this issue. Finally, the beneficial effects of low-to-medium dose ITM on the risk of mortality and myocardial infarction were not investigated because of limited information available from the included studies.

Conclusion

Our results demonstrated that low-to-medium dose intrathecal morphine (i.e., ≤0.5 mg) was associated with a lower pain severity and intravenous morphine consumption without increasing the risk of respiratory depression. Nevertheless, our finding of only a moderate reduction in intravenous morphine consumption associated with the use of low-to-medium dose ITM warrants further studies to investigate the effectiveness of a multimodal analgesic approach in the post-cardiac surgery care setting.

Author contributions

I-WC and C-KS contributed to conceptualization and literature search. C-CK and W-CL contributed to methodology. C-CK and P-HF contributed to trial selection. K-CH contributed to data analysis. P-HF and I-CT contributed to data extraction. K-CH, C-ML, and C-KS contributed to writing—original draft preparation. K-CH and C-KS contributed to writing—review and editing. All authors have read and agreed to the published version of 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.

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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.2022.1017676/full#supplementary-material

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Is esketamine-based opioid-free anesthesia more superior for postoperative analgesia in obstructive sleep apnea patients undergoing bariatric surgery? A study protocol

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Introduction: Opioid-free anesthesia (OFA) can certainly prevent nausea and vomiting after bariatric surgery (BS), but its postoperative analgesic effect is still controversial. Obstructive sleep apnea (OSA) is a prominent feature of morbid obesity in BS and accounts for a very high proportion, which significantly increases the difficulty of patients' airway management. Those patients will be more representative and highlight the advantages of OFA. It is not clear whether esketamine can play a more prominent role in OFA for postoperative analgesia. Therefore, this study aims to explore the postoperative analgesic effect of esketamine-based OFA on BS patients with OSA.

Methods and analysis: This single-center, prospective, randomized, controlled, single-blind study is planned to recruit 48 participants to undergo BS from May 2022 to April 2023. Patients will be randomly assigned to the OFA group and opioid-based anesthesia (OBA) group in a ratio of 1:1. The primary outcome is the Numeric Rating Scale (NRS) at different times postoperatively. Secondary outcomes include analgesic intake, the incidence and severity of postoperative nausea and vomiting (PONV), Leiden Surgical Rating Scale (L-SRS), postoperative agitation and chills, PACU stay time, EuroQol five-dimensional questionnaire (EQ-5D), length of hospital stay, intraoperative awareness, and hemodynamically unstable treatments.

Discussion: The results of this study may explain the analgesic effect of esketamine-based OFA on patients undergoing BS combined with OSA, and provide evidence and insight for perioperative pain management.

Ethics and dissemination: This study is initiated by the Ethics Committee of The First Affiliated Hospital of Shandong First Medical University [YXLL-KY-2022(035)]. The trial results will be published in peer-reviewed journals and at conferences.

Clinical trial registration: [https://clinicaltrials.gov/ct2/show/NCT05386979], identifier [NCT 05386979].

KEYWORDS

esketamine, opioid-free anesthesia, postoperative analgesia, OSA, bariatric surgery

Background

About 500,000 people worldwide have undergone BS surgery, and the number continues to grow by 2015 (1). Morbid obesity is associated with multiple comorbidities, the most common of which is OSA. OSA is present in 35–94% of morbid obesity patients (2–7). Morbid obesity and OSA are often associated with increased perioperative risks and challenges for anesthesiologists (8). Risks conferred by OSA are strongly associated with body mass index (BMI) (9, 10). One study showed a 6-fold increased risk of OSA with 10% weight gain (11). Another study showed that the prevalence of moderate to severe OSA (AHI > 15) was 63% in obese males (BMI > 30 kg/m^2) (12). Morbid obesity is a leading cause of early mortality worldwide, and currently, BS remains the only proven effective and durable therapy. Obese patients undergoing BS have a high probability of developing complications that worsen with opioid use but can be reduced by anesthetic techniques such as OFA (13).

Opioids have long been established as essential for general anesthesia, and in all patients, opioids induce and increase the severity of most sleep-disordered breathing, especially in patients with morbid obesity. OFA shows evidence of its efficacy and safety while its risks and benefits are not well-defined. However, opioid-induced hyperalgesia and tolerance further drive the use of intraoperative opioid-sparing strategies based on a combination of regional nerve block techniques or other anesthetic technical means (14, 15). Crivits et al. (16) reported those who received OFA compared with those who received sufentanil anesthesia had significantly less nausea, cold, shivering or pain in an observational study of 400 patients undergoing laparoscopic gastric bypass. The definition of OFA is varied in literature and in research. However, lidocaine, ketamine, and α-2 agonists (e.g., clonidine or dexmedetomidine) have been proposed to be used alone or in combination to replace opioids (17). Studies show that ketamine has been used as one of the well-established drugs for OFA (18–20). However, ketamine's side effects, including nightmares and delusions, limit its routine use (20, 21).

The analgesic effect of esketamine, the S (+)-isomer of ketamine, is twice of racemic ketamine. Esketamine possesses advantages of a lower incidence of side effects like hallucinations, faster recovery, and the ability to lower MAC value of sevoflurane as well as protect hypoxic pulmonary. Ketamine has been suggested to be used alone or in combination with opioids. Esketamine has long been considered an effective treatment for depression. Currently, it shows that esketamine is effective against remifentanil-induced respiratory depression, which is attributed to increased CO_2 chemosensitivity by esketamine. However, whether esketamine can replace ketamine in playing a more prominent role in the OFA remains unclear. Therefore, this study is designed to investigate the effects of esketamine-based OFA on the analgesic management of patients undergoing BS with OSA.

Methods and analysis

Trial objectives and study design

This single-center, prospective, randomized, controlled and single-blind study will be performed at the First Affiliated Hospital of Shandong First Medical University, located in Jinan City, Shandong Province. Patients will be assigned to receive OFA or OBA randomly. We will evaluate the pain management in randomized morbid obesity patients with OSA undergoing BS by a Numeric Rating Scale (NRS score) in the time points at different times within 27 h after the operation. This trial will be completed in 12 months. This trial is designed following the Standard Protocol Items (SPIRIT guidelines). **Figure 1** and **Table 2** provide an overview of the study plan.

Abbreviations: OFA, opioid-free anesthesia; BS, bariatric surgery; OSA, obstructive sleep apnea; OBA, opioid-based anesthesia; NRS, numeric rating scale; PONV, postoperative nausea and vomiting; BMI, body mass index; PCIA, patient-controlled intravenous analgesia; CRF, case report form; L-SRS, Leiden surgical rating scale; EQ-5D, EuroQol five-dimensional questionnaire.

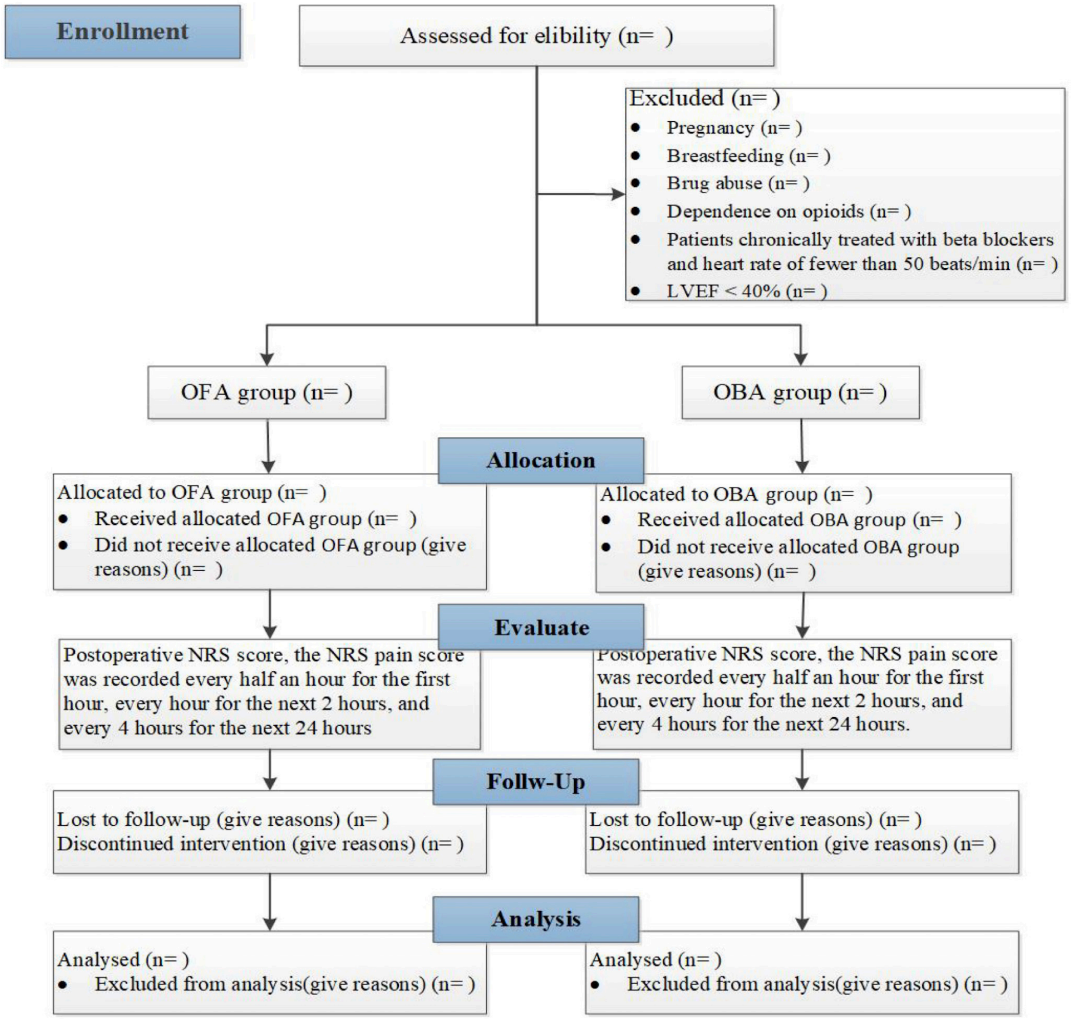

FIGURE 1
General review of study design (flow diagram).

Randomization and blinding

Patients will be randomized using block randomization with random block length, stratified to minimize bias on the primary outcome measure. Randomization will be performed electronically after the assessment of eligibility. The patients and surgical staff will be blinded to the group allocation in this study, whereas, anesthesia providers who did not participate in the assessment of the patients at any time could not be blinded to facilitate intraoperative anesthesia management. A blinded independent researcher will be responsible for preoperative visit and obtaining informed consent with patients. The outcome will be evaluated by this independent researcher to minimize the bias associated with data collection. The statisticians will also be blinded to the allocation.

Participants' inclusion and exclusion criteria

During the anesthesia consultation, investigators will verify inclusion/exclusion criteria. The investigator will invite the patients to participate. Patients will receive complete information in faithful terms and understandable language concerning the objectives, the required follow-up, the risks, the safety measures, and the right to refuse to participate or stop the study at any time. The investigator will obtain written informed consents signed by both the investigator and the patient.

Inclusion criteria

1. Age 18–60 years old.
2. ASA I∼III level.
3. BMI > 35 kg/m^2.
4. Bariatric surgery for patients with moderate to severe OSA.

Exclusion criteria

1. Pregnancy or breastfeeding.
2. Patients with a history of drug abuse or dependence on opioids.
3. Patients chronically treated with beta-blockers and heart rate of fewer than 50 beats/min.
4. Cardiac insufficiency with a left ventricular ejection fraction of less than 40%.

Shedding criteria

1. Reoperation during the observation period.
2. Unconsciousness or mortality during the observation period.
3. Discharge automatically or transferred in advance.
4. The patient or the client refuses the informed consent or requests to withdraw from the study during the observation period.

Intervention

The study aims to compare the OFA protocol with a standard practice-based anesthesia protocol. Patients will be divided into two groups according to the randomization method described later in a ratio of 1:1 in group OFA or OBA. Patients will receive general anesthesia combined with regional anesthesia. The two protocols are detailed in **Table 1**.

In group OFA, anesthesia induction with propofol 2.5 mg/kg, rocuronium bromide 0.6 mg/kg, nalbuphine 10 mg, esketamine 0.5 mg/kg, intubation will be performed when BIS reached 40–60, followed by a continuous intravenous infusion of propofol TCI Ce 2–4 μg/ml and esketamine 0.2–0.5 mg/kg/h and esmolol 20–50 μg/kg/min. Nalbuphine 10 mg will be given at the beginning of the operation. Ondansetron 8 mg and nalbuphine 0.2 mg/kg will be given before abdominal suturing. After the operation, a PCIA will be used (nalbuphine 2 mg/kg + dexmedetomidine 2 μg/kg + ondansetron 24 mg) in a total volume of 100 ml and continuous infusion at a rate of 1.5 ml/h for 48 h. The self-controlled capacity is 0.5 ml, and the locking time is 15 min.

In group OBA, anesthesia induction with propofol 2.5 mg/kg, rocuronium bromide 0.6 mg/kg, nalbuphine 10 mg, sufentanil 0.3 μg/kg, intubation will be performed when BIS reached 40–60 and followed by a continuous intravenous infusion of propofol TCI Ce 2–4 μg/mL and remifentanil TCI Ce 3–6 ng/ml. Nalbuphine 10 mg will be given at the beginning of the operation. Ondansetron 8 mg and sufentanil 10 μg will be given before abdominal suturing. Patients will be equipped with a PCIA (sufentanil 2 μg/kg + dexmedetomidine 2 μg/kg + ondansetron 24 mg, total volume 100 ml, 1.5 ml/h for 48 h). The self-controlled capacity is 0.5 ml, and the locking time is 15 min.

Monitoring and standard practice-based anesthesia protocol

All patients will not receive premedication. After admission to the operating room, the participants are placed in the slope position and will be continuously monitored using ECG, pulse oxygen saturation, end-tidal carbon dioxide concentration, non-invasive blood pressure, and the bispectral index (BIS) of electroencephalography (EEG). Radial artery catheterization will be performed to monitor invasive blood pressure, subsequently, midazolam 2 mg and atropine 0.4 mg were administered intravenously.

We chose the method of endotracheal intubation under a visual laryngeal mask to control the airway. All patients will be regarded as having difficult airway and placed the visual laryngeal mask in the conscious state, ultrasound-guided bilateral recurrent laryngeal nerve block will be injected with 0.375% ropivacaine 2 ml, respectively. Dacronin 10 ml Contained in the mouth for about 5 min. Dexmedetomidine (load capacity 1 μg/kg/10 min maintenance dose 0.6 μg/kg/h until 40 min before the end of the operation) will be injected with a micromedicine infusion pump. The model of laryngeal mask was selected according to the patient's lean weight and 100% oxygen will be delivered after the anesthesia circuit connected. Endotracheal intubation will be performed once the vocal cord and $PetCO_2$ waveform were seen, and it will be used to maintain anesthesia during the operation with the laryngeal mask cuff gas evacuated retained. Both groups will be combined with ultrasound-guided transversus abdominis plane block (with 0.375% ropivacaine 40 ml).

Patients will enter different groups based on the results of randomization and receive OFA and OBA respectively. The methods for induction and maintenance of anesthesia among different groups have been described in detail previously. The systolic blood pressure and heart rate will be maintained within 20% of the baseline during the operation.

Both groups will be ventilated with a tidal volume of 6–8 ml/kg to avoid barotrauma, the respiratory rate is 10–14 times/min, and the positive end-expiratory pressure (PEEP) was 5–10 cmH_2O to maintain $PetCO_2$ 35–45 cmH_2O. We will record the hemodynamic instability (vasoactive drugs for hypotension or hypertension, atropine for bradycardia, beta-blockers for tachycardia) and treatments.

Postoperatively, extubation under deep anesthesia with the laryngeal mask retained and transfer participants to the PACU. Sugammadex sodium will be given to antagonize muscle relaxation at a dose of 2–4 mg/kg. The laryngeal mask is generally well-tolerated after the participants awake and will be removed after monitoring for 1 h, and the patient will be transferred safely to the ward after continuing monitoring for 1 h.

TABLE 1 Detailed interventional protocols in the opioid-free anesthesia group (OFA group) and opioid-based anesthesia group (OBA group).

Opioid-free anesthesia protocol	Opioid-based anesthesia protocol
Before surgery	
• IV: midazolam 2 mg, atropine 0.4 mg • The patient's position: head-high slope • Bilateral recurrent laryngeal nerve block (0.375% ropivacaine 2 ml on each side) under ultrasound guidance • Dyclonine mucilage 10 ml mouth will be contained 5 min • Dexmedetomidine loading capacity: 1 μg/kg/10 min • Use a laryngeal tube to test the feeling of the back of the oropharynx, if there is a nausea reflex, add 2% lidocaine 2 ml. • Insert Video LMA SACOVLM^{TM} while awake • Induction of anesthesia once vocal cords will be visible and end-tidal carbon dioxide waveform is observed	
Anesthesia induction	
• **Propofol** 2.5 mg/kg • **Esketamine** 0.5 mg/kg • **Rocuronium** 0.6 mg/kg • **Nalbuphine** 10 mg • Subcostal ultrasound-guided bilateral transversus abdominis plane block: 0.375% ropivacaine 40 ml	• **Propofol** 2.5 mg/kg • **Sufentanil** 0.3 μg/kg • **Rocuronium** 0.6 mg/kg • **Nalbuphine** 10 mg • Subcostal ultrasound-guided bilateral transversus abdominis plane block: 0.375% ropivacaine 40 ml
Anesthesia maintenance	
• **Propofol TCI Ce** 2–4 μg/ml • **Esketamine** 0.2–0.5 mg/kg/h • **Dexmedetomidine** 0.5–2 μg/kg/h • **Esmolol** 20–50 μg/kg/min • **Rocuronium** 0.6 mg/kg • **Nalbuphine** 10 mg	• **Propofol TCI Ce** 2–4 μg/ml • **Remifentanil TCI Ce** 3–6 ng/ml • **Dexmedetomidine** 0.5–2 μg/kg/h • **Sufentanil** 10 μg after surgery • **Rocuronium** 0.6 mg/kg • **Nalbuphine** 10 mg
Postanesthesia care unit (PACU)	
• **Sugammadex** 2 mg/kg • **Pain management** (VAS ≥ 4, rescue nalbuphine 5 mg) • **PCIA** nalbuphine 2 mg/kg + dexmedetomidine 2 μg/kg + ondansetron 24 mg	• **Sugammadex** 2 mg/kg • **Pain management** (VAS ≥ 4, rescue nalbuphine 5 mg) • **PCIA** sufentanil 2 μg/kg + dexmedetomidine 2 μg/kg + ondansetron 24 mg

LMA SACOVLM^{TM}, Zhejiang UE Medical Corp (Hangzhou, China). IV, intravenous; TCI, target controlled infusion; PACU, postanesthesia care unit; PCIA, patient-controlled intravenous analgesia.

Evaluation and follow-up

One day before the operation, each patient will be given a time-listed NRS form and detailed instructions on how to record score of quiet NRS score and cough NRS score at the different postoperative times (0.5, 1, 2, 3, 7, 11, 15, 19, 23, 27 h, postoperatively) (Showed in Table 2).

Relevant data of participants will be collected by independent researchers. Standardized data collection files (case report forms) will be used to ensure that the data are recorded and used for future statistical analysis. Data collects as follow: gender, age, weight, BMI, polysomnography test results, neck circumference, modified Mallampati score, upper lip bite test, operation time, anesthesia time, days of hospitalization, days of chest drainage, post-operative evaluation, complications, side effects (respiratory depression, hypotension, vomiting, nausea, itching).

Adverse events

1. Tachycardia: When heart rate > 100 beats/min, or increases by more than 20% from baseline if the baseline value is >83 beats/min, esmolol 10 mg will be given and/or adjust the dose of anesthetics.
2. Hypertension: systolic blood pressure >160 mmHg, or increases from baseline 20% or more if the baseline value >133 mmHg, urapidil 10 mg will be given and/or adjust the dose of anesthetics.
3. Bradycardia: Heart rate < 55 beats/min, or reduces by more than 20% from baseline or if the baseline value is <69

TABLE 2 Study timeline and schedule of enrolment, allocation, interventions, and assessments according to SPIRIT 2013 statement.

	Study period												
	Enrolment	Allocation	During surgery	Post-operation									Close-out
Timepoint	$-D_1$	$-D_1$	0	PACU	0.5 h	1 h	2 h	3 h	7 h	11 h	15 h	19 h	23 h	27 h	D_7
Enrolment:															
Eligibility screen	X														
Informed consent	X														
Allocation		X													
Interventions:															
[OFA group]		⟷													
[OBA group]		⟷													
Assessments:															
[Inclusion/exclusion criteria]	X	X													
[Baseline data]	X	X													
[L-SRS]			X												
[Postoperative agitation]				X											
[Postoperative chills]				X											
[Length of stays]				X											X
[Rescue antiemetic medication]				X	X	X	X	X	X	X	X	X	X	X	
[Vital signs]			X	X											
[NRS score]				X	X	X	X	X	X	X	X	X	X	X	
[Incidence and severity of PONV]				X	X	X	X	X	X	X	X	X	X	X	
[Intraoperative awareness]				X	X	X	X	X	X	X	X	X	X	X	
[EQ-5D]															X

beats/min, atropine 0.3 mg and/or isoproterenol 2 μg or adjust the anesthetics dose.

4. Hypotension: systolic blood pressure < 95 mmHg, or drops more than 20% if the baseline value is <119 mmHg, liquid infusion, ephedrine 6 mg or norepinephrine 4 μg and/or anesthetics dose adjustment will be applied.
5. Intraoperative awareness: During general anesthesia and standard treatment, patients can recall intraoperative events.

Safety assessments will include monitoring and recording of all adverse effects and severe adverse effects and regular monitoring of intraoperative and postoperative critical data including type, time, duration, treatment, and sequelae by the attending anesthesiologists until it is completely resolved or treatment is terminated. Before signing the informed consent, patients will be informed of all potential harms before anesthesia, including the risks of OFA such as oversedation, insufficient analgesia, hallucinations, emotional depression, and severe drug allergy. All adverse effects or possible complications will be compiled in the data collection forms.

If significant risks to patient safety occur during the trial, we will report it to the research group and the ethics committee to evaluate whether the trial should be continued. Appropriate actions, including medical attention, will be taken when necessary.

Data collection, handling, and monitoring

Relevant data of participants will be collected by independent researchers who are unaware of the research intervention (Table 3).

Noxious stimuli: Sputum suction or pressure on the eye socket, sternum, or nail bed for 5 s.

Randomization, blinding, allocation, and concealment

Patients will be randomized using block randomization with four-block length, stratified to minimize bias on the primary outcome measure. Randomization will be performed electronically after the assessment of eligibility. The participants will be blinded to the group allocation in this study.

TABLE 3 Description of main and secondary variables.

Primary outcome
Postoperative NRS score (0–10). 0 means absence of pain and 10 is the severest pain imaginable.
Postoperative NRS score was recorded every half an hour for the first hour, every hour for the next 2 h, and every 4 h for the next 24 h.
Secondary outcomes
Range of nalbuphine requirements
0: no use
1: <10 mg/day
2: 10–20 mg/day
3: More than 20 mg/day
PONV, incidence and severity of PONV
NRS: A 10 cm ruler was used as the scale. One end of the scale was 0, indicating no nausea and vomiting, and the other end was 10, indicating the severest unbearable nausea and vomiting (1–4 as mild, 5–6 as moderate, 7–10 as severe).
Need for rescue antiemetic medication
1: Yes
2: No
L-SRS
The surgeon will score the quality of the intra-abdominal conditions at 15 min intervals using the L-SRS [see Martini et al. (22) and Boon et al. (23)]. In brief, the L-SRS is a 5-point Likert scale that enables the quantification of surgical conditions in a standardized fashion. The scale runs from 1 to 5: extremely poor (score = 1), poor (=2), acceptable (=3), good (=4), and excellent (=5) surgical working conditions.
Postoperative agitation
Riker Sedation-Agitation Scale (SAS) (Table 4)
Postoperative chills
Wrench classification: Grade 0, no chills; Grade 1, bundles and/or peripheral vasoconstriction and/or peripheral cyanosis, but no fibrillation; Grade 2,
PACU stay time
EuroQol five-dimensional questionnaire (EQ-5D)
The EQ-5D descriptive system is a preference-based HRQL measure with one question for each of the five dimensions that include mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.
Length of hospital stay (days)
Intraoperative awareness
1: Yes
2: No
Hemodynamically unstable treatments

Surgical staff and researchers responsible for the post-operative follow-up are blind to the randomized allocation of patients.

The anesthesiologists who are responsible for BS surgery will share no information related to patient randomization.

The statistical analysis will be carried out independently by a separately appointed statistician.

Sample size

Based on the research from Marija toleska (24) (A prospective, single-blind, randomized controlled study of laparoscopic cholecystectomy using opioid anesthesia and opioid-free anesthesia, mainly observed the postoperative VAS score), the average VAS score of opioid-free anesthesia was 3.27 ± 1.7, while the opioid anesthesia in the control group was 5.13 ± 2.7. PASS 15.0 was used to compare the two groups of mean superiority tests. The sample size was calculated by two-sided test and test level (α = 0.05) The ratio was 1:1, and the power (1-β) was 80%, and considering the shedding rate (10%), we need to recruit 48 participants (24 in each group).

TABLE 4 Riker sedation-agitation scale.

Score	Term	Description
7	Dangerous agitation	Pulling at endotracheal tube, trying to remove catheters, climbing over the bed rail, striking at staff, thrashing side to side
6	Very agitated	Does not calm, despite frequent verbal reminding of limits; requires physical restraints, biting endotracheal tube
5	Agitated	Anxious or mildly agitated, attempting to sit up, calms down to verbal instructions
4	Calm and cooperative	Calm awakens easily, follows commands
3	Sedated	Difficult to arouse; awakens to verbal stimuli or gentle shaking, but drifts off again; follows simple commands
2	Very sedated	Arouses to physical stimuli, but does not communicate or follow commands, may move spontaneously
1	Unable to rouse	Minimal or no response to noxious stimuli, does not communicate or follow commands

Statistical analysis

All statistical data analyzes will be performed using the SPSS software (IBM SPSS Statistics V.25).

1. The measurement data conforming to the normal distribution are expressed by mean ± standard deviation (x ± s). Methods Repetitive measure analysis of variance (ANOVA) was used in analyzing the repeated measurement data (NRS score) compared within the group. The independent *t*-test or one-way ANOVA are used for inter-group comparison.
2. The measurement data of non-normal distribution are expressed by median (m) and 25th and 75th percentile (P25, p75). Mann-Whitney U test is used for comparison between groups.
3. Categorical variables will be described as counts (percentages) and compared using $\chi 2$ analysis or Fisher's exact test. The overall significance level is set at $p < 0.05$ and Bonferroni correction will be used to control type I errors.
4. Covariance analysis and logistic regression analysis will be introduced into the model to minimize study factors, confounders and their interaction.

Discussion

Although opioid anesthesia is now the mainstay of anesthesia, there are still many deficiencies in postoperative pain management, especially in the postoperative phase. There are fewer available options for opioids, and their clinical use is often limited by their side effects such as postoperative nausea and vomiting, respiratory depression, and over sedation. Currently, the medical literature supports the use of intravenous lidocaine, ketamine, and dexmedetomidine as a balanced anesthetic modality for perioperative period management to replace or reduce opioids (20, 25–27). To our knowledge, the analgesic efficacy and clinical value of esketamine in morbid obesity patients undergoing BS remain unclear. To explore this issue, we designed this single-center, prospective, randomized, controlled, single-blind study to elucidate the efficacy of the analgesic management of esketamine-based OFA in morbid obesity patients with OSA undergoing BS.

Esketamine, the S (+)- isomer of ketamine, is safer and suitable for induction and maintenance of general anesthesia. It is approved by the FDA in 2019 as the first new class of antidepressants (28–30). Esketamine is theoretically more analgesic, and nonetheless, the actual analgesic effect of esketamine remains controversial (25, 31, 32). Cheng et al. (33) reported that esketaminea (bolus of 0.25 mg/kg, followed by an infusion of 0.125 mg/kg/h until 15 min before the end of the surgical procedure) improved the quality of rehabilitation in patients undergoing video-assisted thoracic surgery (VATS), and also improved postoperative analgesia and postoperative depression. Another study of the effects of esketamine sedation on hydrostatic reduction of intussusception ketamine (34) found insufficient evidence for a higher success rate, lower relapse rate, shorter duration, and shorter hospital stay with esketamine compared with morphine analgesia. For the chronic opioid-dependent population, a perioperative bolus of 0.5 mg/kg of ketamine followed by an infusion of 0.25 mg/kg/h reduces pain and reduces opioid dependence 1 year after spinal surgery (35).

Opioid-free anesthesia is an anesthesia method based on the concept of multi-mode analgesia, using a combination of multiple drugs or technologies to achieve anesthesia and analgesia, reduce sympathetic reflex, obtain stable hemodynamics, good organ perfusion and high-quality anesthesia recovery, and to meet the perioperative analgesia of patients (17, 36). Although there are still some controversies about the wide application of OFA in the clinic (37), we also see that this technology has been widely applied to the clinical practice of BS, general surgery, bone and spinal surgery, cesarean section and other operations (24–26, 38–41). The application of OFA in obesity showed that it is a safe, feasible and well-tolerated therapy, which may offer a novel and well-tolerated treatment in morbid obesity patients (42, 43).

However, our study also remains some limitations. One of the main limitations for the interpretation of results will be the small sample size of the study, especially regarding the multiple outcomes we plan to analyze. Secondly, considering the small overall sample size, the randomization of this study will not be stratified, and there are obvious difficulties in anesthesia for super-obese patients (BMI $>$ 50), and the long extubation time and wake time, which may bias the results of the statistical analysis results. Finally, as the study is single-blind, and the personnel who performed the anesthesia will know the specific grouping situation, some bias on the study results may appear.

Ethics statement

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

Author contributions

YS and YW were the principal investigators of this study, obtained grant funding, and refined the study protocol. YG and LC participated in the design of the study protocol, drafted the protocol, and wrote the protocol manuscript. ZG, MZ, ML, XG, YL, XZ, and NG assisted in the development and implementation of the study. YS supervised the study. All authors critically reviewed and approved the final 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.

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Post-operative delirium in the patient with hip fracture: The journey from hospital arrival to discharge

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Delirium- an acute disorder of attention and cognition- is the commonest complication following hip fracture. Patients with hip fracture are particularly vulnerable to delirium, and many of the lessons from the care of the patient with hip fracture will extend to other surgical cohorts. Prevention and management of delirium for patients presenting with hip fracture, extending along a continuum from arrival through to the post-operative setting. Best practice guidelines emphasize multidisciplinary care including management by an orthogeriatric service, regular delirium screening, and multimodal interventions. The evidence base for prevention is strongest in terms of multifaceted interventions, while once delirium has set in, early recognition and identification of the cause are key. Integration of effective strategies is often suboptimal, and may be supported by approaches such as interactive teaching methodologies, routine feedback, and clear protocol dissemination. Partnering with patients and carers will support person centered care, improve patient experiences, and may improve outcomes. Ongoing work needs to focus on implementing recognized best practice, in order to minimize the health, social and economic costs of delirium.

KEYWORDS

delirium, post-operative, hip fracture, prevention, multidisciplinary, acute confusional state, cognitive impairment

Main body

"He's been up all night. He was terrified." The patient's daughter looked as tired as her father, who was snoring now in his bed on our orthopedic ward. Further questioning revealed an exhausting night of agitation, attempted climbing from bed, hallucinations, and intravenous catheters being pulled out by the distressed patient. Despite the brightness of the sunlight streaming through the window, he was now barely rousable, grunting when moved, and had missed his breakfast and morning oral medications.

Sadly, this picture of delirium- an acute disorder of attention and cognition- is common on orthopedic and other hospital wards. The journey of a patient with hip fracture in many ways epitomizes that of the surgical patient at risk of delirium. These patients are older, have fallen, are often frail, and many have underlying cognitive impairment. Here in Australia, almost 1 in 3 is resident in a residential aged care facility (nursing home) even prior to surgery (1), and the recognized 30–40% with existing dementia or cognitive impairment likely underestimates the true number, due to suboptimal assessment (2). Patients with underlying cognitive impairment are 3 times more likely to sustain a hip fracture than those without (3), and are at increased risk of delirium (4, 5). Rates of delirium vary, with reports of up to 65% of patients experiencing delirium following hip fracture (6). It is the commonest complication following hip fracture, yet more than 30% of delirium is likely to be preventable, including in hip fracture cohorts (4, 7, 8), making it a critical and attainable target. Nonetheless, the pathophysiology of delirium, in the post-operative context or otherwise- remains poorly understood, with neuro-inflammation and cerebral metabolic insufficiency being the two most-favored theories explaining the predisposing and trigger events leading to delirium onset (8, 9).

The negative sequelae of delirium- and thus the potential advantages to delirium prevention- encompass the patient, hospital, and society. Delirium is commonly associated with increased hospital LOS, in multiple studies of hip fracture and other surgical/trauma patients, including in a recently published large retrospective analysis of > 4,000 patients from the Australian and New Zealand Hip Fracture Registry (ANZHFR) (10). A US paper noted that delirium was one of the two most notable predictors of prolonged LOS in hip fracture patients (the other being delayed time to surgery) (11). Delirium is also associated with increased risk of in-patient falls, mortality, and future risk of dementia, and with significant distress for patients and family members (12–15). The total costs of delirium in Australia, however, extend beyond easily-captured health system costs; including other financial costs (such as productivity costs, informal care) and that associated with burden of disease and loss of well-being, total annual cost has been estimated to be in the order of AUD$8.8 billion (2016–2017 data) (16), which, with 132,595 occurrences of delirium in Australia alone each year, would mean that each occurrence of delirium would cost approximately AUD$66,000.

Delirium prevention begins at the time of the patient's arrival. Early orthogeriatrician input and comprehensive geriatric assessment are likely to improve outcomes, including reducing delirium incidence and severity (17–20). Best practice guidelines such as the Australian Hip Fracture Care Clinical Care Standard highlight that care at presentation, in addition to diagnostics, should include pain control, assessment of medical reasons for the fall, exclusion of other injuries-including head injury- and specifically highlight the need to "screen for cognitive impairment and risk factors for delirium and put in place interventions to prevent delirium based on this assessment" (21). Comprehensive geriatric assessment commonly incorporates assessment of medical (co-)morbidity, drugs and polypharmacy, cognition, mobility, function, social circumstances, and establishing goals of care. Such assessment is potentially associated with reduced post-operative delirium, improved delirium diagnosis, and reduction in other post-operative complications (17, 22, 23), which may contribute to delirium. Ideally, such an orthogeriatric approach to care should be instituted from admission.

Existing evidence-based guidelines and recommendations note the importance of early cognitive assessment, delirium risk screening and prevention of 'preventable' delirium (2, 21, 24). Yet data consistently highlight that cognitive screening amongst patients with hip fracture remains sub-optimal (2, 25). Tools such as the Delirium Risk Assessment Tool can help identify patients at highest risk (26, 27), and facilitate focused risk management plans. In addition to this, validated screening instruments [e.g., 4AT, Confusion Assessment Methods (CAM)] should be employed to assist in detection, in conjunction with appropriated cognitive screening tools where needed (28–30). Specific patient cohorts, such as those from culturally or linguistically diverse backgrounds, or Aboriginal and Indigenous patients, may benefit from culturally appropriate cognitive assessment (31–33). In patients who are unwell or cognitively impaired, the need for a collateral history is paramount (34, 35). However, evidence suggests that collateral history from family/carer is often neglected- being either absent or sparse- with Fitzpatrick et al. (34) highlighting that it is "alarming that such an essential component of clinical assessment is so often disregarded." In addition to screening for and recognition of delirium, proactive avoidance of triggers-such as constipation, urinary retention and catheterization and deliriogenic medications- and timely pain assessment and management are key in the patient with hip fracture (21, 36, 37). The benefit of addressing delirium risk factors is highlighted by multifaceted interventions which target these risks. For example, data from the wider in-patient population have shown reduced delirium incidence- and other adverse outcomes such as falls- with the Hospital Elder Life Program, which focuses on cognitive impairment, sleep deprivation, immobilization, visual impairment, hearing impairment and dehydration (38, 39).

Despite guidelines recommending early pain assessment (18, 19), early and repeated pain assessment remains suboptimal (2, 40). Along with regular assessment, pain control may require a multimodal approach from amongst simple analgesics, anti-inflammatories in appropriate patients, opiates with appropriate monitoring, and regional nerve blocks such as fascia-iliaca block (FIB) (19, 41). Analgesic-centric multicomponent bundles of care have been associated with reductions in early post-operative delirium amongst patients with hip fracture (42).

In contrast to the relatively strong evidence for addressing delirium risk factors either side of surgery, intra-operative factors have been less convincingly associated with post-operative delirium. In the setting of an imperfect evidence base, regional anesthesia does not seem to confer any delirium-reduction benefits over general anesthetic, although potential advantages in terms of adverse events, hospital length-of-view and even mobilization were identified in a small number of studies (43, 44). Duration of surgery may be associated with increased risk (45). Similarly, despite theoretical advantages, lighter sedation during surgery has not been convincingly associated with delirium risk (46), and the question of whether higher-dose propofol might contribute to post-operative delirium risk remains unanswered (47). On the other hand, the need for intensive care and/or ventilator care post-operatively are likely to increase risk, as demonstrated by a large Brazilian study of almost 60,000 hip fracture patients who underwent regional anesthesia (48).

The principles of pre-operative delirium prevention, assessment and management extend to the post-operative phase. Early, coordinated orthogeriatric and multidisciplinary input aims to reduce post-operative complications in addition to providing benefits regarding care coordination. Nurses will play a vital role in the post-operative phase of the patient's recovery. Factors which will continue to impact on delirium risk in this post-operative will include management of pain, minimizing polypharmacy, rationalizing medications, and avoiding (or planned earliest removal of) invasive devices such as urinary catheters (4, 38, 49, 50). Given the fluctuant course of delirium, and the prolonged post-operative risks for same in hip fracture cohorts, patients should be monitored regularly for cognitive, behavioral, and clinical deterioration; some guidelines suggest that all in-patients should be assessed at least daily (51). The regular assessment of pain assessment and effective analgesic management are critical to post-operative care (21), both to improve the patient's quality of life and comfort, and reduce delirium risk. For patients with cognitive impairment/dementia, many tools have been developed. Tools such as the Faces Pain Scale, Abbey Pain Scale and Pain Assessment in Advanced Dementia (PAINAD), Pain Assessment Checklist for Seniors with Limited Ability to Communicate and Mobilization-Observation-Behavior-Intensity-Dementia (MOBID) scale may be useful in such cohorts (52). Pain management is likely to require a multifaceted approach, including systemic analgesia using paracetamol and short-acting opioid analgesics, aiming to minimize dosage and duration so as to reduce opioid-associated harm (53). A systematic review (2011) has previously indicated that the evidence for strategies such as acupressure, relaxation therapy, transcutaneous electrical neurostimulation, and physical therapy regimens, is inconclusive (54).

Early mobilization is also promoted for patients following hip fracture, to promote recovery of mobility and function and mobility. Mobility is also promoted for patients in terms of delirium prevention (51). However, its potential relationship to delirium prevention in hip fracture patients is complex. Nonetheless, a recent study highlighted that those who mobilized early post-operatively had reduced (post-operative) delirium compared to those who remained bedbound (55), and delirium itself can often be a barrier to early mobilization (55, 56). Early mobilization is associated with improved likelihood of discharge by 30 days, irrespective of delirium status (57).

In patients who do develop delirium, management must focus on the identification of the cause, as well as prevention of complications, such as functional decline, dehydration, malnutrition, falls and pressure injuries, based on their risk (26). Partnering with patients and carers will support person centered care, improve patient experiences, and may improve outcomes (58, 59).

Principles which support a multidisciplinary approach to delirium prevention and pain management need to be embedded in local pathways for the care of patients with hip fracture, complemented by audit and quality improvement initiatives (18, 19). Strategies such as bundles of care have been associated with improved compliance with recommended delirium-reducing strategies (42), clinician support for their implementation (60), as well as with direct benefits in terms of incidence of post-operative delirium (9, 42). Yet the integration of models of care to support best practice is often suboptimal (61). Potential enablers of such integration might, for example, include interactive teaching methodologies, routine individualized feedback, and clear protocol dissemination (60, 62–66), while barriers may include educational deficits, lack of motivation at individual or institutional levels, environmental factors, and specific health professional characteristics such as age, sex or experience (67, 68). Translation of evidence into practice will need to account for local factors specific to the individual setting and local population. Furthermore, newer educational methods such as the "flipped classroom" and "train the trainer" approaches may enhance delirium learning for healthcare professionals, with a study by Sockalingam et al. (65) showing persistent benefit in delirium knowledge and delirium care self-efficacy at 6 months following institution of these strategies, and a mixed-methods study identifying that a delirium simulation-based flipped classroom approach "promoted higher level learning and engagement in inter-professional collaborative practice" (66). Hunter et al note that "dynamic, responsive implementation strategies and accessible educational modalities, which are flexible to needs of individual multidisciplinary team members and adapted to specific settings, will likely prove the most successful approach to adoption of evidence-based protocols [supporting hip fracture care]" (60).

Conclusion

In conclusion, patients presenting to hospital with hip fractures are at high risk of developing delirium. Patients who do develop delirium suffer significantly worse outcomes including death and morbidity, and delirium leads to increased suffering to carers and family, and imposes a large financial burden on the health system. Best practice guidelines emphasize multidisciplinary care including management by an orthogeriatric service, regular delirium screening, and multimodal interventions. Up to 30% of hip fracture-related delirium may be preventable with this approach. The health, social and economic burden of delirium underscore the need for research focusing on reducing the incidence and impact of delirium in our patients with hip fracture.

Author contributions

DN and AC were responsible for drafting, editing, and finalization of the manuscript. Both authors agreed to be accountable for the content of the work, 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.

Publisher's note

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Efficacy and safety of ciprofol for agitation and delirium in the ICU: A multicenter, single-blind, 3-arm parallel randomized controlled trial study protocol

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Background: Agitation is very common in the intensive care unit (ICU). The causes include pain, delirium, underlying disease, withdrawal syndrome, and some drug treatments. The practical goal of ICU treatment is to find an appropriate sedation regimen to reduce pain, restlessness, and delirium. Previous trials have examined the use of dexmedetomidine, but no trials have evaluated the efficacy and safety of ciprofol, a new sedative drug.

Methods: This study was a multicenter, single-blind, 3-arm parallel randomized controlled trial. ICU patients aged ≥ 18 years with agitation and delirium who met the eligibility criteria were included. The main outcome was the proportion of patients who needed additional study medication or midazolam due to agitation within 4 h after the first intravenous injection of the study medication. The secondary outcomes included the pass rate as indicated by a Richmond Agitation-Sedation Scale (RASS) score < +1, the effectiveness rate of improving delirium symptoms, the number of recurrences of agitation within 24 h, the incidence of rescue treatment, the dose and cost of analgesic and sedative drugs, the length and cost of ICU stay, and the 30-day survival period. The safety evaluation included the incidence of adverse events (hypotension, bradycardia, hypoxia, etc.) and the rate of endotracheal intubation. The subjects were randomly assigned to receive ciprofol, dexmedetomidine, or normal saline at a ratio of 1:1:1. The rates of

additional drug administration within 4 h after the first injection of the study drug in the three groups were 40, 50, and 90%, respectively. A total sample size of 81 subjects was required to reach 90% power and an α of 0.05. Considering a 20% loss rate, 102 patients were enrolled and randomly assigned to the three groups in equal proportions.

Ethics and communication: This trial was approved by the Ethics Committee of Dalian Municipal Central Hospital. The communication plan includes presentations at scientific conferences, scientific publications, and presentations to the public through non-professional media.

Clinical trial registration: www.ClinicalTrials.gov, identifier ChiCTR2200062799.

KEYWORDS

ciprofol, agitation, delirium, intensive care unit, sedation

Introduction

Agitation is very common in the intensive care unit (ICU). The causes include pain, delirium, underlying disease, withdrawal syndrome, and some drug treatments. The incidence of agitation varies among ICUs, but 12–70% of critically ill patients develop agitation (1). Agitation is closely related to adverse outcomes. For example, an increased duration of mechanical ventilation and prolonged hospital stay put patients at risk of life-threatening symptoms (2). The economic impact of unplanned removal of medical devices caused by agitation in a single ICU is estimated to exceed $250,000 per year (3). The economic impact of delirium is even greater: more than 164 billion dollars annually in the USA and more than 182 billion dollars annually in 18 European countries (4). Due to the serious negative impacts of agitation and delirium on the prognosis of ICU patients and the heavy burden these conditions impose on the health system, the prevention and treatment of agitation and delirium have become urgent problems in the field of intensive care medicine (5).

The practical goal of ICU treatment is to find an appropriate sedation regimen to reduce pain, restlessness, and delirium. Ciprofol (HSK3486) is a novel 2,6-disubstituted phenol derivative that, similar to propofol, binds to γ-aminobutyric acid-α (GABAA) receptors (6). In a phase 2 study of ICU patients requiring mechanical ventilation (NCT04147416), the success rate of sedation using ciprofol was 100%, with rapid recovery, no significant accumulation, and good safety (7). However, there is no evidence for the sedative effect and safety of ciprofol for ICU patients with agitation and delirium who are not mechanically ventilated. This study aimed to confirm the efficacy and safety of ciprofol in short-term (4–24 h) shallow sedation (RASS −2 to +1) in ICU patients with agitation and delirium and followed up patients for 30 days to investigate the survival, cognition, and recurrence of delirium in these patients.

Study design

This study was a multicenter, randomized, single-blind, parallel-controlled study involving 5 centers/hospitals. This trial was fully approved by the Ethics Committee of Dalian Municipal Central Hospital (20201-094-01). The trial was registered in the Chinese Clinical Trial Registry (ChiCTR2200062799)[1] with the listed primary and secondary endpoints. The study was conducted in accordance with the clinical trial protocol (and any revisions), the Declaration of Helsinki (current revision), the *Guidelines for analgesia and sedation treatment in intensive care unit of Chinese adults*, and *Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU* (2, 8). The implementation time for the study was expected to be 2 years. The technical route is shown in **Figure 1**.

Research environment

The patients were registered and treated in the ICUs of 5 centers/hospitals in China: (1) Dalian Municipal Central Hospital Affiliated Dalian University of Technology, (2) Beijing Friendship Hospital Affiliated Capital Medical University, (3) The Second Hospital of Dalian Medical University, (4) Jinzhou Municipal First People's Hospital, and (5) Central Hospital of Zhuanghe City.

Patient selection

We used detailed inclusion and exclusion criteria consistent with those described in a previous research report (9). Based on

1 http://www.chictr.org.cn/showproj.aspx?proj=174945

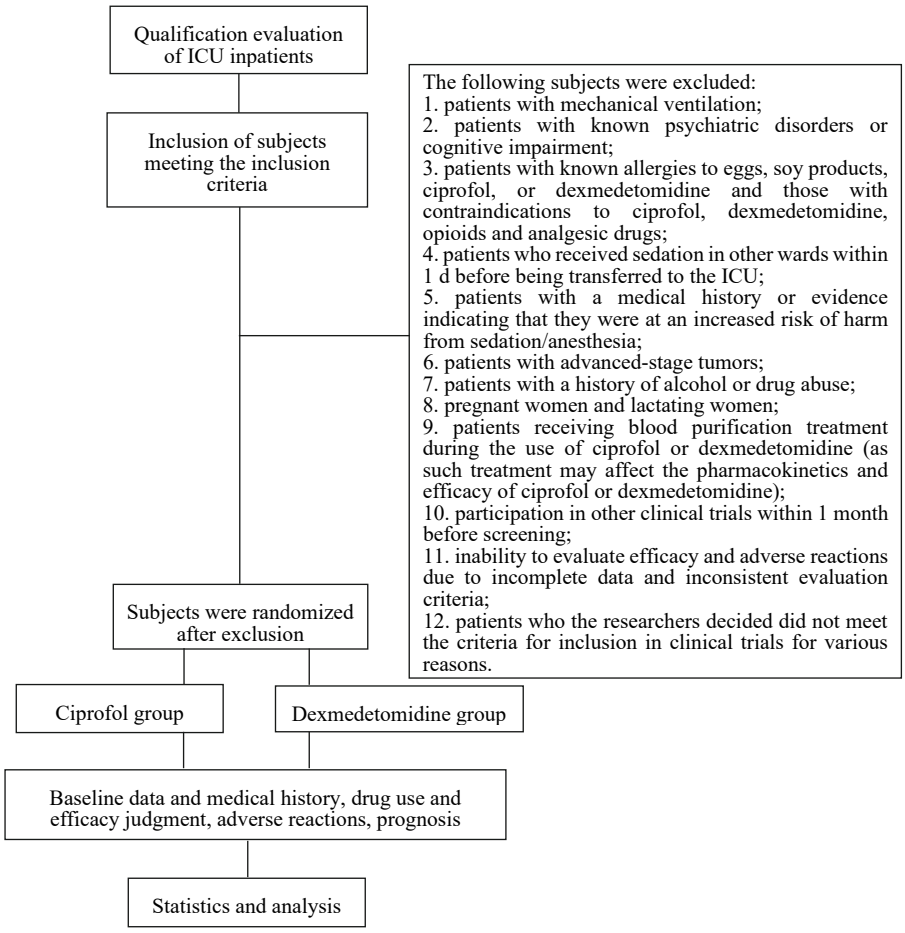

FIGURE 1
Flow chart: screening, recruitment, and grouping of patients.

the inclusion and exclusion criteria, patients were enrolled and randomly assigned to receive continuous intravenous sedation with ciprofol, dexmedetomidine, or normal saline.

The inclusion criteria were as follows: (1) Patients with agitation or active delirium in the ICU were expected to need sedation for 4–24 h after randomization. (2) The expected sedation goal was within the range of the Richmond Agitation-Sedation Scale (RASS) (-2 to +1). (3) The age range of the patients was 18–85 years, and no sex restriction was applied. (4) The body mass index (BMI) of each patient was between 18 kg/m^2 and 30 kg/m^2. (5) Patients or their family members fully understood the purpose and significance of the trial, voluntarily agreed to participation within 24 h of admission to the ICU, and signed informed consent, including providing contact information.

The exclusion criteria were as follows: (1) patients with mechanical ventilation; (2) patients with known psychiatric disorders or cognitive impairment; (3) patients with known allergies to eggs, soy products, ciprofol, or dexmedetomidine and those with contraindications to ciprofol, dexmedetomidine, opioids, and analgesic drugs; (4) patients who received sedation in other ward within 1 day before being transferred to the ICU; (5) patients with a medical history or evidence indicating that they were at increased risk of harm from sedation/anesthesia; (6) patients with advanced-stage tumors; (7) patients with a history of alcohol or drug abuse; (8) pregnant women and lactating women; (9) patients receiving blood purification treatment during the use of ciprofol or dexmedetomidine (as such treatment may affect the pharmacokinetics and efficacy of ciprofol or dexmedetomidine); (10) participation in other clinical trials within 1 month before screening; (11) inability to evaluate efficacy and adverse reactions due to incomplete data and inconsistent evaluation criteria; and (12) patients who the researchers decided did not meet the criteria for inclusion in clinical trials for various reasons.

The levels of sedation and delirium were assessed using the RASS and the Confusion Assessment Method for the ICU (CAM-ICU) (10, 11). Agitation was defined as RASS $\geq +2$, and active delirium was defined as CAM-ICU positive with RASS $\geq +2$.

Test group

To comprehensively determine the efficacy and safety of ciprofol, this study included a blank control group receiving normal saline and a drug control group receiving dexmedetomidine at a ratio of 1:1:1. Dexmedetomidine was selected as the control drug because it is a continuous infusion sedative drug recommended by many guidelines. In many countries, including the USA and China, it is usually used for long-term sedation in the ICU (2, 8, 12). The replacement block randomization method was used (the block size was set to 6), and the subjects were randomly assigned to receive saline, ciprofol, or dexmedetomidine at a ratio of 1:1:1.

This study was designed to be single-blind. The patients and their families and the case report form (CRF) data analysis researchers did not know the identities of the patients in the experimental groups. Because the ICU patients were critically ill, the clinicians and CRF data collection researchers could not be blinded. The clinicians were mainly responsible for deciding when to begin sedation, adjust the dose, and end sedation.

At the time of registration and after signing the consent form, detailed information about prior sedation and analgesic treatment, baseline demographics, delirium occurrence, and disease severity were recorded.

Study drug management

Researchers confirmed that the RASS of each patient reached $\geq +2$ before starting to administrate the study drug. Prior to drug administration, the CAM-ICU was used to assess the patient's delirium status. The sedatives used before study registration were discontinued before the start of the study drugs.

In the experimental group, continuous intravenous pump injection of ciprofol was performed with a loading dose of 0.1 mg/kg and a maintenance dose of 0.05–0.8 mg/kg/h. The control group received a continuous intravenous pump injection of dexmedetomidine for sedation, with a loading dose of 0.1 mcg/kg and a maintenance dose of 0.03–0.7 mcg/kg/h. The specific study drug use is shown in **Table 1**.

The RASS sedation assessment scale (RASS) was used to assess the level of sedation and to control the rate of drug administration. The sedation goal was RASS −2 to +1 points. When the RASS score exceeded the target range, the drug infusion rate was increased or decreased until the target RASS score was reached. If the sedation was too deep (RASS −3 to −5 points), the infusion of the study drug was stopped until the patient returned to the acceptable sedation range. Sedation assessment was performed at least every 4 h, and the dose of the study drug was adjusted by the clinical medical staff according to the RASS score and recorded in the nursing record.

Patients in the two groups who were not sufficiently sedated by study drug titration were given midazolam at a dose of 0.01–0.05 mg/kg. The injection time was 3 min, and the drug was administered again at 15-min intervals until sufficient sedation (RASS −2 to +1) was achieved. The maximum dose within 8 h was 4 mg. The lowest maintenance dose of the study drug was infused continuously for 4 h in patients with RASS scores $< +1$, which indicated that a subject no longer needed sedation, thus warranting discontinuation of study drug infusion. At this time, the CAM-ICU was used to re-evaluate the patient's delirium.

Many guidelines highlight the importance of analgesic treatment, given that it is the basis of sedation treatment (2, 8, 13). Analgesics were used according to a standardized procedure. All subjects were monitored using the Critical-Care Pain Observation Tool (CPOT), and fentanyl analgesia was used to maintain a CPOT score of < 3 (14). Analgesia with a small dose of fentanyl (0.5–1.0 μg/kg) was performed once every 15 min as needed. Fentanyl analgesia was also given before expected harmful stimuli, such as fiberoptic bronchoscopy or arteriovenous catheterization. The use of fentanyl patches was prohibited. The use of other sedatives or analgesics was prohibited during the study. The total time of drug administration (including the loading dose and the maintenance dose) was at least 4 h ± 30 min, and the longest time was not more than 24 h ± 30 min. The study drug infusion was stopped if the investigator believed it was in the patient's best interest to discontinue the drug.

During the drug administration process, circulatory and respiratory functions were always monitored, and airway

TABLE 1 Administration of the study drug.

Study drug	Loading dose	Maintenance dose	Allowed top-up dose during maintenance administration
Ciprofol group	0.1 mg/kg, intravenous infusion (undiluted), administration time 30 s	Start maintenance at 0.3 mg/kg/h, dose can be up- or downregulated at 0.05–0.1 mg/kg/h; range of the maintenance dose: 0.05–0.8 mg/kg/h	0.05 mg/kg each time, each top-up should have at least a 2-min interval
Dexmedetomidine group	0.1 mcg/kg, intravenous infusion (dilute with 0.9% sodium chloride solution to a concentration of 4 mcg/ml), administration time 10 min	Start maintenance at 0.2 mcg/kg/h, dose can be up- or downregulated at 0.03–0.1 mcg/kg/h; range of the maintenance dose: 0.03–0.7 mcg/kg/h	0.1 mcg/kg each time, each top-up should have at least a 15-min interval

assistance measures, artificial ventilation and other resuscitation devices were readily accessible. Symptoms before and after drug administration and their fluctuations were recorded. When adverse reactions occurred, the symptoms, drug doses, intervention measures, and medication time were recorded.

Ciprofol was acquired from Haisco Pharmaceutical Group Co., Ltd., and formulated as 2 ml:50 mg (lot number 20220302). Dexmedetomidine was obtained from the Yangtze River Pharmaceutical Group and formulated as 2 ml:200 mcg (lot number 22071431).

Effectiveness evaluation

The primary endpoint was the proportion of patients who needed additional study medication or midazolam due to agitation within 4 h after the first intravenous injection of the study medication.

The secondary endpoints were as follows: (1) the proportion of patients who achieved a RASS score $< +1$ within 4 h after the first intravenous injection of the study medication; (2) the effective rate for improving delirium symptoms; (3) the number of recurrences of agitation within 24 h; (4) the proportion of patients who underwent tracheal intubation and received emergency drugs within 24 h; (5) the dose and cost of analgesic and sedative drugs; (6) the duration and cost of the ICU stay; and (7) short-term mortality of patients when followed up for 30 days.

Safety evaluation

The incidence of adverse reactions (including respiratory depression, hypoxia, hypotension, hypertension, tachycardia and bradycardia symptoms, and elevated blood bilirubin, alanine aminotransferase, and triglyceride) and the rate of tracheal intubation during medication were evaluated. Two ICU specialists and two neurologists defined each subject's adverse reactions in detail based on the drug instructions and the evidence reported in previous studies (7, 15).

1) Definition of absolute and relative hypotension: systolic blood pressure < 90 mmHg or a decrease of more than 20% of that before medication or diastolic blood pressure < 50 mmHg.
2) Definition of absolute and relative hypertension: systolic blood pressure > 180 mmHg or more than 20% higher than that before medication or diastolic blood pressure > 100 mmHg.
3) Definition of absolute and relative bradycardia: heart rate < 40 beats/min or more than 20% lower than that before medication.
4) Definition of absolute and relative tachycardia: heart rate > 120 beats/min or more than 20% higher than that before medication.
5) Definition of absolute and relative respiratory depression: respiratory rate < 8 breaths/min or lower than baseline by more than 25%.
6) Definition of absolute and relative hypoxia: $SpO_2 < 90\%$ or lower than baseline by 10%.
7) Definition of elevated blood bilirubin: blood bilirubin $> 25\%$ higher than that before medication.
8) Definition of elevated alanine aminotransferase: alanine aminotransferase $> 25\%$ higher than that before medication.
9) Definition of elevated triglycerides: triglycerides $> 25\%$ higher than that before medication.

For any risks that occurred during the study, the investigator promptly provided correct and reasonable individualized medical treatment to the subjects according to the specific conditions of the subjects to protect the rights and interests of the subjects to the maximum extent. The investigators conducted follow-up surveys of all adverse events (including serious adverse events), with regular follow-up according to the disease condition until the final outcome of the adverse events. The follow-up process and the outcome of the adverse events were recorded. Emergency orotracheal intubation is indicated in any situation in which definitive control of the airway is needed. *New England Journal of Medicine* (NEJM)-recommended indications include cardiac or respiratory arrest, failure to protect the airway from aspiration, inadequate oxygenation or ventilation, and impending or existing airway obstruction (16).

Data management and monitoring

All data were collected during the clinical trial. All raw data were recorded on the online data collection form by the appropriate researchers, and the accuracy of the data input was confirmed by two people. The data were processed in an anonymous and encrypted manner, and a limited number of people were allowed to access the data. The data were coded using the unique identification associated with the individual study participants. The decision to lock the database was made by the chief investigator, database administrator, and statistical analyst in charge of the statistical analysis. The research coordinator at each center supervised the conduct of the study. In addition, this experiment was closely monitored by a certified external auditor to ensure that the research activities were conducted in accordance with the protocol, clinical practice guidelines and applicable regulatory requirements. The data will be stored in double backup mode for at least 5 years after the end of the study.

Study quality control and supervision

We established a quality assurance system, and a designated coordinator will guide the investigators when conducting clinical trials in accordance with the protocol, clinical practice guidelines, and applicable regulatory requirements. The coordinator was responsible for reviewing the original data records and case report forms, investigating any violations, ensuring that researchers have a detailed and accurate understanding of the research program, and assessing whether the procedures were correctly implemented. Any quality problems were relayed to the main researcher, and appropriate measures were taken immediately to solve the problems.

When the number of subjects reached half of the expected sample size, a mid-term evaluation was conducted. The drugs' clinical index data were preliminarily analyzed, the risk-benefit relationship of the trial drugs was comprehensively weighed in terms of effectiveness and safety, and a major decision was made regarding whether to "continue the trial," "continue the trial after adjusting the scheme," or "terminate the trial." If problems were found and the protocol needed to be modified or adjusted, all relevant information was submitted to the Ethics Committee for approval before implementation.

Statistics

This study was a clinical randomized controlled trial. The three groups were a blank control group, a ciprofol group, and a dexmedetomidine group, with a ratio of 1:1:1. The rate of additional drug administration within 4 h after the first injection was the main outcome indicator. According to the pre-experiment results, the rates of additional drug administration in the three groups were 90, 40, and 50%, respectively. The type I error (false-positive) was set to 0.05, and the efficacy reached 90%. The total sample size of the three groups calculated by PASS (version 15.0.5) was $N = 81$ cases. Considering a loss rate of 20%, the total number of subjects required for the final three groups was 102, with at least 34 subjects in each group.

The analysis was performed according to intention-to-treat analysis including all randomized participants, and the analysis was performed in their randomized groups, regardless of the actual treatment received. For continuous numerical variables, the numbers, means, medians, standard deviations, minimums, maximums, and coefficients of variation (CVs, if applicable) were analyzed using the independent sample t-test or Wilcoxon rank sum test. Categorical variables were given as rates (percentages) and were analyzed using the Pearson X^2 test or Fisher's exact probability method. The baseline was defined as the last non-missing observation data collected before the first use of the study drug. The normality of the data was examined using the Shapiro–Wilk test and the Q-Q plot in SPSS. We used SPSS (version 26.0) for analysis. All statistical inferences were performed using two-sided tests. The statistically significant test level was set as 0.05, and the confidence interval (CI) of the parameters was estimated using the 95% CI.

Analysis of the main effectiveness results

The purpose of this study was to evaluate the efficacy and safety of ciprofol for agitation and delirium in the ICU. The main effectiveness index was the comparison of the rate of additional drug administration within 4 h after the first injection, which corresponded to qualitative data and was analyzed using the Pearson X^2 test or Fisher's exact probability method.

Analysis of secondary effectiveness results

Study drug use, the number of recurrences of agitation within 24 h, the dose and cost of analgesic and sedative drug application, and the length and cost of the ICU stay were assessed using the independent sample t-test or the Mann–Whitney test. The proportion of patients who achieved a RASS score $< +1$ within 4 h after the first intravenous injection of the study medication, the effective rate for improving delirium symptoms, and the proportions of patients who received tracheal intubation or use of emergency medicine within 24 h in the two groups were compared using the X^2 test.

Safety analysis

The Pearson X^2 test was used to compare the incidence of adverse events between the two groups, and the adverse events in this study were tabulated.

Discussion

As China's first innovative class 1 intravenous anesthetic drug, there are very few clinical trials related to ciprofol. To the best of our knowledge, this is the first clinical trial to investigate the applicability and safety of ciprofol as a continuous pump-in sedative in ICU patients with agitation and active delirium, especially in patients with non-mechanical ventilation.

Dexmedetomidine is a high selectivity α-adrenergic receptor agonist with analgesic and sedative effects. The positive effects of dexmedetomidine have been widely reported, including reducing the incidence of postoperative delirium, prolonging sleep time, delaying the occurrence of delirium, and shortening

the duration of delirium in elderly patients (17–20). Although delirium is not among its indications, some domestic and foreign guidelines recommend dexmedetomidine for the treatment of delirium (13, 21). However, the adverse events of dexmedetomidine should not be ignored, which mainly include cardiovascular system reactions, respiratory system reactions, neuropsychiatric disorders, and others (22, 23). Two recent meta-analyses clearly indicate that dexmedetomidine is associated with a greater risk of bradycardia and hypotension in various ICU patients (24, 25). Considering that ICU patients often have multiple diseases and organ function damage or failure to varying degrees, ICU doctors are always concerned during the medication process. Effective and safe sedative and delirium control drugs have long been goals of ICU physicians.

Ciprofol has a shorter half-life than dexmedetomidine. The plasma concentration of ciprofol showed three-phase elimination, and the corresponding half-lives were 0.54 min ($t_{1/2}$, α), 6.26 min ($t_{1/2}$, β), and 105 min ($t_{1/2}$, γ), respectively (26). Ciprofol is an alkyl phenolic compound. Phase II UDP-glucuronosyltransferases (UGTs) and phase I CYP2B6 are the main metabolic enzymes for ciprofol. Ciprofol is rapidly oxidized in the body or combined with glucuronic acid and sulfuric acid, and its metabolites are inactive (27). Therefore, unlike dexmedetomidine, clinicians do not have to consider the cumulative effect of sedatives.

Because ciprofol has a higher lipid solubility than propofol, the concentration of free molecules in the emulsion is significantly lower than that of propofol, which may reduce injection pain. In an experiment in which hypnosis was induced in rats and dogs, ciprofol had a higher therapeutic index than propofol. At the same dose, the hypnotic efficacy of ciprofol was approximately 4–5 times that of propofol (27). Similar results were observed in healthy subjects in phase I clinical trials (6). Compared with propofol, the average dose per hour, the average loading dose, and the average maintenance dose of ciprofol for sedation during colonoscopy were approximately fivefold lower, and the incidence of cardiovascular adverse events was lower (7). The dosage required for sedation is lower, which reduces the amount of lipid infusion, thereby reducing the adverse reactions caused by excessive lipid infusion for prolonged sedation, such as hypertriglyceridemia or propofol infusion syndrome.

In summary, these findings demonstrate that this drug has great potential as a new sedative drug in the ICU. If the drug shows the same beneficial properties in critically ill patients as in previous studies, it may become a new choice for patients and clinicians.

Ethics statement

This trial was approved by the Ethics Committee of Dalian Municipal Central Hospital. Patients or their family members fully understood the purpose and significance of the trial, voluntarily agreed to participation within 24 h of admission to the ICU, and signed informed consent, including providing contact information.

Author contributions

GL, GW, and DG: methodology, software, formal analysis, investigation, and writing—original draft. HZ, SC, and KG: methodology, software, formal analysis, and investigation. WS and DY: methodology, validation, data curation, and supervision. SL and JL: conceptualization, writing—reviewing and editing, supervision, project administration, and funding acquisition. 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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Delirium in the intensive care unit and its importance in the post-operative context: A review

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The burden of delirium in the intensive care setting is a global priority. Delirium affects up to 80% of patients in intensive care units; an episode of delirium is often distressing to patients and their families, and delirium in patients within, or outside of, the intensive care unit (ICU) setting is associated with poor outcomes. In the short term, such poor outcomes include longer stay in intensive care, longer hospital stay, increased risk of other hospital-acquired complications, and increased risk of hospital mortality. Longer term sequelae include cognitive impairment and functional dependency. While medical category of admission may be a risk factor for poor outcomes in critical care populations, outcomes for surgical ICU admissions are also poor, with dependency at hospital discharge exceeding 30% and increased risk of in-hospital mortality, particularly in vulnerable groups, with high-risk procedures, and resource-scarce settings. A practical approach to delirium prevention and management in the ICU setting is likely to require a multi-faceted approach. Given the good evidence for the prevention of delirium among older post-operative outside of the intensive care setting, simple non-pharmacological interventions should be effective among older adults post-operatively who are cared for in the intensive care setting. In response to this, the future ICU environment will have a range of organizational and distinct environmental characteristics that are directly targeted at preventing delirium.

KEYWORDS

delirium, post-operative, intensive care unit, nursing, multidisciplinary, cognitive impairment

Introduction

The burden of delirium in the intensive care setting is a global priority (1, 2). Delirium is an acute neurocognitive disorder that is characterized by a fluctuating level of consciousness with impaired attention and cognition (3). Delirium affects up to 80% of patients in intensive care units (4). An episode of delirium is often distressing to patients and their families, and in patients within, or outside of, the intensive care unit (ICU) setting, and it is associated with poor outcomes, in the short term, which includes longer stay in intensive care, longer hospital stay, and increased risk of hospital mortality in patients (5–11). Longer term sequelae include cognitive impairment and dependency in activities of daily living (6, 9, 12–16). In the Australian healthcare setting, it has been estimated that

an episode of delirium increases hospital stay by, on average, 2.7 days (17), and in the ICU-based Deli I study, patients experiencing an acute episode of delirium stayed, on average, an extra 6 days longer in hospital (18).

Delirium in the intensive care setting

Each year, there are approximately 175,000 admissions to Australian adult intensive care units (ICUs); this number has been increasing by 6% each year since 2011 (19). While there is considerable variability in the intensive care unit admissions depending on geographic location (20), intensive care unit beds and usage appear to be increasing (20). The majority of patients admitted to intensive care will survive ICU (19, 20); however, as many as one in five patients will experience an acute episode of delirium (21), and being older and frail increases the risk (2, 11, 22–24). The direct healthcare costs associated with delirium and longer hospital stay alone would be approximately $255 million annually in the Australian intensive care setting, excluding the cost due to the loss of healthy life, which has been estimated to be double that of direct healthcare costs (17, 25).

While the medical category of admission may be a risk factor for poor outcomes (26, 27) in critical care populations, outcomes for surgical ICU admissions are not particularly optimistic, with dependency at hospital discharge exceeding 30% (28) and average in-hospital mortality in the order of approximately 2.5–5% but exponentially higher in older patients or those undergoing high-risk procedures (28–31). Thirty-day mortality among non-cardiac surgical patients reaches almost 40% (32); even higher mortality rates have been observed in resource-limited settings (33). A recent study indicated that 28% of 350,000 admissions across 238 ICUs in the United States represented a primary surgical diagnosis (28). While encouraging trends were noted in terms of mortality and length of stay for some surgical cohorts, functional decline appeared to be increasing over time (28). Factors such as delirium, prolonged immobilization, and mechanical ventilation may all contribute to functional decline and other poor outcomes in surgical and general ICU populations, exacerbated by underlying risk factors such as age, frailty, comorbidity, and cognitive impairment (28, 34–36). Although not specific to those requiring intensive care admission, post-operative delirium is reported in upward of 65% of patients (37, 38). Identification of those who have the highest risk may facilitate the implementation of targeted interventions (39). The risk for the development of post-operative delirium may be conceptualized as relating to pre-operative (baseline) factors, intra-operative factors related to the surgery and anesthetic, and post-operative factors (38). A recent study highlighted the potential to predict delirium in older (aged ≥70 years) surgical patients undergoing elective cardiovascular, orthopedic, or general surgery (40), with surgery type, multimorbidity, renal failure, polypharmacy, ASA, cut-to-suture time, and cognitive assessment allowing an ability to predict delirium with an AUC of 0.8 (40). This information is helpful not only just in planning care but also in discussing risk with patients and families and managing expectations. Furthermore, embedding assessment in formal multi-faceted structures such as comprehensive geriatric assessment (CGA) may reduce post-operative delirium in older patients such as those undergoing vascular or hip fracture surgery (41, 42).

The good news is that high-quality evidence suggests that at least 30% of episodes of hospital-acquired delirium are preventable, including, for example, in post-operative hip fracture cohorts (3, 43, 44). Multi-component, multidisciplinary interventions have been shown to reduce the incidence of delirium, in general wards, post-operative, and aged care settings (3, 45–48). However, evidence for the effectiveness of interventions to reduce the burden of delirium in the intensive care has been inconclusive (49–54), and none of these intensive care studies focused purely on post-operative populations. Gaps are in part attributable to a lack of focus on the effective implementation and dissemination of evidence into practice (55–57). There is a lack of good evidence supporting the use of pharmacological interventions to prevent delirium in the intensive care setting. A recent Cochrane systematic review (45) concluded that "the effects of other pharmacological, sedation, environmental, and preventive nursing interventions is unclear and warrants further investigation," while a meta-analysis of bundle interventions likewise failed to show an association with delirium prevalence or duration (58). Nonetheless, previous trials, systematic reviews, and meta-analyses have shown promise in terms of the effectiveness of non-pharmacological interventions to reduce the burden of delirium in the hospital and critical care settings (43–47, 52).

A recent review of pharmacological therapy in the ICU highlighted the significant limitations of existing trials, with heterogeneity in terms of agents used, primary outcome measures, timing of treatment, and delirium diagnosis (59). Among the available pharmacological agents, dexmedetomidine has some evidence supporting its benefit in reducing post-operative delirium in older patients undergoing elective non-cardiac surgery (60). A slightly more recent meta-analysis of 14 melatonin/ramelteon studies suggested that these formulations might significantly reduce delirium in surgical (49% risk reduction) and ICU (34%) patient groups (61), but optimum duration, dosing, and formulation are yet to be identified.

In addition to delirium prevention, early recognition of delirium is key. Improving detection through the use of screening tools (3, 62, 63) may facilitate improved diagnosis, which can in turn trigger prompts to guide investigation and management (3, 64, 65). Simple screening tools may in fact be utilized to assist in the diagnosis of delirium in the intensive care setting. The Confusion Assessment Method (CAM) and its ICU version have been validated as a reliable (kappa = 0.96; 95% CI 0.91–0.99) and valid (sensitivity 0.81–0.82 and specificity 0.99) tool to diagnose delirium in the intensive care setting (66–68). Hypoactive delirium, which is common in older patients, is associated with a poorer prognosis than the hyperactive form (3) but is more likely to be under-recognized (69), highlighting the need to maintain an appropriate index of suspicion in older patients. While DSM-V criteria for the diagnosis of delirium no longer explicitly refer to the level of arousal for the diagnosis of delirium, the level of arousal is fundamental to the assessment of attention and cognition and should be included in the assessment of the potentially delirious patient (70). The issue of coma is also pertinent to the ICU setting, and it is worth noting that a diagnosis of delirium is precluded in patients with a severely reduced level of arousal such as coma (71).

TABLE 1 Non-pharmacological interventions reduce the risk of delirium.

Component	Intervention
Cognitive impairment.	Establish a baseline using the validated CAM, CAM-ICU assessment tool and use orientation techniques (14, 53, 74).
	All patients will be re-orientated to time/place/people/event such as reason for hospitalization, at regular intervals (53, 75–77)
Sensory functions.	Optimise sensory function for vision and hearing by ensuring glasses and hearing aids are available and appropriately used when patient is awake. Families will be reminded to have these items available, and nurses will ensure their appropriate use (78, 79)
	Use appropriate communication technique (verbal/written/pictures) to compensate sensory loss and overcome language barriers (76, 79, 80)
Environmental interventions	Provide visible clock, calendar and schedule for each patient (74–77, 80–85)
	Provide sleep management (night light, foot massage, back massage) (74, 76, 77, 84)
	Provide comfortable physical environment (reducing noise, persistent nursing, the limited movement to other beds, beds areas, and allow to bring home favorites) (16, 78, 79, 81, 84–90)
	Remove physical restraints as soon as feasible, contingent to patient's safety (16, 87, 90)
	Arrange familiar people to visit and encourage family visitors to stay longer and frequently when possible, especially for patients with non-English speaking background and during planned sedation weaning (76, 80, 91)
Early therapeutic interventions	Encourage early mobilization and plan mobility schedule (74, 92)
	Provide appropriate nutrition; keep fluid and electrolyte balance (67)
	Assessing and addressing pain management effectively and early (87, 93)
	Careful use of sleeping pills, anticholinergics and opiates (87)
	Avoid hypoxia.
	Early detection and management of infection.
	Removal of unnecessary catheters (87, 94)
	Routinely screen alcohol history and commence Alcohol Withdrawal Assessment where appropriate (87)

Thus, a practical approach to delirium prevention and management in the ICU setting is likely to require a multi-faceted approach. Some examples of non-pharmacological interventions to reduce the risk of delirium are presented in the Table 1. Environmental factors may also be a focus of risk-reduction strategies, with design modifications potentially targeting sound and light, floor planning, and room arrangement, aiming to reduce stressors and positively influence the patient experience (4). Harnessing the expertise and manpower of family members, to assist with aspects of care such as orientation and memory cueing, cognitive stimulation, and sensory checks, may also be feasible and acceptable (72).

Implications for clinical practice

Good quality evidence suggests that at least 30% of episodes of delirium among older adults admitted to the hospital are preventable, with interventions being delivered by an interdisciplinary team of nursing, medical, and allied health clinicians (3). There is consistent evidence that these multi-component interventions are effective in preventing delirium, in general wards and aged care settings (43, 45). However, evidence for the effectiveness of interventions to reduce the burden of delirium in the intensive care has been inconclusive. While and small single-site, non-pharmacological multi-component interventional studies have shown promising results (45), larger studies, often among patients at high risk, have not shown a clear benefit (43, 49). In particular, older cardiothoracic surgery patient appears to be resistant to intervention in the ICU, even when other similar-aged surgical patients can have the risk of reduced post-operative delirium (43). Importantly, several significant organizational and design changes to the intensive care setting have been proposed, as "the future of intensive care: delirium should no longer be an issue" (73).

Conclusion

Given the good evidence for the prevention of delirium among older post-operative outside of the intensive care setting, simple non-pharmacological interventions should be effective among older adults post-operatively cared for in the intensive care setting. In response to this, the future ICU environment will have a range of organizational and distinct environmental characteristics that are directly targeted at preventing delirium.

Author contributions

DN, EA, and SF were responsible for drafting, editing, and finalization of the manuscript. All authors agreed to be accountable for the content of the study.

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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