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STUDY PROTOCOL

Opioid-Free Anesthesia Alleviates Postoperative Nausea and Vomiting in Patients Undergoing Laparoscopic Cholecystectomy: Study Protocol for a Randomized, Controlled Trial

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Introduction: Postoperative nausea and vomiting (PONV) remains a prevalent complication following laparoscopic cholecystectomy, often linked to perioperative opioid use. This randomized controlled trial aims to evaluate the efficacy of opioid-free anesthesia (OFA) in reducing PONV incidence and improving postoperative recovery quality compared to conventional opioid-based anesthesia (OBA).

Methods/Analysis: This study is a prospective randomized, controlled clinical trial with a concealed allocation of patients scheduled to undergo elective laparoscopic cholecystectomy 1:1 to receive either a standard anesthesia protocol or an OFA. A total of 96 patients were recruited in the study. Primary outcomes include the Rhodes Index of Nausea and Vomiting and the incidence of nausea and vomiting at 6 and 24 hours postoperatively.

Ethics and Dissemination: This trial has been approved by the Institutional Review Board of Beijing Friendship Hospital of China Capital University. The trial study protocol was approved on April 16, 2025, with an anticipated patient recruitment period of 12 months. The ethical approval number was BFHHZS20250091. The trial started recruiting patients after registered on the Chinese Clinical Trial Registry.

Trial Registration Number: CTR2500102278; Pre-results.

Keywords: opioid-free anesthesia, opioid anesthesia, laparoscopic cholecystectomy, postoperative nausea and vomiting

Introduction

Postoperative nausea and vomiting (PONV) remain prevalent adverse events following surgical procedures. It is defined as nausea or vomiting that occurs during the first 24 to 48 hours after surgery. Contemporary research indicates that, even with prophylactic interventions, 20–60% of patients experience PONV.[1,2] In patients undergoing laparoscopic cholecystectomy, PONV incidence remains significantly elevated, influenced by procedural variables (eg, pneumoperitoneum duration) and patient-specific risk factors. Established independent predictors for postoperative nausea and vomiting (PONV) encompass younger patient age, female sex, prior episodes of PONV or motion sickness, non-smoking status, and perioperative exposure to volatile inhalational anaesthetics or opioid analgesics.[3] Study have indicated that without prophylactic antiemetic therapy, PONV rates range from 53% to 72%.[4] Notably, Tamrakar et al reported that patients undergoing this procedure feared PONV rather than postoperative pain.[5] Opioids induce PONV through agonism of μ-opioid receptors in the chemoreceptor trigger zone (medulla oblongata), vestibular apparatus, and gastrointestinal tract, which disrupts emetic regulatory pathways.[6] Studies have shown that the occurrence of PONV is correlated with the dosage of opioid use.[7] Perioperative opioid administration is further correlated with adverse outcomes beyond PONV, including hypoxemia (respiratory depression), pruritus, dizziness, sedation, and urinary retention.[8] Moreover, as day surgery programs have evolved in recent years, the Enhanced Recovery After Surgery (ERAS) protocol has gained increasing emphasis, laparoscopic cholecystectomy meets the criteria for day surgery. However, opioid-induced

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complications not only negatively impact patient's experience but may also impede recovery, delay discharge, and reduce hospital bed turnover efficiency. Therefore, ERAS have promoted several opioid alternatives, including neuraxial anaesthesia, peripheral nerve blocks and non-opioid adjuncts. The components of opioid-free anaesthesia (OFA) commonly comprise dexmedetomidine, N-methyl-D-aspartate antagonists (ketamine or esketamine), lidocaine, magnesium sulfate, and regional anaesthesia.[9,10] The concept of OFA has thus garnered significant interest as a promising strategy to enhance recovery by mitigating opioid-related adverse effects, particularly in populations at high risk for PONV and respiratory depression. Proponents suggest that OFA may not only improve immediate postoperative outcomes but also potentially reduce the risk of persistent opioid use. Notably, a large multicenter randomized controlled trial by Beloeil et al[11] found that a dexmedetomidine-based OFA regimen did not significantly reduce 48-hour postoperative morphine consumption compared to a conventional opioid-based regimen in patients undergoing major noncardiac surgery, challenging the presumed primary benefit of this technique. A comprehensive systematic review by Salomé et al[12] concluded that although OFA might reduce postoperative opioid consumption and incidence of PONV, the certainty of evidence is low to moderate, and the significant heterogeneity across studies—stemming from varying surgical procedures and diverse OFA protocols—makes it difficult to draw definitive conclusions.

Furthermore, while some meta-analyses suggest benefits, they also underscore the limitations of the current body of evidence. Lavand'homme et al[13] emphasize that the risk-benefit profile of OFA is not uniform and may be influenced by factors such as type of surgery and individual patient comorbidities, warning against a blanket application of OFA strategies that could inadvertently introduce risks associated with alternative non-opioid analgesics. Therefore, there is a pressing need for more robust and specific clinical evidence to clarify the role of OFA. The conflicting findings and highlighted limitations from these studies necessitate a well-designed randomized controlled trial to determine the true efficacy and safety of a standardized OFA protocol.

Based on these considerations, we designed a prospective, randomized, controlled study to primarily evaluate the impact of OFA on PONV and postoperative quality of recovery after laparoscopic cholecystectomy. We hypothesized that the reduced opioid use during and after surgery allowed by OFA compared with opioid-based anaesthesia will be associated with a reduction of postoperative opioid-related adverse events and the incidence of PONV after laparoscopic cholecystectomy.

Methods and Analysis

Trial Design

This is a prospective, randomized, controlled clinical trial utilizing concealed allocation. Eligible patients scheduled for elective laparoscopic cholecystectomy are assigned in a 1:1 ratio to either receive a conventional opioid-based anesthesia protocol or an OFA approach. The study commenced in April 2025, with an anticipated patient recruitment period of 12 months. The trial was registered on the Chinese Clinical Trial Registry prior to initiating patient enrollment, ensuring adherence to ethical and regulatory standards.

Eligibility Criteria

Inclusion Criteria

1. Patients scheduled for laparoscopic cholecystectomy.
2. American Society of Anesthesiologists (ASA) I or II.
3. Voluntary participation in this trial and signing of informed consent.
4. Age 18–65 years old.

Exclusion Criteria

1. History of severe PONV.
2. Long-term use of opioid and psychotropic drugs.
3. Pregnancy or lactation.
4. Previous abnormal surgical anesthesia and allergy to intraoperative drugs.
5. Hyperthyroidism.

6. Nerve infection at the puncture site or refusal to perform nerve block.
7. Body Mass Index (BMI) > 28kg/m^2.
8. Preoperative heart rate < 50 beats/min, sick sinus syndrome, severe heart block.
9. Significant gastroesophageal reflux disease (GERD).
10. Hiatal hernia.

Enrolled Patients Were Excluded from the Study if They Met Any of the Following Conditions

1. Failure to complete the case report form or loss to follow-up, resulting in an inability to assess effectiveness or safety.
2. A change in anesthesia method due to unforeseen surgical requirements or unexpected events.
3. Inability to continue the surgery due to intraoperative complications.
4. Development of other conditions requiring immediate intervention after surgery.

Participant Eligibility and Consent

Study investigators at each trial site will systematically screen potential participants based on the predefined eligibility criteria. Consecutively eligible patients will be provided with detailed written and verbal study information. Formal enrollment will occur only after investigators have secured written informed consent from the participants.

Randomization and Blinding

Prior to trial initiation, unique participant identification numbers were sequentially generated based on the predetermined sample size. A computer-generated randomization sequence was created using Excel's RAND function, with allocation ratios of 1:1 for the two study groups. These randomization codes were securely sealed in sequentially numbered, opaque envelopes (SNOSE) and entrusted to a dedicated anesthesia nurse who had no other involvement in trial procedures or assessments.

On the day of surgery, the envelope corresponding to each enrolled patient was opened by a separate anesthesia provider responsible only for intraoperative management and immediate perioperative data collection. Participants were allocated according to the following scheme: those assigned odd numbers received opioid-free anesthesia/analgesia (OFA group), while even-numbered participants received conventional opioid-based anesthesia (OBA group). Importantly, the postoperative evaluation team (including follow-up anesthesiologists), surgical team members, and all patients remained blinded to group assignment throughout the study period.

Interventions

All included patients will be allocated to one of the following two study groups:

OBA group: patients will receive standardized conventional opioid anesthesia and analgesia.

OFA group: patients will receive a standard anesthesia protocol with no opioid anesthesia and analgesia.

Intravenous Induction of General Anesthesia and Intubation Will Include

All patients receive routine monitoring, including electrocardiogram (ECG), heart rate (HR), non-invasive blood pressure (NIBP), pulse oxygen saturation (SpO_2), and depth of anesthesia monitoring (BIS). Both groups received standardized premedication with intravenous dexamethasone 10 mg for antiemesis and flurbiprofen axetil 50 mg for preemptive analgesia prior to induction.

OFA group: a loading dose of dexmedetomidine hydrochloride (0.5 $\mu g \cdot kg^{-1}$) was infused over 10 minutes following peripheral venous cannulation. Then proceeded with sequential intravenous administration of scopolamine 1 mg, midazolam 2 mg, propofol 2 $mg \cdot kg^{-1}$, esketamine 0.5 $mg \cdot kg^{-1}$, and rocuronium 0.6 $mg \cdot kg^{-1}$, followed by laryngeal mask insertion after 2 minutes.

OBA group: a loading dose of normal saline (0.5 $\mu g \cdot kg^{-1}$) was infused over 10 minutes following peripheral venous cannulation. Midazolam 2 mg, propofol 2 $mg \cdot kg^{-1}$, sufentanil 0.3–0.5 $\mu g \cdot kg^{-1}$, and rocuronium 0.6 $mg \cdot kg^{-1}$, followed by laryngeal mask insertion after 2 minutes.

All medications were prepared by a designated anesthesiologist uninvolved in outcome assessment to preserve blinding.

Standardized Maintenance of General Anesthesia

OFA group: following laryngeal mask insertion, the OFA group received continuous intravenous infusions of propofol (2 $mg \cdot kg^{-1} \cdot h^{-1}$) and a premixed solution containing esketamine (50 mg) and dexmedetomidine hydrochloride (100 μg) diluted in 50 mL 0.9% saline. This combined solution was administered at a rate of 0.1–0.2 mL/kg/h, equivalent to esketamine 0.1–0.2 $mg \cdot kg^{-1} \cdot h^{-1}$ and dexmedetomidine 0.2–0.4 $\mu g \cdot kg^{-1} \cdot h^{-1}$, to maintain a bispectral index (BIS) between 40–60. Intraoperative adjustments included supplemental esketamine boluses (0.1 $mg \cdot kg^{-1}$) based on hemodynamic parameters (blood pressure/heart rate). The esketamine-dexmedetomidine infusion was discontinued 30 minutes prior to surgical closure. Prophylactic tropisetron (5 mg) was administered 15 minutes before surgery, with propofol infusion stopped at surgery completion.

OBA group: following laryngeal mask insertion, the OBA group received continuous intravenous infusions of propofol (5–8 $mg \cdot kg^{-1} \cdot h^{-1}$) and remifentanil (0.15–0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$) to maintain a BIS between 40–60. Intraoperative adjustments included supplemental sufentanil boluses (5–10 μg) based on hemodynamic parameters (blood pressure/heart rate). Prophylactic tropisetron (5 mg) was administered 15 minutes before surgical closure. Both propofol and remifentanil infusions were stopped at the end of surgery.

The laryngeal mask airway was removed only after meeting all three criteria:

1. Full consciousness (patient responsive to verbal commands).
2. Complete neuromuscular blockade reversal (achieved with intravenous atropine 0.5 mg and neostigmine 1 mg).
3. Muscle strength recovery (sustained head lift ≥ 5 seconds and adequate tidal volume).

Intraoperative Analgesia: Ultrasound-Guided Transversus Abdominis Plane (TAP) Block Procedure

The ultrasound-guided TAP block was performed by placing a high-frequency linear probe (8–15 MHz) subcostally along the midclavicular line, then sliding it laterally to the axillary midline to visualize the abdominal muscle layers: external oblique, internal oblique, transversus abdominis, and peritoneum. After sterile preparation (probe sheathed in a sterile cover, skin disinfection), a 22-gauge nerve-stimulating needle was advanced in-plane under real-time ultrasound guidance to the fascial plane between the internal oblique and transversus abdominis muscles. Following negative aspiration for blood or air, 20 mL of 0.33% ropivacaine was injected per side, with direct visualization confirming spindle-shaped fluid spread within the fascial layer. The procedure was repeated bilaterally, with color Doppler monitoring to avoid vascular structures. Conducted jointly by an anesthesiologist and general surgeon, needle trajectory and injection pressure (<15 psi) were dynamically adjusted to ensure safety and anatomical precision, followed by post-procedural sensory testing to verify blockade efficacy.

Postoperative Management

Both groups were transferred postoperatively to the PACU (Post-Anesthesia Care Unit) under standardized monitoring by anesthesiologists and nurses blinded to group allocation. Patients meeting discharge criteria (Aldrete score > 9) were transferred to the surgical ward.

Rescue Analgesia: The primary rescue analgesic was intravenous sufentanil. It was administered in boluses of 2.5–5 μg if the VAS pain score exceeded 3. The administration was titrated to achieve a VAS score ≤3.[14]

Scheduled Non-Opioid Analgesia: patients received scheduled intravenous flurbiprofen axetil 50 mg based on clinical requirements.

Rescue Anti-emesis: Intravenous prophylactic tropisetron 5 mg was available as rescue medication for any patient experiencing nausea or vomiting.

Pain scores, opioid consumption, and adverse events were documented for the first 24 hours by blinded observers using validated assessment tools.

Relevant Complications of Management During Anesthesia

Bradycardia (heart rate < 50 beats/min) was treated with intravenous atropine 0.5 mg; tachycardia (heart rate > 100 beats/min) received esmolol 10–20 mg IV; hypertension (>20% above baseline blood pressure) was addressed with urapidil 5–10 mg IV after excluding inadequate anesthetic depth or insufficient analgesia; hypotension (>20% below baseline) was managed using methoxamine 5 mg or ephedrine 5–10 mg IV following exclusion of hypovolemia or excessive anesthetic depth. All interventions followed protocol-specified safety checks and were documented in real-time.

Outcome Measures

Primary Outcome Measure

1. The Rhodes Index of Nausea and Vomiting was employed to evaluate nausea and vomiting before surgery and at 6 and 24 hours after surgery.[15]

Secondary Outcomes Measures

1. Demographic information such as age, gender, whether there is a history of motion sickness, smoking history.
2. The incidence of nausea and vomiting at 6h and 24h after operation.
3. The global score Quality of Recovery-15 scale (QoR-15) scale, comprising 15 items, was utilized to assess recovery quality at 6 and 24 hours postoperatively.[16]
4. Record hemodynamic parameters (blood pressure, heart rate) and BIS at baseline upon operating room entry (T0), anesthesia induction (T1), laryngeal mask insertion (T2), 5 minutes post-insertion (T3), surgical incision (T4), pneumoperitoneum establishment (T5), and extubation (T6). Total anesthetic dosage, surgical duration, pneumoperitoneum time, anesthesia duration, awakening time, time to extubation and anesthesia-related complications (hypotension, hypertension, arrhythmias, respiratory depression) were also systematically recorded.
5. Record postoperative PACU Aldrete score > 9 minutes, postoperative 6h,12h, 24h VAS pain score, analgesic rescue times, and patient satisfaction.

Statistical Analysis and Sample Size Calculation

Statistical analysis and generation of data plots for the future study will be performed using GraphPad Prism version 6.0 and SPSS 23.0. All data will be checked for normal distribution using the Kolmogorov test. For normally distributed data, continuous variables will be analysed using the independent Student's *t* test, and the variables will be presented as the mean ± standard deviation (SD). Non-normally distributed data will be compared using the Mann–Whitney *U*-test where appropriate, and data will be presented as the median and interquartile range (IQR). For categorical variables, cross-tabulation and the Pearson chi-squared test will be applied, and variables will be categorized as numbers and/or percentages of the total. A p value <0.05 with two tails will be considered statistically significant.

Our pre-experimental results showed that the standard deviation (SD) of the Rhodes Index of Nausea and Vomiting score were (4.15 vs 3.74) observed between the OFA and OBA groups, respectively, and a 3-point difference in the Rhodes Index of Nausea and Vomiting score indicates significant difference. Using PASS 15.0, with $\alpha = 0.05$ and power = 80%. The minimal required sample size was 84 participants. To account for potential attrition, the final target enrollment was 96 patients, 48 in each group.

Ethical Considerations, Amendments and Dissemination

This trial adheres to the ethical principles of the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines, with approval granted by the Institutional Review Board of Beijing Friendship Hospital, Capital Medical University. Protocol modifications impacting patient safety, study design, or outcomes will require formal amendment submissions to the ethics committee, accompanied by updated Trial Registry documentation and reconsent procedures when necessary. All data are anonymized through the removal of personal identifiers and pseudonymization of sensitive information in publications; shared datasets undergo rigorous deidentification, retaining only numerical identifiers. Access is restricted to authorized personnel via password-protected systems with audit trails. Results—positive, negative, or inconclusive—

will be disseminated through peer-reviewed journals and scientific conferences, ensuring transparency and alignment with open science principles.

Trial Status

This trial has been approved by the Institutional Review Board of Beijing Friendship Hospital of China Capital University. The trial study protocol was approved on April 16, 2025. The ethical approval number was BFHHZS20250091. The trial started recruiting patients after registered on the Chinese Clinical Trial Registry.

Discussion

Laparoscopic cholecystectomy (LC) is the "gold standard" technique in the surgical treatment of symptomatic cholelithiasis.[17] As the concept of Enhanced Recovery After Surgery (ERAS) evolves, outpatient laparoscopic cholecystectomy (OLC) was initially introduced in 1990 by Reddick and Olsen.[18] Since its inception, surgeons globally have progressively adopted this outpatient approach. When combined with laparoscopic techniques, OLC offers benefits such as reduced hospital expenses, shorter surgical wait times and higher levels of patient satisfaction.[19–21] However, PONV is one of the most frequent causes of unpredicted delay in discharge after ambulatory surgery and laparoscopic cholecystectomy is one of the potentially PONV-inducing types of surgery.[22] Although multiple measures have been implemented to reduce their frequency, they still occur in 50–70% of cases.[23] One of the reasons is perioperative use of opioids, Opioids activate mu receptors in the chemoreceptor trigger zone (CTZ) and cholinergic receptors in the vestibular system.[24] They also directly influence gastrointestinal (GI) function by reducing intestinal motility, slowing peristalsis, decreasing secretions, and delaying gastric emptying.[25] These effects can result in symptoms such as abdominal bloating, constipation, postoperative ileus, bowel distension, and cramping—all of which contribute to nausea and vomiting.[26,27] Additionally, opioids enhance the vestibulo-ocular reflex, making head movements more likely to trigger nausea.[28]

OFA refers to the administration of anesthesia during surgery without the use of opioids, a method that has been demonstrated as a safe and viable approach to sedation. A key strategy in OFA involves enhancing non-opioid adjuncts as part of a multimodal or balanced analgesia regimen. However, as noted in recent systematic reviews,[12,29] there is no standardized OFA protocol, and significant variations exist in the choice of adjunctive medications (eg, dexmedetomidine, ketamine, lidocaine, magnesium, NSAIDs), their dosages, timing of administration, and the specific surgical populations studied. In this trial, we chose esketamine, dexmedetomidine combined TAP for OFA scheme. TAP, esketamine, and dexmedetomidine alone in surgery had been approved to reduce the amount of sedative drugs, block nociceptive afferents, and analgesia during general anesthesia. And the dosages and combinations were selected based on preliminary evidence from smaller studies[30,31] and pharmacological principles, but we acknowledge they represent one of many possible permutations. Furthermore, our multimodal approach was designed to target the multifaceted nature of postoperative pain following laparoscopic cholecystectomy. As highlighted in a recent randomized study by Abdelsamad et al,[32] postoperative pain in this procedure is complex, arising from somatic, visceral, and inflammatory components. The cited study provides important insights into the etiology of this pain, which informed our rationale for selecting specific agents: esketamine for its NMDA receptor antagonism to prevent hyperalgesia and NSAIDs to combat inflammatory pain at the port sites and in the peritoneal cavity. This context helps frame our results and underscores the importance of a procedure-specific, mechanism-based approach to constructing OFA regimens.

Meanwhile, previous study demonstrated that TAP block is associated with equivalent or improved nausea and vomiting compared to both no block (standard care) and active comparators. Any reduction in these outcomes may be as a result of the corresponding reduction in opioid use associated with TAP block.[33] In addition, Zhao et al's study demonstrated that administering a preoperative dose of 0.5 mg/kg of esketamine, followed by an intraoperative maintenance infusion of 2 μg/kg·min, could effectively maintain hemodynamic stability and minimize surgical stress and inflammation in patients undergoing laparoscopic cholecystectomy.[34] And Ziemann-Gimmel et al reported the risk of PONV to be 1.27 (1.01–1.61), $p = 0.04$ with fentanyl-inclusive anaesthesia compared with a ketamine-dexmedetomidine-based strategy at equivalent postoperative hydromorphone consumption in both groups.[35] Moreover, low-dose dexmedetomidine may improve gastrointestinal transit by acting on central α2-adrenergic receptors to reduce sympathetic tone.[36] Chen et al found that intraoperative use of dexmedetomidine (a loading dose of 1 μg/

kg over 10 minutes, followed by a maintenance dose of 0.3 μg/kg per hour) was associated with reductions in time to first flatus, first feces, and return to a regular solid diet.[37] Lu Y's study proved that the reduced consumption of sufentanil and remifentanil following intraoperative dexmedetomidine administration may contribute to improved postoperative gastrointestinal recovery and reduced incidence rate of PONV.[38] In our study, the continuous maintenance infusion was prepared as a mixture of 50 mg esketamine, 100 μg dexmedetomidine hydrochloride, and 0.9% saline in a total volume of 50 mL. The infusion rate was maintained at 0.1–0.2 mL/kg/h, equivalent to esketamine 0.1–0.2 mg/kg/h and dexmedetomidine 0.2–0.4 μg/kg/h. The dosages selected for this study were all within the established safe ranges reported in previous studies.[9,39,40] Furthermore, our preliminary experiments verified the efficacy of these drug dosages under our study conditions.

The selection of the Rhodes Index of Nausea, Vomiting as our primary instrument for assessing PONV was grounded in its validated psychometric properties and comprehensive nature. The Rhodes Index of Nausea, Vomiting is a multi-item, self-report questionnaire that quantifies the subjective experience of nausea through eight items evaluating its duration, frequency, and distress level, alongside the objective occurrence of vomiting and retching. This provides a nuanced, graded assessment of the entire emetic episode, capturing its impact on the patient with greater sensitivity. This sensitivity is crucial for several reasons. First, it allows for the detection of clinically meaningful differences in symptom severity between intervention groups that might be missed by a cruder measure. Second, by measuring the subjective distress associated with nausea, it directly assesses a dimension that is paramount to the patient's quality of recovery and overall experience. Consequently, the Rhodes Index of Nausea, Vomiting offers a more patient-centered and comprehensive evaluation of the efficacy of our opioid-free anesthesia regimen in mitigating PONV, aligning with modern trends in outcomes research that prioritize patient-reported outcomes (PROs).[41]

Despite the careful design of this trial, there are still some limitations. First, there is no standardized balanced OFA protocol, and further research is still needed to determine the optimal OFA approach for laparoscopic cholecystectomy. Second, blinding of anesthesiologists was not possible due to technique differences, though they were excluded from other study aspects, and the questionnaires in the study are mostly subjective in nature, PONV data were patient-reported. Thus, before the initiation of this trial, the investigator and site staff received systemic training for the use of these questionnaires and were certificated to avoid subjective bias as much as possible. Third, patients with BMI >28 kg/m^2 were excluded to reduce pharmacological variability and potential safety risks associated with non-opioid drug dosing in obesity, as well as to minimize confounding in outcome assessment given the established independent association between obesity and PONV. This exclusion of obese patients may affect the generalizability of our findings. Future studies should validate and adapt OFA protocols for obese populations—a direction we are actively pursuing. Fourth, as a single-center trial, multicenter studies will be necessary to validate these OFA regimen findings.

Conclusion

This study protocol outlines a rigorous evaluation of opioid-free anesthesia (OFA) as a strategy to mitigate postoperative nausea and vomiting (PONV) in patients undergoing laparoscopic cholecystectomy. By integrating dexmedetomidine, esketamine, and regional analgesia via TAP block, OFA aims to circumvent opioid-induced gastrointestinal and central nervous system effects, thereby reducing PONV incidence and improving postoperative recovery quality. Despite the potential advantages of opioid-free anesthesia (OFA) in reducing opioid-related side effects, its clinical application presents several challenges. The efficacy of OFA in improving both short-term recovery and long-term patient outcomes requires further validation through large-scale, well-designed studies.

Data Sharing Statement

Availability of data and materials: The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Disclosure

The authors report no conflicts of interest in this work.

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