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ORIGINAL RESEARCH

Esketamine-Based Opioid-Free versus Opioid-Based Anesthesia for Recovery Quality After Laparoscopic Transabdominal Preperitoneal Repair: A Randomized Noninferiority Trial

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Purpose: This study aimed to compare the quality of postoperative recovery between esketamine-based opioid-free anesthesia (OFA) and opioid-based anesthesia (OBA) in patients undergoing laparoscopic transabdominal preperitoneal (TAPP) repair.

Patients and Methods: In this prospective, randomized, double-blind, noninferiority trial, 126 adults scheduled for elective laparoscopic TAPP repair were randomized to OFA (n = 63) or OBA (n = 63) group. The OFA group received esketamine (0.5 $mg \cdot kg^{-1}$ induction, 0.4–0.5 $mg \cdot kg^{-1} \cdot h^{-1}$ maintenance), while the OBA group received sufentanil (0.4 $\mu g \cdot kg^{-1}$ induction) and remifentanil (0.1–0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ maintenance). The primary outcome was the 15-item Quality of Recovery (QoR-15) score at 24 hours postoperatively, with a noninferiority margin of −8. Secondary outcomes included pain scores, rescue analgesia, sleep quality, safety outcomes.

Results: The OFA group showed a higher QoR-15 score at 24 hours postoperatively than the OBA group (median difference: 2; median [IQR]: 129 [125 to 132] vs 127 [123 to 130]; 95% CI, 0 to 4; P=0.014). Pruritus incidence was lower (P=0.027), vasopressor use was reduced (P = 0.012), and hypotensive episodes tended to be fewer (P=0.106) in the OFA group. Pain scores on coughing at 24 and 48 hours postoperatively were also lower in the OFA group (P=0.002 and P< 0.001, respectively).

Conclusion: Esketamine-based OFA provided a noninferior quality of postoperative recovery compared with OBA in patients undergoing laparoscopic TAPP repair, offering a safer alternative to OFA regimens that minimizes opioid-related complications while maintaining perioperative comfort and supporting enhanced recovery.

Keywords: esketamine, transabdominal preperitoneal, noninferiority trial, opioid-free anesthesia, postoperative recovery

Introduction

Opioids are widely regarded as the most effective analgesics for perioperative management. However, opioid-based anesthesia (OBA) is associated with several adverse events, including postoperative nausea and vomiting (PONV), impaired respiratory function, delayed gastrointestinal recovery, opioid-induced hyperalgesia, and an increased risk of dependence.[1–4] These adverse effects are among the factors contributing to the global opioid crisis. In response, enhanced recovery after surgery (ERAS) protocols aim to minimize opioid exposure, thereby promoting faster functional recovery and reducing complications, particularly in minimally invasive procedures. Consequently, opioid-free anesthesia (OFA) has emerged as a multimodal strategy that employs nonopioid agents to provide effective analgesia while minimizing opioid-related risks.[5]

Among nonopioid agents, esketamine is an effective adjunct in OFA regimens, providing analgesic effects through NMDA receptor antagonism and activation of the sympathetic nervous system.[3,6,7] Compared with racemic ketamine, esketamine exhibits higher NMDA receptor affinity and a lower incidence of psychomimetic side effects, which facilitates its use in continuous perioperative infusion.[8] In addition to its analgesic effects, preclinical and clinical studies indicate that esketamine exerts anti-inflammatory effects by suppressing IL-6 and TNF-α, potentially enhancing postoperative recovery and patient comfort.[9,10]

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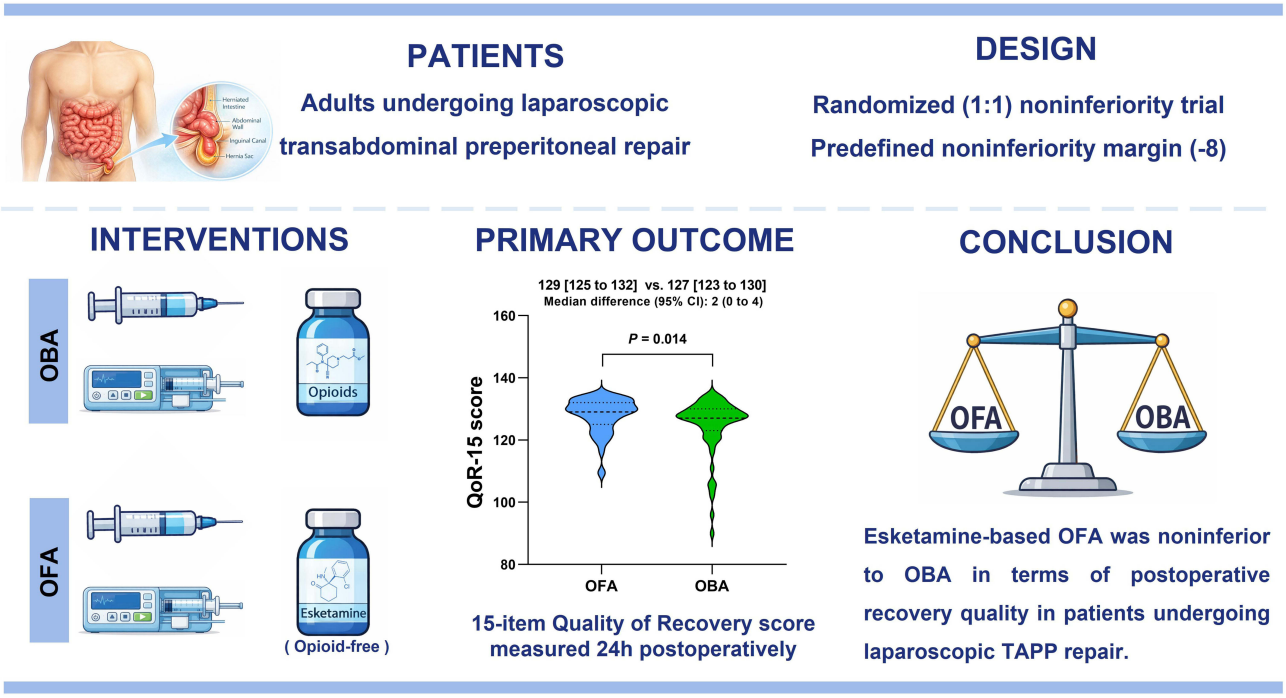
Graphical Abstract



Recent randomized trials have demonstrated that OFA significantly reduces PONV, facilitates early ambulation, and shortens hospital stay across abdominal, spinal, and cardiac surgeries.[11–14] Laparoscopic transabdominal preperitoneal (TAPP) repair is a minimally invasive and widely performed technique for inguinal hernia repair, with over 20 million procedures performed annually worldwide.[15] While TAPP is compatible with ERAS principles promoting minimally invasive recovery, optimal pain management remains a critical challenge. Despite its minimally invasive nature, moderate-to-severe pain occurs in approximately 50% of patients on the first postoperative day after laparoscopic hernia repair. These patients are often treated with opioids, which may delay ambulation and increase complications.[16] Although OFA has demonstrated success in a variety of procedures, including laparoscopic cholecystectomy, thoracic surgery, bariatric surgery, and colorectal surgery, its application in TAPP repair has not been fully investigated, particularly with esketamine-based regimens.[11,17–19]

This study aimed to test whether esketamine-based OFA provides postoperative recovery quality noninferior to that of OBA in patients undergoing elective TAPP repair. By focusing on esketamine-based OFA in TAPP repair, it is expected to provide clinically relevant evidence that can inform future ERAS protocols, support safer perioperative care, and contribute to global opioid stewardship.

Materials and Methods

Study Design

This study was approved by the Clinical Medical Research Ethics Committee of the First Affiliated Hospital of Anhui Medical University (approval no. PJ 2023–06-17, approval date: 11 May 2023, chairperson: Heng Wang) and was registered with the Chinese Clinical Trial Registry (www.chictr.org.cn, registration no. ChiCTR2300072534, principal investigator: H.L., registration date: 16 Jun 2023). All participants were fully informed about the trial's purpose and procedures, and written informed consent was obtained before enrollment. The trial was conducted in accordance with the ethical principles of the Declaration of Helsinki and its subsequent amendments, and followed the CONSORT reporting guidelines.

Participants

Patients were recruited for participation between July 6, 2023, and August 7, 2024. The study cohort consisted of patients scheduled for elective laparoscopic TAPP repair. Anesthesia was administered via a laryngeal mask airway according to standardized protocols. Inclusion criteria were: (1) age ≥18 years and (2) American Society of Anesthesiologists (ASA) physical status I–III. Patients with incarcerated or recurrent hernia; severe hypertension (systolic ≥180 mmHg or diastolic ≥110 mmHg despite medical therapy); cognitive impairment or communication difficulties; chronic pain requiring regular analgesics; a history of allergic reactions to study drugs; contraindications to laryngeal mask use; severe cardiovascular disease; liver failure; or obesity (body mass index [BMI] >30 $kg \cdot m^{-2}$) were excluded.

Randomization and Blinding

Patients were randomly assigned using the Sealed Envelope platform (www.sealedenvelope.com) with a 1:1 allocation ratio and block sizes of 2 and 4. An independent research staff member prepared opaque, sequentially numbered envelopes with the group assignments concealed inside. Immediately before anesthesia induction, a research assistant not involved in the study opened the envelopes, and patients were assigned to either the OFA or OBA group. Only the attending anesthesiologist, who was uninvolved in the trial, was aware of the group assignments. Patients, postoperative outcome assessors, and statistical analysts were blinded to group assignments.

Anesthesia and Study Interventions

All patients adhered to standard preoperative fasting guidelines. Upon arrival in the operating room, standard monitoring was applied, including electrocardiography, pulse oximetry (SpO_2), and noninvasive blood pressure measurement. In all patients, anesthesia was induced after preoxygenation with etomidate (0.2 $mg \cdot kg^{-1}$) and cisatracurium (0.2 $mg \cdot kg^{-1}$), supplemented by sufentanil (0.4 $\mu g \cdot kg^{-1}$) in the OBA group or esketamine (0.5 $mg \cdot kg^{-1}$) in the OFA group. Propofol (4–6 $mg \cdot kg^{-1} \cdot h^{-1}$) was used for maintenance in both groups, supplemented by remifentanil (0.1–0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$) in the OBA group and esketamine infusion (0.4–0.5 $mg \cdot kg^{-1} \cdot h^{-1}$) in the OFA group.[20,21] All patients were ventilated via a laryngeal mask airway, with end-tidal CO_2 maintained at 35–40 mmHg. Active warming measures were applied to maintain normothermia. Intraoperative hemodynamics were managed according to a standardized protocol applied in both groups. Mean arterial pressure was maintained within 20% of the baseline value. Hypotension, defined as a decrease in mean arterial pressure >20% from baseline, was treated with intravenous norepinephrine (4–8 μg) or ephedrine (6 mg) administered as bolus doses and repeated as needed. Bradycardia, defined as a >20% decrease in heart rate from baseline or a heart rate <50 bpm, was treated with intravenous atropine (0.3 mg). Before the end of surgery, the OBA group received sufentanil (0.2 $\mu g \cdot kg^{-1}$) for postoperative analgesia, whereas the OFA group received esketamine (0.25 $mg \cdot kg^{-1}$).

Post-anesthesia care was conducted according to a standardized protocol for all patients. After recovery of spontaneous breathing and emergence from anesthesia, the laryngeal mask airway was removed. Residual neuromuscular blockade was antagonized with neostigmine (0.05 $mg \cdot kg^{-1}$) as needed. Postoperative pain was assessed using the numeric rating scale (NRS), and patients with an NRS score ≥4 received intravenous sufentanil (5 μg), repeated as necessary until pain was reduced below an NRS score of 4.[11] Patients were transferred to the surgical ward upon reaching a Steward score of 6. Postoperative analgesia in the surgical ward consisted of intravenous flurbiprofen ester (50 mg) administered according to the same standardized protocol.

Study Outcomes

The primary outcome was the 15-item Quality of Recovery (QoR-15) score assessed at 24 hours after surgery (H24) during the hospital stay. The QoR-15 generates a total score ranging from 0 to 150, with higher scores indicating better postoperative recovery.

Secondary outcomes included the QoR-15 score at 72 hours postoperatively (H72). For patients who had been discharged before H72, the QoR-15 was administered via telephone interview.[22] Secondary outcomes also comprised numeric rating scale (NRS) pain scores at rest and on coughing at 6, 12, 24, and 48 hours after surgery (H6, H12, H24, and H48). For each patient, the area under the curve (AUC) of NRS scores from H6 to H48 was calculated using the

trapezoidal method, separately for pain at rest (AUC_rest) and pain on coughing (AUC_cough). Additional secondary outcomes included the requirement for rescue analgesia within 48 hours postoperatively, duration of post-anesthesia care unit (PACU) stay, and sleep quality on the night of surgery, which was evaluated using a five-point Likert scale (0 = very poor sleep quality; 5 = excellent sleep quality).[23]

Safety outcomes were recorded intraoperatively and postoperatively. Hemodynamic adverse events included hypotension (mean arterial pressure [MAP] decrease >20% from baseline), hypertension (MAP increase >20% from baseline), bradycardia (heart rate <50 beats·min^{-1}), and tachycardia (heart rate >100 beats·min^{-1}), along with the corresponding pharmacologic interventions (norepinephrine, ephedrine, atropine, nicardipine, or esmolol). Other recorded safety events included PONV, pruritus, dizziness, headache, and hallucinations or nightmares.

Statistical Analysis

Previous studies have established the minimum clinically important difference (MCID) for the QoR-15 as 8 points.[24] On this basis, the noninferiority margin was set at −8 points for the between-group difference in QoR-15 scores, reflecting the largest clinically acceptable decrease in postoperative recovery quality. Noninferiority of esketamine-based OFA compared with OBA was concluded if the lower bound of the two-sided 95% confidence interval (CI) for the between-group difference in QoR-15 scores exceeded −8 points. Based on previous studies, assuming a common standard deviation of 15 points, a total sample size of 114 patients (57 per group) was calculated to provide 80% power to demonstrate noninferiority using a one-sided α level of 0.025.[25,26] Allowing for an anticipated 10% dropout rate, the final target sample size was increased to 126 patients (63 per group).

Normality of continuous variables was assessed using the Shapiro–Wilk test before parametric analyses. Continuous variables are presented as mean ± standard deviation or median (interquartile range), as appropriate, whereas categorical variables are expressed as counts (percentages). Comparisons were performed according to data distribution: the Student's *t* test for normally distributed continuous variables, the Mann–Whitney *U*-test for non-normally distributed continuous variables, and the chi-square or Fisher's exact test for categorical variables. The Hodges-Lehmann estimator of the between-group median difference with its 95% CI was reported for non-parametric continuous outcomes. Statistical significance was defined as a two-sided p-value < 0.05. All statistical analyses were performed using SPSS software (version 27; IBM Corp., Armonk, NY, USA).

Results

The CONSORT flow diagram of participant enrollment and allocation is presented in Figure 1. A total of 156 patients were assessed for eligibility between July 2023 and August 2024. After exclusion of 30 patients, 126 participants were randomly assigned in a 1:1 ratio to the OBA or OFA group. All 126 randomized participants (63 in each group) were included in the final analysis.

Baseline Demographic Characteristics and Intraoperative Data

Baseline demographic and intraoperative characteristics were comparable between the two groups (Table 1). No clinically meaningful differences were observed with respect to age, sex distribution, ASA physical status, comorbidities, baseline QoR-15 scores, surgical duration, or the proportion of bilateral procedures. The total intraoperative dose of propofol was significantly higher in the OFA group than in the OBA group (P=0.003).

Primary and Secondary Outcomes

Primary and secondary outcomes are summarized in Table 2. The QoR-15 score at H24 was significantly higher in the OFA group than in the OBA group (129 [125 to 132] vs 127 [123 to 130]; 95% CI, 0 to 4; P=0.014), and this difference persisted at H72 (142 [140 to 144] vs 140 [138 to 142]; 95% CI, 1 to 3; P<0.001). The lower bound of the 95% CI exceeded the prespecified noninferiority margin of −8, thereby demonstrating noninferiority of OFA compared with OBA.

Postoperative pain scores were comparable between groups at early postoperative time points. Lower pain scores were observed in the OFA group at 24 and 48 hours postoperatively. Consistently, the AUC of NRS pain scores from 6 to 48 hours

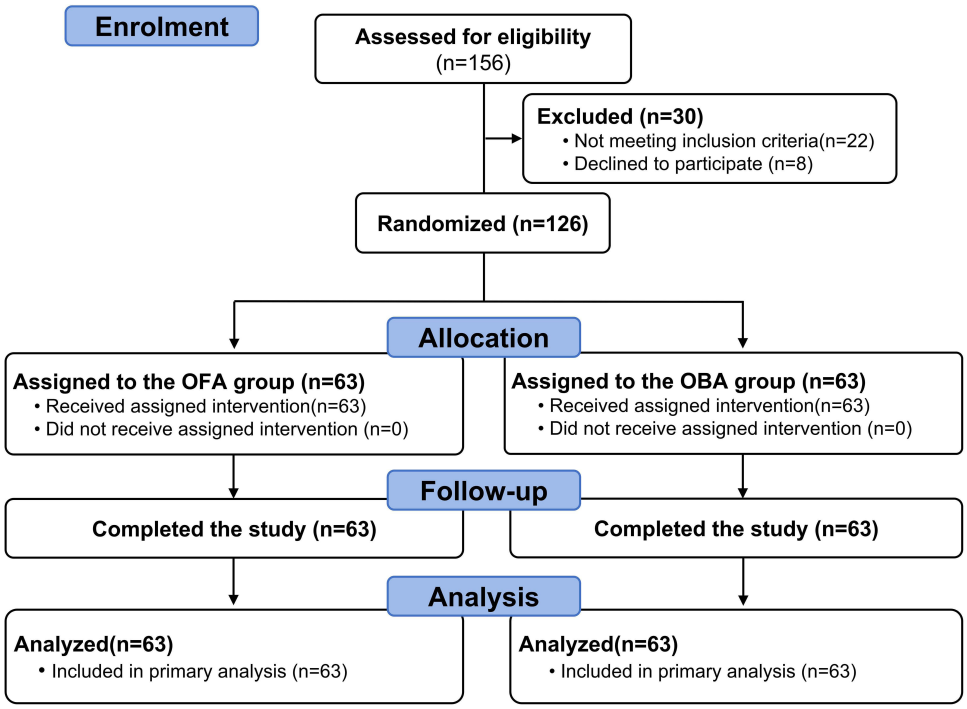


Figure 1 CONSORT study flow diagram.

was lower in the OFA group than in the OBA group, both at rest (12 [9 to 21] vs 21 [12 to 51]; 95% CI, 3 to 15; P=0.002) and on coughing (45 [21 to 78] vs 72 [45 to 114]; 95% CI, 12 to 39; P<0.001). The proportion of patients requiring rescue analgesia did not differ significantly between groups. The duration of PACU stay was longer in the OFA group than in the

Table 1 Demographic Characteristics and Intraoperative Data

	All Patients	OFA Group (n=63)	OBA Group (n=63)	*P* value
Age (yr)	60 [53 to 70]	59 [54 to 69]	61 [52 to 70]	0.671
Male (n, %)	115 (91.3)	58 (92.1)	57 (90.5)	0.752
Body height (cm)	169 [165 to 170]	168 [163 to 170]	170 [166 to 171]	0.177
Weight (kg)	66.3 ± 9.6	65.9 ± 9.9	66.6 ± 9.3	0.711
BMI ($kg \cdot m^{-2}$)	23.5 ± 2.8	23.5 ± 2.9	23.4 ± 2.6	0.763
ASA physical status				0.798
1	10 (8.0)	6 (9.6)	4 (6.4)	
2	91 (72.2)	45 (71.4)	46 (73.0)	
3	25 (19.8)	12 (19.0)	13 (20.6)	
Comorbidities				0.099
Hypertension	26 (20.6)	12 (19.0)	14 (22.2)	
Diabetes	3 (2.4)	1 (1.6)	2 (3.2)	
History of stroke	1 (0.8)	0	1 (2.6)	
Other	5 (4.0)	2 (3.2)	3 (4.8)	

(*Continued*)

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Table 1 (Continued).

	All Patients	OFA Group (n=63)	OBA Group (n=63)	*P* value
Surgical procedure				1.000
Unilateral	120 (95.2)	60 (95.2)	60 (95.2)	
Bilateral	6 (4.8)	3 (4.8)	3 (4.8)	
Preoperative QoR-15 scores	145 [142 to 146]	144 [142 to 146]	145 [143 to 146]	0.261
Surgical duration (min)	65 [55 to 80]	65 [55 to 80]	68 [54 to 80]	0.595
Propofol (mg)	360 [310 to 451]	400 [340 to 480]	342 [300 to 408]	0.003

Notes: Data are presented as median [IQR], *n* (%), and mean ± SD.
Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiology; OBA, opioid-based anesthesia; OFA, opioid-free anesthesia.

Table 2 Primary and Secondary Outcomes

	OFA Group (n=63)	OBA Group (n=63)	Median or Odds Ratio Difference (95% CI)	*P* value
Primary outcome				
QoR-15 score at H24	129 [125 to 132]	127 [123 to 130]	2 (0 to 4)	0.014
Secondary outcomes				
QoR-15 score at H72	142 [140 to 144]	140 [138 to 142]	2 (1 to 3)	<0.001
NRS score at rest				
H6	0 [0 to 1]	0 [0 to 1]	0 (0 to 0)	0.813
H12	0 [0 to 1]	1 [0 to 1]	0 (0 to 0)	0.137
H24	0 [0 to 1]	1 [0 to 1]	0 (−1 to 0)	0.033
H48	0 [0 to 0]	0 [0 to 1]	0 (0 to 0)	0.001
AUC_rest (H6–H48)	12 [9 to 21]	21 [12 to 51]	9 (3 to 15)	0.002
NRS score during cough				
H6	1 [1 to 2]	1 [1 to 2]	0 (0 to 0)	0.679
H12	2 [1 to 2]	2 [2 to 3]	0 (−1 to 0)	0.005
H24	1 [1 to 2]	2 [1 to 3]	−1 (−1 to 0)	0.002
H48	0 [0 to 1]	1 [0 to 3]	−1 (−1 to 0)	< 0.001
AUC_cough (H6–H48)	45 [21 to 78]	72 [45 to 114]	27 (12 to 39)	< 0.001
Rescue analgesia	10 (15.9)	11 (17.5)	−1.1 (−2.9 to −0.4)	0.811
Duration of PACU stay (min)	45 [35 to 50]	32 [30 to 45]	10 (5 to 15)	< 0.001
Sleep quality on the night of surgery	5 [4 to 5]	4 [4 to 5]	0(0 to 1)	0.018

Notes: Data are presented as median [IQR], n (%), median difference (95% CI), and odds ratio (95% CI).
Abbreviations: QoR-15, 15-item quality of recovery scale; PACU, post-anaesthesia care units; NRS, numeric rating scale; OBA, opioid-based anaesthesia; OFA, opioid-free anaesthesia; H6, 6 hours postoperatively; H12, 12 hours postoperatively; H24, 24 hours postoperatively; H48, 48 hours postoperatively.

OBA group (45 [35 to 50] vs 32 [30 to 45]; 95% CI, 5 to 15; $P<0.001$). Sleep quality on the night of surgery was slightly higher in the OFA group than in the OBA group (5 [4 to 5] vs 4 [4 to 5]; 95% CI, 0 to 1; $P=0.018$).

Safety Outcomes

Safety outcomes are summarized in Table 3. Compared with the OBA group, the OFA group required significantly fewer interventions for hemodynamic events (11.1% vs 35.0%, 95% CI, −8.1% to −1.3%; $P=0.012$) and had a lower incidence of pruritus (3.2% vs 14.3%; 95% CI, −24.6% to −1.1%; $P=0.027$) compared with the OBA group. Lower incidences of hypotension and bradycardia were observed in the OFA group, although the between-group differences did not reach statistical significance. The incidences of hypertension, tachycardia, headache or dizziness, PONV, and postoperative nightmares or hallucinations were low and comparable between groups.

QoR-15 Subdomain Scores at H24

Among the QoR-15 subdomains (Table 4), physical comfort scores were significantly higher in the OFA group than in the OBA group (45 [43–47] vs 44 [41–45]; 95% CI, 1 to 3; $P<0.001$). No significant between-group differences were observed in physical independence, emotional state, psychological support, or pain.

Table 3 Safety Outcomes

	OFA Group (n=63)	OBA Group (n=63)	Odds Ratio (95% CI)	*P* value
Hypotension	8 (12.7)	15 (23.8)	−2.1 (−5.5 to −0.8)	0.106
Hypertension	2 (3.2)	0	−1.0 (−1.1 to −1.0)	0.496
Bradycardia	7 (11.1)	13 (20.6)	−2.1 (−5.6 to −0.8)	0.144
Tachycardia	2 (3.2)	0	−1.0 (−1.1 to −1.0)	0.496
Interventions for hemodynamic events	7 (11.1)	22 (35.0)	−3.2 (−8.1 to −1.3)	0.012
Headache or dizziness 0–48 h	6 (9.5)	3 (4.8)	−0.5 (−2.0 to −0.1)	0.491
Pruritus	2 (3.2)	9 (14.3)	−5.1 (−24.6 to −1.1)	0.027
PONV	2 (3.2)	4 (6.3)	−2.1 (−11.7 to −0.4)	0.680
Nightmare or hallucination 0–48 h	1 (1.6)	0	1.0 (1.0 to 1.0)	1.000

Notes: Data are presented as n (%), odds ratio (95% CI).
Abbreviations: PONV, post-operative nausea and vomiting; OBA, opioid-based anesthesia; OFA, opioid-free anesthesia.

Table 4 Subdomain Analysis of the QoR-15 Score at H24

Variable	OFA Group (n=63)	OBA Group (n=63)	Median Difference (95% CI)	*P* value
Physical comfort (0–50)	45 [43 to 47]	44 [41 to 45]	2 (1 to 3)	< 0.001
Physical independence (0–20)	5 [4 to 7]	5 [4 to 6]	0 (0 to 1)	0.278
Emotional state (0–40)	40 [39 to 40]	40 [39 to 40]	0 (0 to 0)	0.421
Psychological support (0–20)	20 [20 to 20]	20 [19 to 20]	0 (0 to 0)	0.244
Pain (0–20)	20 [20 to 20]	20 [19 to 20]	0 (0 to 0)	0.060

Notes: Data are presented as median [IQR], median difference (95% CI).
Abbreviations: H24, 24 hours after surgery; OBA, opioid-based anesthesia; OFA, opioid-free anesthesia.

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Sensitivity Analysis

To assess the robustness of the primary outcome, QoR-15 scores were categorized by recovery quality: excellent (136–150), good (122–135), moderate (90–121), or poor (<90).[27] The proportion of patients achieving good or excellent recovery was higher in the OFA group than in the OBA group (88.9% vs 77.8%; *P*=0.094) (Figure 2).

Subgroup Analyses

Subgroup analyses were conducted according to three established predictors of recovery: age (<65 vs ≥65 years), BMI (<25 vs ≥25 kg·m^{-2}), and surgery duration (<60 vs ≥60 minutes).[24,28,29] Logistic regression was applied to compare the proportion of patients achieving good recovery (QoR-15≥122) between the OFA and OBA groups. No significant interactions were observed between treatment effect and any subgroup, indicating that the treatment effect of OFA on achieving good recovery was consistent across clinically relevant patient subgroups (Figure 3).

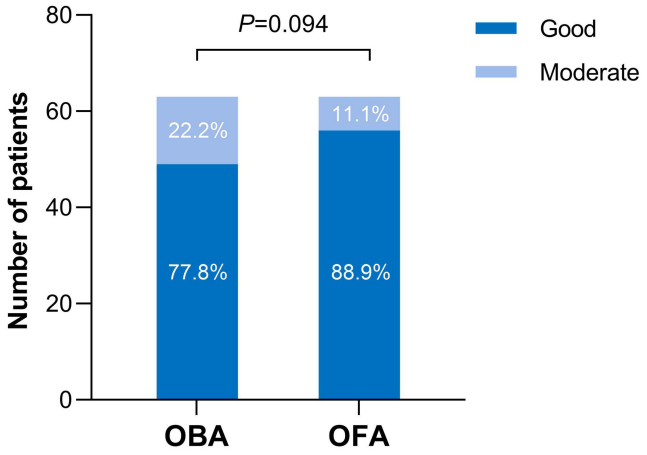

Figure 2 Distribution of patients according to categories of QoR-15 at H24. OBA, opioid-based anesthesia; OFA, opioid-free anesthesia; Excellent, 136–150; Good, 122–135; Moderate, 90–121; Poor, 0–89.

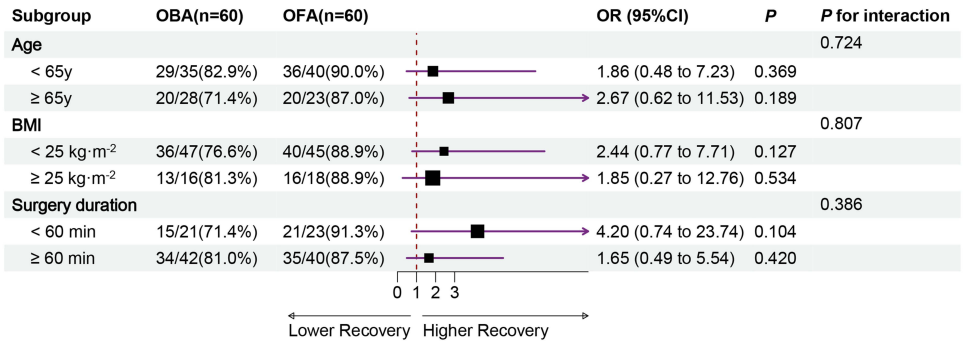

Figure 3 Subgroup analysis of patients with good quality of recovery (QoR-15 score ≥122).

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Discussion

In this study, esketamine-based OFA was noninferior to OBA with respect to early postoperative recovery in patients undergoing elective laparoscopic TAPP repair. Comparable QoR-15 scores at 24 and 72 hours indicate that OFA provides a level of recovery equivalent to that of OBA. The noninferiority margin of −8 points was predefined on the basis of the MCID of the QoR-15 validated in abdominal surgery,[24] and our results are consistent with thresholds reported in laparoscopic cholecystectomy studies, supporting its applicability to TAPP procedures.[17] Additionally, OFA was associated with improved hemodynamic stability and a lower incidence of pruritus, consistent with ERAS objectives of minimizing opioid exposure.

These findings extend the existing evidence supporting the use of OFA in abdominal surgery.[30,31] Notably, although laparoscopic TAPP shares the minimally invasive advantages of other laparoscopic procedures, it is characterized by a distinct pain profile, predominantly deep visceral pain related to peritoneal traction.[16] Esketamine, a selective NMDA receptor antagonist, exerts inhibitory effects on central sensitization and hyperalgesia,[32,33] which may partly explain the improved control of cough-related pain at 24 and 48 hours postoperatively, as well as the higher physical comfort scores observed in the OFA group. Effective control of movement-evoked pain and improved physical comfort are critical determinants of early mobilization after laparoscopic TAPP repair. Compared with opioid-sparing strategies reported in other surgical populations, the OFA regimen in the present study achieved comparable analgesia without compromising recovery-related outcomes, underscoring its potential adaptability across different surgical settings. To our knowledge, this is the first study to evaluate the impact of esketamine-based OFA on postoperative quality of recovery following laparoscopic TAPP repair, providing preliminary evidence to inform future clinical practice and guideline development.

The clinical implications of the secondary outcomes warrant careful interpretation, particularly with respect to their practical relevance. Although the OFA regimen was associated with a prolonged length of stay in the PACU, this finding may be attributable to the synergistic sedative effects of propofol in combination with esketamine.[34] Similar observations have been reported in an OFA trial involving thoracic surgery,[11] suggesting that delayed PACU discharge may represent a reproducible phenomenon across different surgical populations. To mitigate this limitation, future optimization of OFA protocols could focus on individualized dose adjustments or the use of alternative sedative agents in place of propofol, especially in the context of outpatient or fast-track surgical pathways. Importantly, OFA was associated with hemodynamic advantages, particularly a lower incidence of hypotension and a reduced need for vasopressor. These benefits may help offset the increased demand on PACU resources in high-risk or hemodynamically vulnerable patient populations. These preliminary observations merit confirmation in larger, adequately powered studies. From a safety perspective, the findings further support the potential advantages of OFA. The significantly lower incidence of pruritus is consistent with the avoidance of opioid-induced histamine release, while the observed trend toward fewer hypotensive events may be related to the sympathoexcitatory properties of esketamine.[35,36]

In addition to the primary outcome, subgroup analyses demonstrated consistent directional trends favoring OFA across categories defined by age, BMI, and surgery duration. Notably, patients with a BMI of <25 $kg \cdot m^{-2}$ or a duration of surgery of <60 minutes showed clinically meaningful improvements in recovery rates with OFA, although these differences did not reach statistical significance. These consistently favorable patterns across subgroups suggest the potential applicability of OFA across a range of patient characteristics. However, larger, adequately powered studies are required to formally evaluate potential effect modification.

The use of validated, patient-centered outcome measures is essential to capture the multidimensional nature of postoperative recovery, including comfort, pain control, and functional well-being. The QoR-15, endorsed by Myles et al as a core perioperative outcome measure, has been widely adopted for evaluating postoperative recovery and patient comfort following general anaesthesia.[37–39] Accordingly, the QoR-15 was selected as the primary outcome in the present study. Its suitability as a primary endpoint is further supported by its extensive international use and the availability of a validated Chinese version with robust psychometric properties (Cronbach's alpha = 0.76; intraclass correlation coefficient = 0.99).[40] Using this validated and patient-centered outcome measure, our findings demonstrate that esketamine-based OFA achieved noninferior postoperative recovery compared with opioid-based anesthesia.

Several methodological limitations should be acknowledged. First, the OFA regimen was developed based on pilot observations and existing literature rather than formal dose-finding studies. Although this approach reflects current clinical practice, further research is required to optimize OFA regimens for laparoscopic TAPP repair and other surgical procedures. Second, the depth of anesthesia was not monitored, as we were concerned about the reliability of electroencephalogram-derived indices in the presence of NMDA receptor antagonism by esketamine.[41] Third, recovery quality during the immediate postoperative period was not assessed using standardized quantitative tools. As a result, transient differences between anesthetic techniques during the very early recovery phase may not have been fully characterized. Fourth, our study primarily focused on early postoperative recovery as reflected by the QoR-15 score at 24 hours postoperatively and did not evaluate longer-term outcomes such as chronic pain. Finally, the relatively homogeneous study population constrains the generalizability of our findings to high-risk patients and female populations, who may exhibit distinct pharmacodynamic responses to esketamine.

In conclusion, esketamine-based OFA provides postoperative recovery that is noninferior to OBA in patients undergoing laparoscopic TAPP repair. Although the observed QoR-15 scores were slightly higher in the OFA group, no prespecified superiority hypothesis was tested; therefore, superiority cannot be inferred. Future multicenter studies are warranted to establish standardized OFA protocols, evaluate efficacy across diverse patient populations, and explore the broader applicability of esketamine-based OFA in other surgical settings.

Data Sharing Statement

Deidentified data are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

This study was approved by the Clinical Medical Research Ethics Committee of the First Affiliated Hospital of Anhui Medical University (approval no. PJ 2023-06-17, approval date: 11 May 2023, chairperson: Heng Wang).

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Disclosure

The authors declare no competing interests in this work.

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