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CLINICAL TRIAL REPORT

Effects of Intravenous Subanesthetic-Dose Esketamine on Early Postoperative Pain in Elderly Patients Undergoing Thoracoscopic Lung Surgery: A Randomized Double-Blind Controlled Trial

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Purpose: Thoracic surgery is one of the postoperative surgical procedures with the most severe pain. This study aimed to assess whether intraoperative subanesthetic esketamine could reduce the proportion of elderly patients experiencing moderate-to-severe pain following thoracoscopic lung resection.

Patients and Methods: A total of 136 elderly patients undergoing thoracoscopic pulmonary surgery were randomly assigned to two groups: the esketamine group (0.25 mg/kg loading, 0.25 mg/kg/h infusion) and the control group (received normal saline). The primary outcome was the proportion of patients experiencing moderate-to-severe pain on the first postoperative day (POD1), defined as a Numerical Rating Scale (NRS) pain score ≥4 during coughing. The secondary outcomes were the postoperative Athens Insomnia Scale (AIS), Hospital Anxiety and Depression Scale (HADS) scores, opioid consumption, hemodynamics, and adverse events.

Results: The primary outcome incidence was lower in the esketamine group (51.5% [35/68]) than in the control group (69.1% [47/68]; relative risk [RR], 0.75; 95% confidence interval [CI], 0.56–0.99; P = 0.035). The proportion of patients with moderate-to-severe pain in the esketamine group decreased by 25.5%. The analysis revealed an absolute risk reduction (ARR) of 17.6% and a number needed to treat (NNT) of 5.7 (rounded to 6). The incidence of postoperative sleep disturbance (PSD) on POD1 (23.5% vs 44.1%; RR, 0.53; 95% CI, 0.32–0.88; $P = 0.011$) is lower in patients who receive esketamine. Compared to the control group, the esketamine group demonstrated lower HADS scores and reduced opioid consumption, without significant differences in hemodynamic parameters or an increased incidence of neuropsychiatric adverse events.

Conclusion: This study demonstrated that intraoperative subanesthetic esketamine reduced the proportion of moderate-to-severe pain in elderly patients after thoracoscopic surgery, decreased the incidence of sleep disturbances, improved anxiety and depression scores, and lowered opioid consumption, without increasing neuropsychiatric adverse events.

Keywords: esketamine, postoperative analgesia, sleep, multimodal analgesia, thoracoscopic lung surgery

Introduction

As a minimally invasive alternative to conventional open thoracotomy, video-assisted thoracoscopic surgery (VATS) demonstrates superior clinical outcomes: attenuated postoperative pain, enhanced respiratory performance, condensed hospitalization periods, and expedited patient rehabilitation.[1–3] However, effective postoperative analgesia remains a major challenge, with up to 65% of VATS patients experiencing moderate-to-severe pain.[4,5] This challenge is particularly pronounced in the elderly population, who are more susceptible to the adverse effects of conventional analgesics. Inadequate pain control not only causes significant distress but also increases the risk of complications, delays

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recovery, and may contribute to the development of chronic postsurgical pain (CPSP).[6,7] Therefore, optimizing postoperative analgesia for patients undergoing VATS lung resection, particularly in the elderly, is imperative.

Within the Chinese population, lung carcinoma represents the predominant oncologic diagnosis and the primary driver of cancer-associated fatalities.[8] The increasing adoption of low-dose CT screening has led to more frequent diagnoses at earlier stages.[9] Coupled with a rapidly growing and aging population,[10] which is a major risk factor for cancer, this has resulted in a substantial rise in the number of VATS lung resections performed. Elderly patients undergoing VATS frequently experience perioperative sleep disturbances and negative emotional states, such as anxiety (with an incidence rate of approximately 43.5%) and depression (around 57.1%).[11,12] Postoperative sleep disruption is not merely a symptom but a critical factor in recovery, significantly impairing cognitive function, immunity, wound healing, and emotional regulation.[13] Crucially, a bidirectional relationship is well-established: compromised acute pain control is a primary disruptor of normal sleep architecture, and the resultant sleep deprivation markedly lowers pain thresholds, amplifies pain perception, and concurrently exacerbates anxiety and depression.[14] This self-perpetuating pain-sleep-mood triad poses a significant barrier to recovery in this vulnerable elderly surgical population. Consequently, interventions capable of simultaneously alleviating acute pain and improving sleep are paramount for this expanding patient group, yet effective comprehensive strategies remain inadequate.

Esketamine, the S(+) enantiomer of racemic ketamine, is a potent noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist. Compared to the racemate, esketamine possesses approximately twice the analgesic potency and is associated with fewer side effects, particularly a reduced incidence of psychiatric symptoms.[15] Perioperative intravenous administration of esketamine has been demonstrated to effectively reduce acute postoperative pain intensity and opioid consumption in the short term, and it has also shown potential in alleviating postoperative depression.[16,17] Although the evidence remains preliminary, there are indications that ketamine enantiomers may influence sleep architecture, suggesting the possibility of broader benefits with esketamine.[18,19] The theoretical rationale lies in ketamine's potential to simultaneously suppress central pain sensitization (via NMDA receptor antagonism) and exert positive effects on sleep/neural circuits. This dual action renders it a highly relevant intervention for mitigating the detrimental pain-sleep cycle in elderly patients following VATS.

Current research on the analgesic efficacy and safety profile of esketamine in elderly patients undergoing thoracoscopic lung resection is limited. More importantly, its impact on postoperative sleep quality and negative mood states in this specific population remains largely unexplored. Thus, this study aims to evaluate the impact of continuous intraoperative infusion of a subanesthetic dose (loading dose: 0.25 mg/kg, infusion dose: 0.25 mg/kg/h) of esketamine on early postoperative outcomes in elderly patients, with the objective of providing high-level evidence for medication protocols in this specific population. We postulated that such esketamine intervention would diminish severe pain incidence, enhance perioperative sleep, and mitigate the development of negative emotions.

Materials and Methods

Study Design

This prospective, double-blind, placebo-controlled randomized clinical trial was conducted at Jinling Hospital Affiliated to the Medical School of Nanjing University. The study protocol was approved by the Clinical Trial Ethics Committee of Jinling Hospital Affiliated to the Medical School of Nanjing University (Approval No.: 2025DZK-Y-010-01) and was registered in the Chinese Clinical Trial Registry (ChiCTR2500098525; http://www.chictr.org/) on March 10, 2025. The protocol was explained to the patients before the trial commenced, and written informed consent was obtained from all participants. The study adhered to the 2010 Consolidated Standards of Reporting Trials (CONSORT) guidelines and complied with the Declaration of Helsinki.

Inclusion and Exclusion Criteria

Researchers screened eligible patients one day prior to surgery (on the preceding Friday if surgery was scheduled for the following Monday). Inclusion Criteria: (1) Age ≥ 60 years, scheduled for elective VATS, including wedge resection, segmentectomy, or lobectomy; (2) American Society of Anesthesiologists (ASA) physical status classification I to III; (3)

Willingness to participate in the trial and ability to provide signed informed consent. Exclusion Criteria: (1) Contraindication or allergy to esketamine; (2) Severe psychiatric illness, severe hepatic dysfunction (Child-Pugh class C), renal failure, unstable ischemic heart disease, or risk of elevated intracranial pressure; (3) Body mass index (BMI) > 30; (4) Conversion to thoracotomy; (5) Cognitive impairment or inability to communicate.

Randomization and Blinding

Patients were randomly allocated in a 1:1 ratio to either the esketamine group or the normal saline control group using a computer-generated randomization sequence. The allocation sequence was concealed using sequentially numbered, opaque, and sealed envelopes prepared by an independent study coordinator. On the day of surgery, the study coordinator opened the randomization envelopes in the order of recruitment, prepared the investigational drug according to the assigned group, and delivered it to the operating room. Both esketamine and normal saline were packaged in identical 20-mL syringes. The trial coordinator was not involved in anesthetic management, perioperative care, or postoperative follow-up. Patients, investigators responsible for data collection and postoperative follow-up assessments, as well as clinical staff remained blinded to treatment allocation throughout the entire study period.

Anesthesia Management

Standard intraoperative monitoring was established, including pulse oximetry, electrocardiography (ECG), and invasive arterial blood pressure monitoring. All patients received intravenous dexamethasone 10 mg and tropisetron 5 mg at the start of surgery.

During anesthesia induction, all patients were administered intravenous midazolam (0.03–0.05 mg/kg), propofol (1.5–2.5 mg/kg), sufentanil (0.4–0.6 μg/kg), and cisatracurium besylate (0.15–0.25 mg/kg). After administration of these induction drugs, patients in the esketamine group immediately received an intravenous bolus of 0.25 mg/kg esketamine, while those in the control group received an equivalent volume of normal saline. Subsequently, tracheal intubation was performed using a video laryngoscope according to surgical requirements, followed by placement of a bronchial blocker in the surgical lung under fiberoptic bronchoscopic guidance. For anesthesia maintenance, the esketamine group received continuous intravenous infusions of remifentanil (0.1–0.2 μg/kg/min), propofol (4–8 mg/kg/h), and esketamine (0.25 mg/kg/h). The control group received continuous intravenous infusions of remifentanil (0.1–0.2 μg/kg/min) and propofol (4–8 mg/kg/h). A lung-protective ventilation strategy was implemented: tidal volume (TV) was set at 6–8 mL/kg predicted body weight (PBW) during two-lung ventilation; TV was reduced to 4–6 mL/kg PBW during one-lung ventilation; positive end-expiratory pressure (PEEP) was maintained at 5–10 cmH_2O. Intraoperatively, we will dynamically adjust intraoperative analgesic medications based on blood pressure and heart rate. Additional cisatracurium besylate was given as required for intraoperative muscle relaxation. Infusion of esketamine was discontinued 15 minutes before the end of the procedure.

Surgical Procedures

All patients underwent thoracoscopic pulmonary resection performed by the same surgical team, utilizing either uniportal or multiportal endoscopic approaches. A single 24-French chest tube was routinely placed postoperatively.

Postoperative Pain Management

All patients received hydromorphone Patient-Controlled Intravenous Analgesia (PCIA) postoperatively. The PCIA pump was prepared by dissolving 8 mg of hydromorphone, 5.26 mg of betamethasone, and 3 mg of dolasetron in normal saline to a total volume of 100 mL. The pump was programmed with a continuous background infusion rate of 1.5 mL/h for 48 hours, a patient-administered bolus dose of 1.5 mL, and a lockout interval of 15 minutes. Subsequently, the patient was transferred to the cardiothoracic surgery intensive care unit. The tracheal tube was removed after the patient's spontaneous breathing had fully recovered. All patients admitted to the intensive care unit routinely received a standard intravenous dose of 50 mg flurbiprofen axetil. Supplemental analgesia with oral acetaminophen was administered when the patient's resting pain intensity reached or exceeded a score of 4 on the Numerical Rating Scale.

Outcome Measurements

Primary Outcome: The proportion of patients experiencing moderate-to-severe pain (defined as a NRS pain score ≥ 4 during coughing) on POD1. Secondary Outcomes: NRS pain scores at rest and during coughing at the following time points: 4 hours postoperatively (PO4H), PO8H, POD1, and POD3; AIS and HADS scores on POD1 and POD3; inflammatory indicators on POD1; total volume of PCIA administered and the quantities of its individual active components consumed; total intraoperative consumption of remifentanil and sufentanil; hemodynamic parameters, including mean arterial pressure (MAP) and heart rate (HR), were monitored at predefined time intervals: prior to anesthesia induction (T0), before tracheal intubation (T1), immediately following tracheal intubation (T2), after conversion to the lateral decubitus position (T3), 5 minutes after surgical incision (T4), 30 minutes after surgical incision (T5), 60 minutes after surgical incision (T6), and at the end of the operation (T7). Additionally, the following postoperative adverse events were systematically monitored: nausea and vomiting (PONV), delirium, and esketamine-related psychotomimetic reactions, including hallucinations, nightmares, confusion, or disorientation.

NRS ranges from 0 (0 = no pain) to 10 (worst imaginable pain). For pain intensity scores, a change of ≥1 is considered the Minimal Clinically Important Difference (MCID).[20] The AIS is a self-reported psychometric instrument designed to measure difficulties related to sleep, in accordance with the criteria outlined in the International Classification of Diseases, 10th Edition (ICD-10).[21] The total AIS score ranges between 0 and 24, with a score of 6 or above suggesting the presence of insomnia.[22] The HADS comprises a total of 14 questions divided equally into two subscales: one for anxiety and the other for depression. Each question is rated on a scale from 0 to 3, and the total scores for each subscale are calculated separately, resulting in an anxiety score (HADS-A) and a depression score (HADS-D). A subscale score of 8 or more suggests the presence of clinically relevant anxiety or depression. Delirium was evaluated using the 3-Minute Diagnostic Confusion Assessment Method (3D-CAM) from postoperative day 1 to day 3. The investigators responsible for postoperative follow-up received training on the 3D-CAM guideline from the psychiatry department prior to the initiation of the trial.

Sample Size Calculation

Previous studies have reported an incidence of moderate-to-severe pain following VATS of 67%. This aligns with our observed incidence of approximately 69%.[4,23] However, prior research suggests that a relative reduction of 35–40% in the incidence of moderate-to-severe pain is clinically relevant.[4,5] We hypothesized that the esketamine group would achieve a 37.5% relative reduction in the incidence of moderate-to-severe postoperative pain (from 69% to 43%). For the hypothesis test, a significance level (α) of 0.05 and 80% statistical power were set. A sample size of 114 patients was calculated as necessary to detect this difference. Accounting for potential dropouts or withdrawal of consent, 136 patients were enrolled in the trial.

Outcome Analysis

Statistical analysis was performed using the intention-to-treat approach. The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Normally distributed data are presented as mean (standard deviation, SD) and were compared using the independent-sample *t*-tests. Non-normally distributed data are reported as median (interquartile range, IQR) and were analyzed using the Mann–Whitney *U*-test. Categorical variables are presented as number (%) and were compared using Pearson's chi-square (χ^2) test or Fisher's exact test, as appropriate.

For the primary outcome, group comparisons were conducted using the chi-square test, with between-group differences presented as relative risk along with the corresponding 95% confidence interval (CI). A post hoc logistic regression analysis was carried out to identify independent risk factors associated with moderate to severe postoperative pain in elderly patients. Covariates included in the multivariate logistic regression model were selected based on clinical relevance and previously documented evidence suggesting potential associations with the outcomes.[24–27] Candidate variables encompassed demographic, surgical, and preoperative psychological factors. All variables demonstrating a p-value of less than 0.1 in univariate analyses were incorporated into the final multivariate model. The number of covariates was determined according to the events-per-variable (EPV) criterion to ensure model stability.

For categorical outcomes, between-group differences were reported as relative risk accompanied by the corresponding 95% confidence interval (CI). For continuous variables, between-group differences were presented as median differences with 95% confidence intervals, which were calculated using the Hodges-Lehmann estimator.

To assess the potential confounding effects arising from differential exposure to analgesic adjuvants (betamethasone and dolasetron) attributable to variations in Patient-Controlled Intravenous Analgesia (PCIA) utilization, a post hoc correlation analysis was performed within the control group. Secondary outcomes, including the Athens Insomnia Scale and the Hospital Anxiety and Depression Scale, were assessed with Spearman's rank correlation. The point-biserial correlation was used for the dichotomous outcome of postoperative nausea and vomiting.

The Generalized Estimating Equations (GEE) approach was employed to analyze the repeated-measures data, which included outcomes such as the Numeric Rating Scale (NRS) score and hemodynamic parameters, specifically mean arterial pressure (MAP) and heart rate (HR). Statistical significance was set at $P < 0.05$.IBM SPSS Statistics software (version 27.0) was used for all statistical analyses.

As an exploratory analysis, we calculated the area under the curve (AUC) of postoperative pain intensity over 24 hours, as well as the Pain Intensity and Opioid Consumption (PIOC) over 24 hours.[28,29] Intergroup differences were compared using the Mann–Whitney *U*-test, with the median difference and its 95% confidence interval (CI) calculated using the Hodges-Lehmann estimator.$AUC = \frac{1}{2}\sum_{i=1}^{n-1}(t_{i+1} - t_i)(y_i + y_{i+1})$, where t refers to the specific time point at which pain was evaluated, and y indicates the corresponding pain score obtained through the NRS.[28] $PIOC = \frac{AUC_{\text{mean rank}} - AUC_{\text{rank}}}{AUC_{\text{mean rank}}} + \frac{OC_{\text{mean rank}} - OC_{\text{rank}}}{OC_{\text{mean rank}}}$ POIC denotes pain intensity and opioid consumption. $AUC_{\text{mean rank}}/OC_{\text{mean rank}}$ represents the mean rank of AUC/OC for all patients (including the supplement and placebo cohorts). $AUC_{\text{rank}}/OC_{\text{rank}}$ indicates an individual patient's rank in terms of AUC/OC. The range of the sum is −200% to +200%. A value greater than 0 signifies greater total AUC and higher opioid consumption relative to all patients.[29,30] The number needed to treat (NNT) is calculated as the reciprocal of the absolute risk reduction (ARR) between two treatment groups,[31,32] according to formula: $NNT = \frac{1}{\pi_1 - \pi_0} = \frac{1}{ARR}$,$\pi_1$ denotes the incidence rate of moderate-to-severe pain in the control group, whereas π_0 denotes the incidence rate of moderate-to-severe pain in the esketamine group.

Results

Patient Inclusion and Demographic Characteristics

Of the 155 patients who underwent eligibility assessment, 19 were excluded based on the criteria, resulting in 136 participants being randomly assigned to either the control group or the esketamine group. During the study period, there were no withdrawals of consent and no protocol deviations. The final intention-to-treat analysis comprised 136 patients (Figure 1). Baseline characteristics did not differ significantly between the two groups (Table 1).

Intraoperative Characteristics

No significant differences were observed between the groups in terms of intraoperative variables, including the extent of surgery, duration of both surgery and anesthesia, fluid administration, estimated blood loss, and urine output. Remifentanil consumption was significantly lower in the esketamine group compared to the control group (1.2 [0.9–1.7] vs 1.45 [1.1–1.9] mg; $P = 0.04$). However, no significant difference was found in sufentanil consumption between the two groups (Table 2).

Primary Outcome Analyses

Compared to the control group, patients receiving esketamine exhibited a significantly reduced occurrence of moderate-to-severe pain within 24 hours (51.5%, 35/68 vs 69.1%, 47/68; RR: 0.75; 95% CI: 0.56–0.99; $P = 0.035$) (Table 3). Similarly, the post hoc logistic regression model demonstrated that intraoperative esketamine administration (odds ratio [OR]: 0.385; 95% CI: 0.164 to 0.908; $P = 0.029$) was independently associated with a reduced risk of moderate-to-severe postoperative pain.

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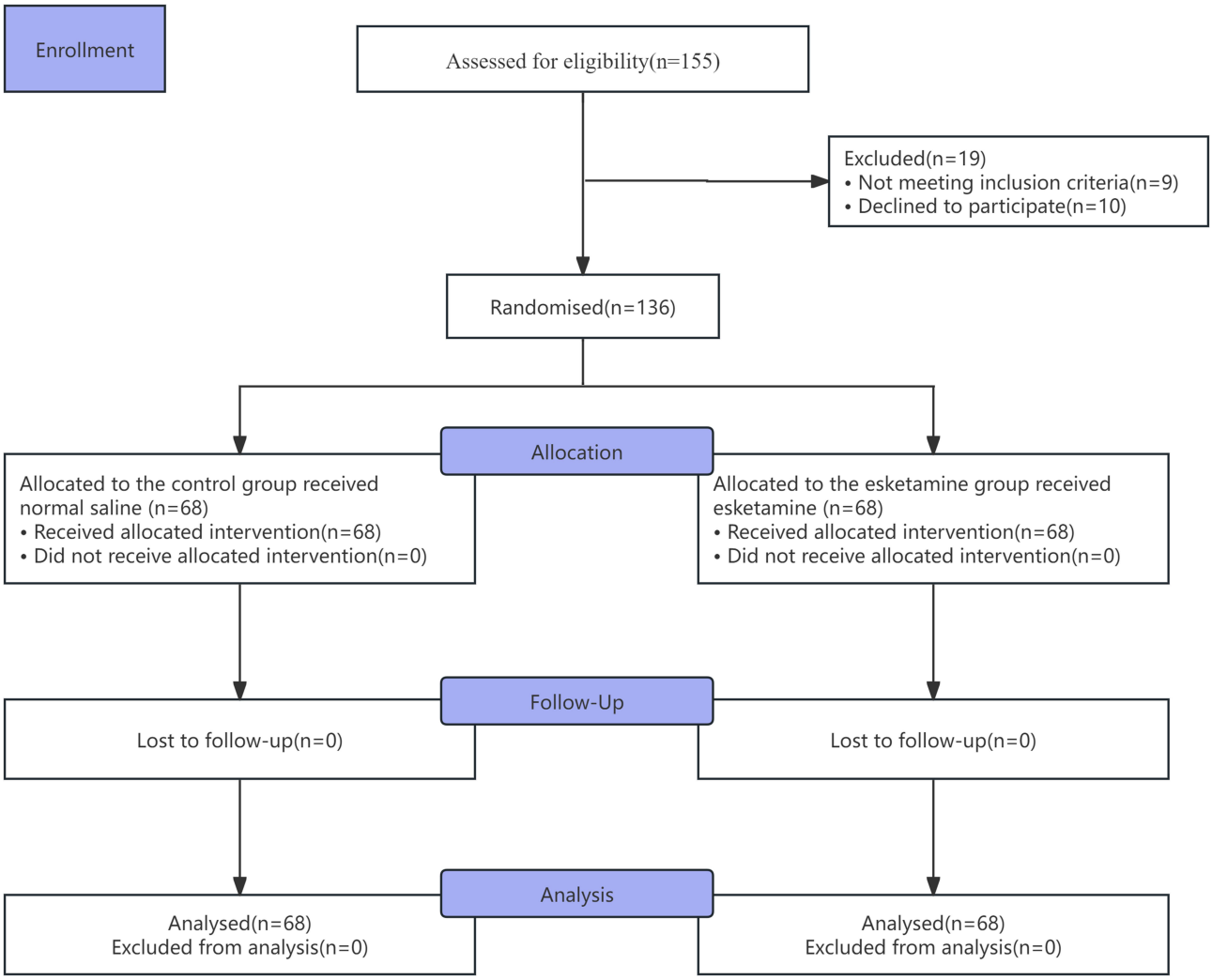

Figure 1 Flow diagram.

Secondary Outcomes Analyses

Esketamine-administered patients demonstrated reduced resting pain intensity relative to controls, with median NRS scores significantly lower at PO8H (MD: −2; 95% CI: −2 to −1; $P < 0.001$) and POD1 (MD: −1; 95% CI: −2 to −1; $P < 0.001$). Similarly, cough-provoked NRS pain scores were attenuated in the intervention group versus controls at identical

Table 1 Demographic and Clinical Characteristics at Baseline

	Control Group(n=68)	**Esketamine Group(n=68)**	***P* value**
Age, median (IQR), y	68(62–71)	66(61–70)	0.454
Sex, females	37(54.4)	35(51.5)	0.731
BMI, mean (SD), kg/m^2	23.6(2.8)	24.5(3.5)	0.096
ASA physical status score			0.488
I	15(22.1)	10(14.7)	
II	36(52.9)	37(54.4)	
III	17(25.0)	21(30.9)	

(*Continued*)

Table 1 (Continued).

	Control Group(n=68)	Esketamine Group(n=68)	*P* value
Smoking status	17(25.0)	15(22.1)	0.686
Drinking status	21(30.9)	14(20.6)	0.170
Comorbidities			
Diabetes	15(22.1)	11(16.2)	0.383
Hypertension	30(44.1)	35(51.5)	0.391
COPD	4(5.9)	1(1.5)	0.366
Cardiovascular disease	20(29.4)	19(27.9)	0.850
Liver disease	3(4.4)	2(2.9)	1.000
Kidney disease	1(1.5)	3(4.4)	0.619
Preoperative examination			
NE($\times 10^9$/L)	3.0(2.3–3.9)	2.8(2.3–3.8)	0.687
IL-6(pg/mL)	2.8(1.5–4.7)	3.3(1.8–5.3)	0.462
HADS-A score, median (IQR)	8(6–9)	8(6–9)	0.598
HADS-D score, median (IQR)	6(5–7)	6(5–7)	0.650
AIS score, median (IQR)	4(3–7)	4(3–6)	0.575
Preoperative sleep disorders, No (%)	26(38.2)	28(41.2)	0.726

Notes: Data are expressed as a mean ± standard deviation, median (interquartile range), or number (%).$P < 0.05$ was considered statistically significant.

Abbreviations: BMI, body mass index; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; NE, Neutrophil; IL-6, Interleukin-6; HADS-A, Hospital Anxiety and Depression Scale - Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale - Depression subscale; AIS, Athens Insomnia Scale; Preoperative sleep disorders, AIS≥6.

Table 2 Intraoperative Characteristics

	Control Group(n=68)	Esketamine Group(n=68)	*P* value
Surgical type			0.307
Wedge resection	19(27.9)	20(29.4)	
Segmentectomy	28(41.2)	20(29.4)	
Lobectomy	21(30.9)	28(41.2)	
Type of Endoscopic Approach			0.600
Single-Port	26(38.2)	29(42.6)	
Multi-Port	42(61.8)	39(57.4)	
Direction of surgery			0.387
Right	41(60.3)	36(52.9)	
Left	27(39.7)	32(47.1)	
Duration of surgery, median (IQR), min	150(100–210)	150(105–210)	0.884
Duration of anesthesia, median (IQR), min	175(130–230)	165(120–235)	0.948
Sufentanil dose, median (IQR), μg	45(40–50)	40(40–50)	0.239
Remifentanil dose, median (IQR), mg	1.45(1.1–1.9)	1.2(0.9–1.7)	0.040
Total fluid infusion, median (IQR), mL	1000(800–1400)	1100(900–1500)	0.387
Urine output, median (IQR), mL	200(200–300)	200(150–300)	0.473
Estimated blood loss, median (IQR), mL	50(50–100)	50(50–100)	0.642

Notes: Data are expressed as a mean ± standard deviation, median (interquartile range), or number (%).$P < 0.05$ was considered statistically significant.

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Table 3 Comparison of Outcomes Between the Two Groups

	Control Group(n=68)	Esketamine Group(n=68)	RR or MD (95% CI)	*P* value
Primary outcome	47(69.1)	35(51.5)	0.75(0.56–0.99)	0.035
Incidence of moderate to severe pain, n (%)				
Secondary outcomes				
NRS pain score at rest, median (IQR)				
At 4h	2(1–3)	2(1–3)	0(0–1)	0.126
At 8h	4(2–5)	3(2–4)	2(1–2)	<0.001
POD1	3(2–4)	2(2–4)	1(1–2)	<0.001
POD3	1(1–2)	1(0–2)	0(0–0)	0.556
NRS pain score during coughing, median (IQR)				
At 4h	3(2–4)	3(2–4)	0(0–1)	0.267
At 8h	6(3–7)	4(3–5)	2(1–3)	<0.001
POD1	4(3–6)	3(3–5)	1(1–2)	<0.001
POD3	2(2–3)	2(1–3)	0(0–1)	0.342
AIS score, median (IQR)				
POD1	5(4–9)	4(3–5)	1(1–2)	<0.001
PSD, No (%)	30(44.1)	16(23.5)	0.53(0.32–0.88)	0.011
POD3	4(2–5)	3(2–5)	0(0–1)	0.183
PSD, No (%)	14(20.6)	8(11.8)	0.57(0.26–1.27)	0.162
HADS-A score, median (IQR)				
POD1	6(5–7)	5(4–6)	1(0–1)	0.004
POD3	4(4–6)	4(3–5)	0(0–1)	0.306
HADS-D score, median (IQR)				
POD1	5(4–6)	4(3–5)	1(1–2)	0.002
POD3	3(2–4)	2(1–3)	1(0–1)	0.015
Inflammatory indicators on POD1, median (IQR)				
NE($\times 10^9$/L)	11.2(9.9–14.2)	10.1(7.8–13.8)	1.6 (0.4–2.8)	0.011
IL-6(pg/mL)	43.2(21.6–62.2)	24.2(12.4–46.9)	12.1(2.5–21.7)	0.013
PCIA utilization, median (IQR)				
PCIA volume, mL	93(84.25–97.75)	87(78–92)	5(3–8)	<0.001
Hydromorphone, mg	7.44(6.74–7.82)	6.96(6.24–7.36)	0.4(0.24–0.64)	<0.001
Betamethasone, mg	4.89(4.43–5.14)	4.58(4.10–4.84)	0.27(0.16–0.42)	<0.001
Dolasetron, mg	2.79(2.53–2.93)	2.61(2.34–2.76)	0.15(0.09–0.24)	<0.001
Postoperative outcomes				
Time to first ambulation, median (IQR), h	25(23–27)	24(22–27)	1(−1to2)	0.398
Chest tube duration, median (IQR), day	2(2–3)	2(2–3)	0(0–0)	0.846
Duration of hospital stay after surgery, median (IQR), day	4(3–5)	4(3–5)	0(0–0)	0.893
Exploratory analysis				
Area under the curve of pain intensity over 24 h				
At rest	68(38–88)	50(38–78)	28(10–38)	<0.001
During coughing	98(58–126)	70(58–98)	28(18–40)	<0.001
Pain intensity and opioid consumption over 24h (%)				
At rest	52(−85 to132)	−37(−109 to 56)	65(27–109)	0.002
During coughing	62(−85 to133)	−41(−109 to 47)	70(29–115)	<0.001

Notes: Data are expressed as a mean ± standard deviation, median (interquartile range), or number (%).P < 0.05 was considered statistically significant.
Abbreviations: NRS: numeric rating scale; AIS: Athens Insomnia Scale; PSD: postoperative sleep disturbance; HADS-A: Hospital Anxiety and Depression Scale - Anxiety subscale; HADS-D: Hospital Anxiety and Depression Scale - Depression subscale; POD1: postoperative day 1; POD3 postoperative day 3; NE: Neutrophil; IL-6: Interleukin-6.

timepoints (PO8H: MD: −2; 95% CI: −3 to −1; $P < 0.001$; POD1: MD: −1; 95% CI: −2 to −1; $P < 0.001$). Notably, intergroup NRS scores remained comparable at PO4H and POD3 (Table 3, Figure 2A and B).

Generalized Estimating Equations (GEE) were employed to analyze the differences in resting and coughing NRS pain scores between the esketamine and control groups at various postoperative time points (4h, 8h, 1 day, and 3 days). The results revealed a significant main effect of group: the esketamine group exhibited significantly lower pain scores both at rest and during coughing compared to the control group. A significant main effect of time was also observed, indicating that pain scores in both groups decreased over time, with the overall trend being PO8H > POD1 > PO4H > POD3. A significant interaction effect was found between group and time. Post hoc comparisons demonstrated that the esketamine group had significantly superior analgesic effects at 1 day and 8 hours postoperatively compared to the control group, whereas no statistically significant differences were observed between the two groups at 4 hours and 3 days postoperatively (Tables 4–6).

Similarly, the esketamine group showed significantly lower HADS-A (MD: −1; 95% CI: −1 to 0; P =0.004) and HADS-D scores (MD: −1; 95% CI: −2 to −1; P = 0.002) compared with control group at POD1. Moreover, the esketamine group exhibited statistically significant reductions in HADS-D scores compared with the control group on POD3 (MD: −1; 95% CI: −1 to 0; P = 0.015). HADS-A scores revealed comparable intergroup levels at POD3 assessment (Table 3, Figure 2C and D).

On POD1, the esketamine arm demonstrated superior sleep quality profiles, evidenced by significantly reduced median AIS subjective scores compared to controls (MD: −1; 95% CI: −2 to −1; $P < 0.001$). Concurrently, this esketamine group showed a 46.7% reduction in PSD incidence relative to controls (23.5% vs 44.1%; RR: 0.53; 95%

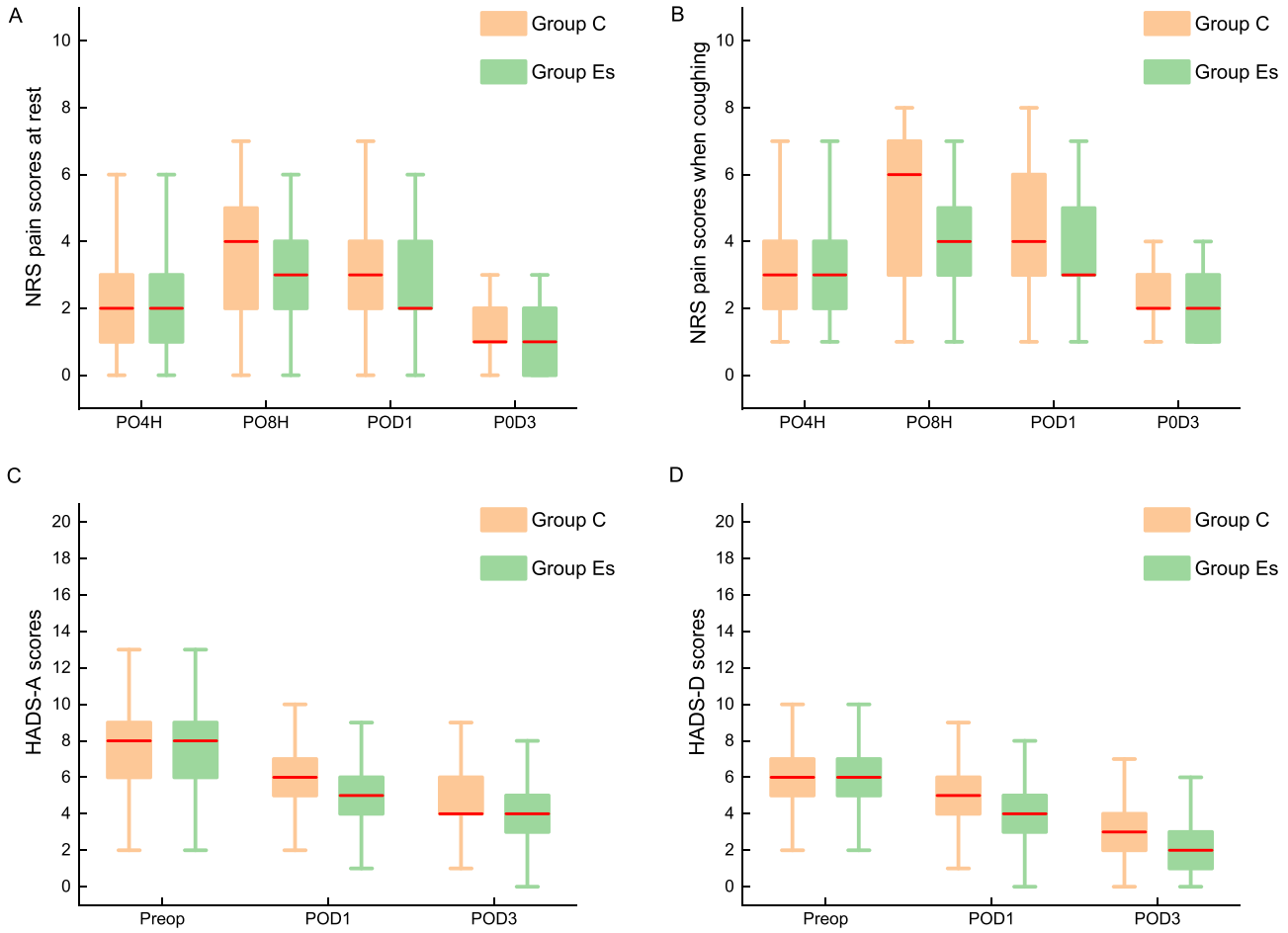

Figure 2 Comparison of NRS pain scores and HADS scores between two groups: (**A**) NRS pain scores at rest; (**B**) NRS pain scores when coughing; (**C**) HADS-A scores; (**D**) HADS-D scores.

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Table 4 The Analysis Results of the GEE Model for the NRS Pain Score

Effect	Wald X^2	df	*P* value
NRS pain scores at rest			
Intercept	419.077	1	<0.001
Group	10.197	1	0.001
Time	543.709	3	<0.001
Group*Time	84.655	3	<0.001
NRS pain scores during coughing			
Intercept	828.849	1	<0.001
Group	12.332	1	<0.001
Time	651.006	3	<0.001
Group*Time	85.727	3	<0.001

Note: NRS = numeric rating scale. Treatment coded as 1 = Saline, 2 = Esketamine; Time coded as 1 = postoperative 4 hour, 2 = postoperative 8 hours; 3 = postoperative 1 days; 4 = postoperative 3 days. The QIC (Quasi-likelihood under the Independence Model Criterion) values were 1186.838 for the resting pain model and 1289.309 for the cough pain model.*P* < 0.05 was considered statistically significant.

Table 5 Estimated Marginal Means of NRS Pain Scores

Time	Group	Emmean	SE	95% CI Lower	95% CI Upper
NRS pain scores at rest					
Postop 4 h	Saline	2.59	0.189	2.22	2.96
	Esketamine	2.15	0.156	1.84	2.45
Postop 8 h	Saline	3.93	0.241	3.45	4.40
	Esketamine	2.62	0.179	2.27	2.97
Postop 1 d	Saline	3.54	0.221	3.11	3.98
	Esketamine	2.35	0.181	2.00	2.71
Postop 3 d	Saline	1.22	0.108	1.01	1.43
	Esketamine	1.12	0.101	0.92	1.32
NRS pain scores during coughing					
Postop 4 h	Saline	3.65	0.197	3.26	4.03
	Esketamine	3.24	0.159	2.92	3.55
Postop 8 h	Saline	5.22	0.259	4.71	5.73
	Esketamine	3.74	0.177	3.39	4.08
Postop 1 d	Saline	4.79	0.234	4.34	5.25
	Esketamine	3.41	0.172	3.08	3.75
Postop 3 d	Saline	2.37	0.130	2.11	2.62
	Esketamine	2.16	0.109	1.95	2.38

Abbreviations: CI, confidence interval; Emmean, estimated marginal mean; SE, standard error; NRS, numeric rating scale.

CI: 0.32–0.88; $P = 0.011$). However, the AIS sleep quality scores and incidence of PSD were not significantly different on POD3 between the groups. Notably, while PSD incidence remained stable compared to preoperative baseline in controls on POD1, the esketamine arm manifested a significant reduction (41.2% vs 23.5%; $P = 0.043$) (Table 3 and Figure 3).

Compared with the control group, the esketamine group showed a significant reduction in both the total volume of PCIA solution consumed and the consumption of its constituent medications, including hydromorphone, betamethasone, and dolasetron. Additionally, the esketamine group exhibited significantly lower levels of interleukin-6 (IL-6) and neutrophil count on POD1 compared to the control group. Hospitalization duration, chest tube indwelling time, and time to first ambulation demonstrated comparable perioperative metrics between groups (Table 3).

Table 6 Post-Hoc Comparisons of NRS Pain Scores Between Groups

Time	Comparison	ΔEmmean	SE	95% CI Lower	95% CI Upper	*P* value
NRS pain scores at rest						
Postop 4 h	Esketamine vs Saline	−0.44	0.245	−1.21	0.32	1.000
Postop 8 h	Esketamine vs Saline	−1.31	0.300	−2.25	−0.37	<0.001
Postop 1 d	Esketamine vs Saline	−1.19	0.285	−2.08	−0.30	0.001
Postop 3 d	Esketamine vs Saline	−0.10	0.148	−0.56	0.36	1.000
NRS pain scores during coughing						
Postop 4 h	Esketamine vs Saline	−0.41	0.253	−1.20	0.38	1.000
Postop 8 h	Esketamine vs Saline	−1.49	0.314	−2.47	−0.51	<0.001
Postop 1 d	Esketamine vs Saline	−1.38	0.290	−2.29	−0.48	<0.001
Postop 3 d	Esketamine vs Saline	−0.21	0.170	−0.74	0.32	1.000

Note: ΔEmmean = difference in estimated marginal mean; *P* values adjusted by Bonferroni method. $P < 0.05$ was considered statistically significant.
Abbreviations: SE, standard error; CI, confidence interval.

Generalized Estimating Equations (GEE) were used to analyze the mean arterial pressure (MAP) and heart rate (HR) of the two patient groups at different time points. The results demonstrated that the main effect of group was not statistically significant, indicating that, overall, there were no significant differences in hemodynamics between the esketamine and normal saline groups. The main effect of time was statistically significant, suggesting that the patients' MAP and HR levels changed significantly over the course of the surgery. More importantly, the group-by-time interaction effect was statistically significant, implying that the effect of esketamine on MAP and HR varied depending on the specific intraoperative time point. Further simple effects analysis (with Bonferroni correction) revealed that significant between-group differences in MAP and HR were observed only at time point T1 (before tracheal intubation). At this time point, both MAP and HR were significantly higher in the esketamine group compared to the normal saline group ($P = 0.014$; $P = 0.035$). At all other measured time points, no significant differences in MAP or HR were found between the two groups (Table 7 and Figure 4).

Analysis of Potential Confounding by PCIA Adjuncts

To address the potential confounding influence of differential exposure to betamethasone and dolasetron resulting from variations in PCIA consumption, post hoc correlation analyses were conducted exclusively within the control group (Table 8). The total consumption of neither betamethasone nor dolasetron showed any statistically significant correlation

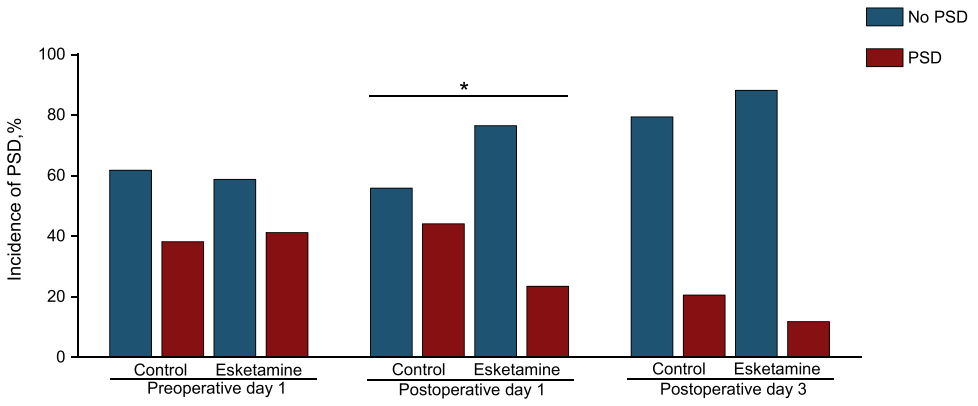

Figure 3 Incidence of Postoperative Sleep Disturbance (PSD) on Preoperative Day 1, Postoperative Day 1, and Postoperative Day 3.
Notes: Statistical significance was set at *$P<0.05$.

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Table 7 The Analysis Results of the GEE Model for the Hemodynamics

Effect	Wald X^2	df	*P* value
MAP			
Intercept	20147.838	1	<0.001
Group	0.053	1	0.818
Time	28010.846	7	<0.001
Group*Time	888.738	7	<0.001
HR			
Intercept	17486.310	1	<0.001
Group	0.262	1	0.608
Time	75172.423	7	<0.001
Group*Time	2595.461	7	<0.001

Notes: MAP = Mean arterial pressure. HR = Heart rate.Treatment coded as 1 = Saline, 2 = Esketamine; Time coded as 0 = prior to anesthesia induction; 1 = before tracheal intubation; 2 = immediately following tracheal intubation; 3 = after conversion to the lateral decubitus position; 4 = 5 minutes after surgical incision; 5 = 30 minutes after surgical incision; 6 = 60 minutes after surgical incision; 7 = at the end of the operation. The QIC (Quasi-likelihood under the Independence Model Criterion) values were 75527.60 for the MAP model and 47320.41 for the HR model. $P < 0.05$ was considered statistically significant.

with sleep quality (AIS scores), anxiety (HADS-A scores), depression (HADS-D scores), or the incidence of PONV at any assessed time point. All correlation coefficients were negligible, and all p-values were well above the threshold for statistical significance.

We observed that the correlation results for betamethasone and dolasetron with various outcome measures were completely consistent. This consistency represents a mathematical inevitability inherent in our experimental design, as both adjuvants were administered in a fixed ratio via the analgesic pump; therefore, each patient's exposure to these agents was determined by a single variable—the total number of pump activations. As a result, any correlation analysis involving either drug and a clinical outcome is mathematically equivalent to an analysis of the relationship between total pump activations and that outcome.

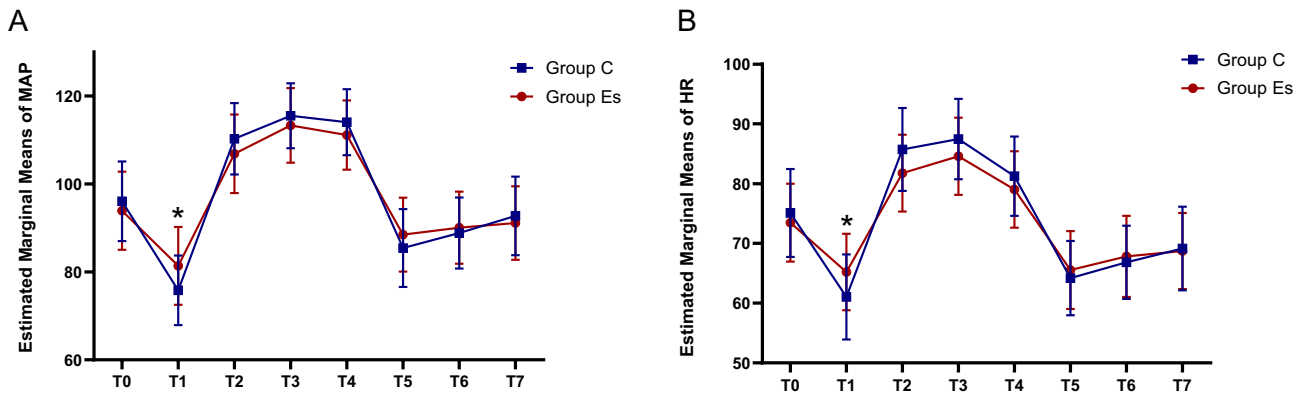

Figure 4 Estimated Marginal Means of MAP and HR over Time by Group Using GEE: (**A**) MAP; (**B**) HR.
Notes: (T0) prior to anesthesia induction; (T1) before tracheal intubation; (T2) immediately following tracheal intubation; (T3) after conversion to the lateral decubitus position; (T4) 5 minutes after surgical incision; (T5) 30 minutes after surgical incision; (T6) 60 minutes after surgical incision; (T7) the end of the operation. Statistical significance was set at *P<0.05.

Table 8 Correlation Between Exposure to Analgesic Pump Adjuvants (Betamethasone and Dolasetron) and Sleep, Negative Emotions, and Vomiting in the Control Group (n=68)

Outcome Measure	Statistical Test	Correlation Coefficient	*P* value
Sleep Quality			
AIS Score on POD1	Spearman's rank	0.079	0.524
AIS Score on POD3		0.094	0.447
Anxiety			
HADS-A Score on POD1	Spearman's rank	0.078	0.529
HADS-A Score on POD3		0.024	0.846
Depression			
HADS-D Score on POD1	Spearman's rank	0.104	0.400
HADS-D Score on POD3		0.132	0.282
PONV Incidence	Point-Biserial	0.010	0.934

Note: The correlation coefficients and p-values for betamethasone and dolasetron are identical.*P* < 0.05 was considered statistically significant.

Exploratory Outcomes Analyses

Compared with the control group, both the AUC of pain intensity over 24h, measured at rest (MD: −28; 95% CI: −38 to −10; $P < 0.001$) and during coughing (MD: −28; 95% CI: −40 to −18; $P < 0.001$), and the PIOC within 24h, measured at rest (MD: −65%; 95% CI: −109% to −27%; P=0.002) and during coughing (MD: −70%; 95% CI:−115% to−29%; $P < 0.001$), were markedly reduced in the esketamine group (Table 3).

The Logistic Regression Model

A logistic regression model was employed to identify risk factors associated with moderate to severe postoperative pain. The analysis revealed that preoperative anxiety (OR, 2.69; 95% CI, 1.13–6.40; $P = 0.026$) and duration of surgery (OR, 1.03; 95% CI, 1.01–1.04; $P < 0.001$) were significant predictors. Notably, intraoperative administration of esketamine was identified as a protective factor (OR, 0.39; 95% CI, 0.16–0.91; $P = 0.029$) (Figure 5).

Incidence of Adverse Events

The esketamine group exhibited a significantly reduced incidence of PONV compared to the control group (16.2% vs 30.9%; $P = 0.043$). Apart from PONV, no notable differences between the groups were found in terms of other adverse events (Table 9).

Variable	Univariate analysis		Multivariate analysis	
	OR(95% CI)	*P* value	OR(95% CI)	*P* value
Age，per y	1.066(0.994-1.143)	0.075	1.020(0.936-1.112)	0.646
Duration of surgery，per min	1.016(1.009-1.023)	＜0.001	1.025(1.014-1.036)	＜**0.001**
Surgical type		0.085		0.249
Surgical type(1)	1.944(0.824-4.590)	0.129	0.364(0.107-1.236)	0.105
Surgical type(2)	2.644(1.102-6.343)	0.029	0.362(0.086-1.535)	0.168
Preoperative anxiety	2.333(1.155-4.713)	0.018	2.687(1.128-6.403)	**0.026**
Preoperative depression	1.406(0.580-3.412)	0.451	2.186(0.757-6.317)	0.148
Preoperative sleep disorders	2.358(1.129-4.925)	0.022	2.281(0.945-5.507)	0.067
Esketamine use	0.474(0.235-0.955)	0.037	0.385(0.164-0.908)	**0.029**

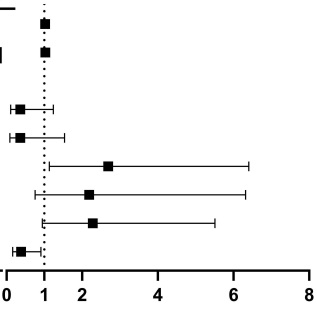

Figure 5 Logistic regression model to predict postoperative moderate-to-severe pain.
Note: Statistical significance was set at *P* <0.05. Significant results are in bold. Pseudo $R^2 = 0.415$; the overall model was statistically significant ($P < 0.001$). C-statistic = 0.706, indicating good discriminative ability of the model. The Hosmer-Lemeshow goodness-of-fit test ($P = 0.794$) indicated that the model demonstrates a good fit.

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Table 9 Postoperative Adverse Events

	Control group(n=68)	Esketamine group(n=68)	*P* value
Nausea and Vomiting	21(30.9)	11(16.2)	0.043
Delirium	7(10.3)	6(8.8)	0.771
Psychotomimetic reactions			
Hallucinations	1(1.5)	2(2.9)	1.000
Nightmares	4(5.9)	6(8.8)	0.511
Confusion and disorientation	3(4.4)	2(2.9)	1.000

Note: $P < 0.05$ was considered statistically significant.

Discussion

For elderly patients undergoing thoracoscopic lung resection, intravenous administration of a subanesthetic dose of esketamine during surgery can reduce the proportion of moderate to severe pain on POD1. It concurrently reduced sleep disturbances, improved anxiety and depression scores, decreased opioid consumption without increasing neuropsychiatric adverse events. Thus, incorporating esketamine as a component of multimodal analgesia is recommended for this patient group.

The main findings showed a 25.5% relative reduction in moderate-to-severe pain among esketamine-treated patients versus controls, a difference that was statistically significant. Although this result falls below the previously reported minimal clinically important difference (MCID) threshold of 35% derived from studies in younger and middle-aged populations,[4,5] directly extrapolating this threshold to elderly patients lacks scientific justification due to distinct physiological profiles, pharmacokinetic responses, therapeutic goals, and risk-benefit ratios. Moreover, no high-quality evidence establishing an MCID specific to the geriatric population currently supports the application of this 35% threshold.

Consequently, we further analyzed the practical clinical value of the 25.5% relative reduction in moderate-to-severe pain incidence. The calculated number needed to treat (NNT) was 5.7 (approximately 6), indicating that for every 6 elderly patients treated, one additional case of moderate-to-severe pain could be prevented. Furthermore, compared with the dichotomous primary outcome measure, continuous variables (NRS scores) more accurately capture patient benefit, with a median reduction ≥1 point being clinically meaningful. The 24h AUC and PIOC are metrics that more accurately reflect the cumulative burden of postoperative pain and the dynamic nature of analgesic drug efficacy.[28,29] Collectively, the ≥1-point reductions in NRS scores at both PO8H and POD1 coupled with significant improvements in 24h AUC and PIOC metrics provide robust evidence confirming the definitive clinical value of this intervention.

A randomized controlled trial demonstrated that adding esketamine to patient-controlled analgesia (PCA) in middle-aged patients reduced the incidence of moderate-to-severe pain after thoracoscopic surgery by up to 43.1%.[5] The 25.5% pain reduction observed in our study was lower than that in the middle-aged cohort (43.1%), potentially attributable to age-related decline in NMDA receptor function leading to reduced drug sensitivity,[33,34] combined with intraoperative bolus administration (vs postoperative PCA infusion) resulting in limited duration of analgesic coverage. Although postoperative PCA infusion of esketamine may further reduce moderate-to-severe pain, continuous administration increases risks of sedation and neuropsychiatric adverse effects in the elderly. Consequently, intraoperative dosing offers a superior safety profile for this population.

Esketamine markedly improved sleep quality on POD1, a finding consistent with prior studies.[19,35] Pain relief served as the primary contributor to sleep improvement,[36] with esketamine effectively breaking the "pain-sleep disturbance" vicious cycle through its analgesic action. Beyond this, it is plausible that esketamine's influence on circadian rhythms and neural circuits involved in sleep regulation, as suggested by previous research,[37,38] might have contributed to the improved sleep quality. However, this remains a testable hypothesis for future studies designed with objective sleep measures (eg, polysomnography) and specific biomarker analyses. Patients receiving esketamine also demonstrated improved postoperative emotional status, as evidenced by HADS scores. We postulate that this improvement is likely contributed to by multiple factors, with pain relief potentially serving as the primary contributor.

The observed reduction in levels of pro-inflammatory markers (IL-6 and neutrophil count) in the esketamine group aligns with its anti-inflammatory properties. The anti-inflammatory mechanism of esketamine is multifactorial.[39–41] It acts as a non-competitive NMDA receptor antagonist, suppressing central sensitization and reducing excitatory glutamate-mediated neuroinflammation. Furthermore, esketamine inhibits microglial activation, downregulates the NF-κB/TLR4 signaling pathway and the NLRP3 inflammasome, thereby diminishing pro-inflammatory cytokine production. An indirect anti-inflammatory effect may also result from its opioid-sparing properties. This systemic anti-inflammatory state may contribute to attenuating peripheral and central sensitization, thereby reducing postoperative pain and possibly mitigating neuroinflammation-related mood and cognitive disturbances. Although our study was not designed to elucidate the precise molecular mechanisms, the observed reductions in IL-6 and neutrophil counts provide clinical evidence supporting an anti-inflammatory component of esketamine's mechanism within a multimodal enhanced recovery framework.

We observed a transient elevation in mean arterial pressure (MAP) and heart rate (HR) before intubation, attributable to esketamine's sympathomimetic effects. This mild pressor effect may be beneficial as it effectively counteracts induction-related hypotension. This is particularly relevant for elderly patients with diminished cardiocerebrovascular reserve.

Esketamine demonstrated a significant opioid-sparing effect, which was consistently evidenced by reduced intraoperative remifentanil consumption and decreased postoperative hydromorphone requirements. The reduced incidence of PONV in the esketamine group is likely attributable to this opioid-sparing effect. This finding holds particular importance for elderly patients seeking to minimize opioid-related adverse effects.[42]

This study closely monitored potential adverse reactions associated with esketamine, particularly psychotomimetic reactions (eg, hallucinations, nightmares and confusion and disorientation). The results indicated that no statistically significant differences were observed between the groups regarding other adverse events, except for PONV. Notably, this finding contrasts with a previous study suggesting an increased risk of dissociative symptoms with esketamine in elderly patients undergoing laparoscopic abdominal surgery.[43] The absence of increased psychiatric symptoms observed in the present study may be associated with the following factors: a stringent exclusion criterion: patients with a history of psychiatric disorders were excluded; an optimized dosing regimen: intraoperative continuous infusion at a subanesthetic dose (0.25 mg/kg), avoiding rapid peak concentrations; and potential individual susceptibility differences. Given these factors and potential population differences, future studies with larger sample sizes are warranted to further validate the safety profile of esketamine in the elderly population.

A key strength of this study design is the adoption of a standardized multimodal PCIA protocol, which enhances the generalizability of the findings. Moreover, in elderly patients, the benefits afforded by multimodal PCIA may far outweigh the potential risks associated with low-dose glucocorticoids. However, it introduced a theoretical concern that the opioid-sparing effect of esketamine could lead to reduced concurrent exposure to the adjuncts (betamethasone and dolasetron), which might themselves influence the secondary outcomes. Our post hoc analyses within the control group effectively mitigate this concern. The unequivocal lack of correlation between the exposure to either adjunct and all measured outcomes provides robust evidence that the observed improvements in sleep, mood, and PONV in the esketamine group are unlikely to be mediated by differential adjunct exposure. This strengthens the inference that the benefits are indeed attributable to the biological effects of esketamine itself.

Several limitations exist in this study. Firstly, the short follow-up duration of this study precludes a comprehensive understanding of the long-term trajectory of these parameters, necessitating further validation through extended follow-up periods in future research. Secondly, Our study did not employ bispectral index (BIS) monitoring for precise quantification of anesthetic depth. Although we ensured a standardized anesthetic protocol and comparable hemodynamic profiles between groups, future studies incorporating objective depth-of-anesthesia monitoring would provide greater robustness to the findings. Finally, the assessment of sleep quality and emotional states primarily relies on questionnaire-based evaluations, without incorporating objective measures such as polysomnography or biomarkers. This dependence on subjective assessments is prone to bias, and future studies should integrate both subjective and objective methodologies for further validation.

Conclusion

In summary, for elderly patients undergoing thoracoscopic lung surgery, a continuous intraoperative infusion of esketamine with a loading dose of 0.25 mg/kg followed by a maintenance dose of 0.25 mg/kg/h appears to be an effective and safe regimen within a multimodal analgesia strategy. This regimen effectively reduced the incidence of moderate-to-severe pain on the first postoperative day, improved sleep quality and emotional status, decreased the demand for opioids, without increasing neuropsychiatric adverse events. We recommend this dosing and timing strategy as a reference for future clinical practice and guideline development targeting this vulnerable population.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article. The datasets may be made available from the corresponding author, Professor. Lidong Zhang, upon reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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