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CLINICAL TRIAL REPORT

The Effects of Low-Dose Esketamine Combined with Paravertebral Block on Postoperative Hyperalgesia and Enhanced Recovery in Non-Intubated Video-Assisted Thoracic Surgery: A Randomized Controlled Trial

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Purpose: Non-intubated video-assisted thoracic surgery (NIVATS) reduces airway trauma but may lead to postoperative hyperalgesia and opioid dependence, contradicting enhanced recovery after surgery (ERAS) principles. We hypothesized that combining low-dose esketamine with a paravertebral block (PVB) may mitigate hyperalgesia, decrease opioid requirements, and improve recovery quality in NIVATS.

Patients and Methods: This prospective single-center, double-blind randomized controlled trial (RCT) enrolled 82 patients undergoing uniportal NIVATS. Patients were randomized into two groups: esketamine (0.25 mg/kg pre-induction + 0.15 mg/kg/h intraoperatively) and control. Both groups received ultrasound-guided T4 and T6 PVB (with 0.375% ropivacaine). The primary outcome was mechanical pain threshold (MPT; central/peripheral), quantified preoperatively and at 0.5–48 h postoperatively using pressure algometry after laryngeal mask airway (LMA) removal. Secondary outcomes included quality of recovery-40 (QoR-40) scores, intraoperative sufentanil/norepinephrine use, postoperative rescue analgesia use, and other related complications.

Results: Compared to controls, the esketamine group exhibited significantly higher MPT at 6 h postoperatively (central: 2.77 ± 0.80 vs 2.17 ± 0.59 kgf/cm², $P < 0.001$; and peripheral: 2.95 ± 0.89 vs 2.17 ± 0.62 kgf/cm², $P < 0.001$). It also showed markedly improved QoR-40 scores (POD1: 182.3 ± 6.0 vs 175.8 ± 7.2, $P < 0.001$; and POD3: 190.3 ± 2.9 vs 186.8 ± 3.6, $P < 0.001$). Compared to controls, the esketamine group also showed significantly lower intraoperative sufentanil consumption (median 5.0 vs 17.5 μg) and norepinephrine requirement (219.1 ± 124.7 vs 393.7 ± 182.3 μg), as well as postoperative rescue analgesia use ($P < 0.05$). Except for postoperative nausea and vomiting (PONV) incidence ($P < 0.05$), both groups had similar profiles in other adverse events.

Conclusion: Low-dose esketamine combined with PVB attenuates postoperative hyperalgesia, reduces intraoperative opioid use by 71.4%, and enhances recovery in NIVATS, offering a clinically effective opioid-sparing strategy for ERAS protocols.

Keywords: esketamine, non-intubated video-assisted thoracic surgery, paravertebral block, postoperative hyperalgesia, multimodal analgesia, ERAS

Introduction

Compared to conventional intubation techniques, non-intubated video-assisted thoracic surgery (NIVATS) offers more clinical utility in minimizing airway trauma, ventilator-induced lung injury, and postoperative recovery time.[1] Nonetheless, it poses unique pain management challenges. Specifically, continuous intraoperative diaphragmatic

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movement and pleural manipulation have been established to enhance peripheral injurious signaling, while the lack of controlled ventilation could result in limited use of analgesic medications, further exacerbating the central sensitization of pain signals.[2] Yu et al reported that up to 75% of NIVATS patients experience moderate to severe postoperative pain within 48 h of surgery, a phenomenon often exacerbated by opioid-induced hyperalgesia (OIH) and central sensitization.[3]

Thoracic surgery activates dual nociceptive pathways, exacerbating acute pain and chronic pain risk.[4] Although effective, traditional opioid-centered treatments have been associated with respiratory depression, postoperative nausea and vomiting (PONV), and delayed recovery, phenomena that conflict with the goals of enhanced recovery after surgery (ERAS).[5] Consequently, multimodal analgesia is critical for NIVATS. Evidence suggests that NIVATS requires higher intraoperative opioid doses to suppress stress responses compared to intubated procedures, potentially increasing the risk of OIH and PONV.[6] Based on these insights, developing opioid-sparing strategies for NIVATS could be imperative.

Esketamine is an NMDA receptor antagonist that attenuates OIH and central sensitization while exerting anti-inflammatory effects, attributes that make it a promising adjunct.[7] In recent randomized trials, low-dose esketamine (0.25–0.5 mg/kg) was found to reduce postoperative opioid consumption by 30–50% in patients who underwent abdominal and orthopedic surgeries, without significant psychomimetic side effects.[8,9] However, its role in NIVATS, especially in combination with other regional techniques such as Paravertebral Blocks (PVBs), is yet to be fully explored. As a major thoracic analgesia, PVBs suppress afferent nociceptive signals at thoracic nerve roots, offering targeted somatic and visceral pain relief.[10,11] While PVBs alone might reduce postoperative opioid requirements, their synergy with systemic NMDA antagonists in mitigating hyperalgesia in NIVATS patients is yet to be validated. Multimodal analgesic interventions encompassing regional techniques and systemic adjuvants are increasingly being advocated in ERAS protocols.[12,13] Preclinical evidence suggests that NMDA receptor blockades disrupt pain signal amplification at the spinal and supraspinal levels, potentiating the effects of regional anesthesia.[14] This synergistic effect was clinically observed in thoracoscopic surgery, where esketamine combined with epidural analgesia significantly decreased pain scores and opioid dosage.[15] Nevertheless, the efficacy of esketamine + PVB in NIVATS patients is yet to be explored, particularly in preserving spontaneous respiration and early mobility, thus optimizing pain control with minimal sedation.

In this randomized controlled trial (RCT), we hypothesized that the dual mechanisms of esketamine (central sensitization inhibition) and PVB (peripheral nociceptive blockade) could simultaneously reduce hyperalgesia, decrease opioid reliance, and accelerate functional recovery, thus providing a novel strategy for ERAS pathways in thoracic surgery. To our knowledge, this is the first RCT to investigate the efficacy of low-dose esketamine combined with PVB in NIVATS—a model demanding precise analgesia-respiration balance.

Materials and Methods

Study Design and Ethics

This single-center, randomized, double-blind, placebo-controlled trial involved NIVATS patients recruited from the Third Affiliated Hospital of Chongqing Medical University between October 10, 2024 (first patient enrolled) and February 26, 2025. The study protocol was approved by the Ethics Committee of the Third Affiliated Hospital of Chongqing Medical University (Approval No. 2024-KL-051) on July 8, 2024 and submitted to the Chinese Clinical Trial Registry (Registration Number: ChiCTR2400090516; October 8, 2024). All participants provided written informed consent; the CONSORT (Consolidated Standards of Reporting Trials) guidelines were followed; and the study was conducted in accordance with the Declaration of Helsinki.

Participants

The inclusion criteria were: (1) Patients aged 18–65 years; (2) Patients with American Society of Anesthesiologists (ASA) physical status I–II; (3) Patients with a body mass index (BMI) ranging between 18 and 25 kg/m²; and (4) Patients scheduled for elective single-port NIVATS (eg, wedge resection, segmentectomy, or lobectomy). Patients with abnormal airway anatomy, chronic pain syndromes, psychiatric disorders, high intracranial pressure, chronic opioid use, severe cardiopulmonary dysfunction, or contraindications to PVB were excluded.

Randomization and Blinding

Based on a simple randomized sequence generated by an independent statistician using SPSS 25.0, the patients were assigned to two groups (1:1 ratio): esketamine or control. Sequentially numbered, opaque, sealed envelopes containing group assignments were prepared by this statistician. On the surgery day, a designated anesthesia nurse (who was not involved in patient care or data collection) opened the envelope prior to anesthesia induction and prepared the corresponding solution: the esketamine group [esketamine (2 mL: 50 mg, Jiangsu Hengrui) diluted to 2.5 mg/mL with normal saline (total 20 mL/syringe)] or the control group [identical volume (20 mL) of 0.9% saline placebo]. All solutions were prefilled into identical 20 mL syringes (Brand: WEGO, Model: 20 mL), labeled only with patient ID, and covered by opaque tape to mask contents. Patients, surgeons, anesthesiologists, outcome assessors, and postoperative staff remained blinded throughout the trial. The nurse who prepared solutions was not involved in the subsequent activities of the study.

Intervention Protocol and Perioperative Management

A standardized monitoring approach was employed, encompassing electrocardiography (ECG), pulse oximetry (SpO_2), end-tidal carbon dioxide ($EtCO_2$), invasive radial arterial pressure (IAP), and bispectral index (BIS). Before anesthesia induction, the esketamine group was intravenously administered esketamine (0.25 mg/kg for 5 min), followed by a continuous infusion at 0.15 mg/kg/h until skin closure. On the other hand, the controls received an equivalent volume of 0.9% saline at matching time points. Induction was achieved via sequential intravenous administration of midazolam (0.05 mg/kg), propofol (1.5–2.5 mg/kg), remifentanil (2 μg/kg), and cisatracurium (0.05 mg/kg). Laryngeal mask airway (LMA) placement was performed at BIS = 45–60. Approximately 30 min before anesthesia induction, 15 mL of 0.375% ropivacaine (total 30 mL) was injected at each of the T4 and T6 levels on all patients' operative sides under ultrasound guidance. An attending anesthesiologist qualified in ultrasonography (having performed ≥ 30 PVBs) conducted all PVB procedures. PVB-related complications were systematically recorded at 12, 24, and 48 h postoperatively, using a standardized checklist protocol. The recorded complications included local hematoma formation, nerve injury, local infection, paraspinal muscle pain, and block failure (defined as a >20% increase in heart rate [HR]/pulse rate during skin incision). Patients were given a slow infusion of dexmedetomidine (0.6 μg/kg) for 15 min after the PVB was performed, followed by a maintenance infusion at 0.5 μg/kg/h until the end of the procedure. Propofol (target plasma concentration: 1.6–2 μg/mL) with remifentanil (0.05–0.08 μg/kg/min) was continuously infused while dexmedetomidine was administered, and the BIS was controlled between 45 and 60. All patients received standardized postoperative patient-controlled intravenous analgesia (PCIA), comprising sufentanil (2 μg/kg) and tropisetron (5 mg) diluted in normal saline to a total volume of 100 mL. The pump was programmed with a continuous basal infusion rate of 2 mL/h, a bolus dose of 1 mL/demand, and a 15 min lockout interval. Rescue analgesia with intramuscular tramadol (100 mg/dose) was administered as needed within 72 hours postoperatively, based on the individualized pain assessment results.

A 4-cm incision was made in the fourth or fifth intercostal space in the mid-axillary line and adjusted according to the lung lobe in which the lesion was located (upper versus middle/lower lobes). The procedure was supplemented with an intrathoracic vagus nerve block (4 mL of 1% lidocaine). A 16-Fr gastric tube was placed postoperatively as a closed drainage system.

Anesthesia depth was dynamically adjusted based on real-time monitoring. Specifically, propofol infusion rates were increased at BIS > 60 while maintaining stable hemodynamics (systolic blood pressure [SBP] ≥ 90 mmHg and HR 50–100 beats per min [bpm]). For BIS values between 45 and 60 accompanied by elevated mean arterial pressure [MAP] (> 20% above baseline), HR ≥ 100 bpm, or respiratory rate (RR) ≥ 16 breaths/min, remifentanil infusion rates were increased, with supplemental sufentanil boluses (0.05–0.1 μg/kg) also administered if analgesia remained inadequate. At an RR ≤ 6 breaths/min, hand-controlled assisted ventilation was initiated, and the propofol infusion rate was adjusted downward. Persistent hypoxia (SpO_2 < 90% lasting for > 2 min and unresponsive to oxygenation) or hypercapnia ($ETCO_2 \geq 80$ mmHg) mandated conversion to double-lumen endotracheal intubation with controlled ventilation, possibly leading to study exclusion. Hemodynamic interventions included atropine (0.3–0.5 mg IV) for bradycardia (HR < 50 bpm) and norepinephrine boluses (4–8 μg IV), followed by continuous infusion (0.01 μg/kg/min) for refractory

hypotension (SBP < 90 mmHg lasting > 2 min). Furthermore, conversion to intubated general anesthesia was required for uncontrolled massive hemorrhage or severe mediastinal oscillation that could compromise surgical progress.

Outcome Measures

Mechanical pain threshold (MPT) was assessed preoperatively and at 30 min, 6, 24, and 48 h following LMA removal using a handheld pressure algometer (YIISDA-DS2; Hong Kong, China). The device was calibrated daily with certified weights (500 g, 1 kg, and 5 kg) in accordance with ISO 6789:2017 standards, ensuring a maximum deviation of less than 2% to maintain measurement validity. All MPT measurements were performed by trained investigators following a standardized protocol. Prior to the study, the investigators completed a training program involving 10 pilot cases to ensure consistent measurement techniques. To minimize bias, the algometer display was remained concealed during measurements and was only revealed at the end of each test. Measurements were performed at the non-dominant forearm (3, 5, and 7 cm proximal to the anterior elbow joint) and peri-incisional area (5 cm left lateral, right lateral, and ventral to the incision site in supine positioning). The mean of three measurements near each location was taken as the primary measure.

Secondary measures included the quality of early postoperative recovery [assessed using the Quality of Recovery-40 (QoR-40) scale on PODs 1 and 3] and sleep quality [assessed using the Pittsburgh Sleep Quality Index (PSQI) scale on preoperative day 1 and POD3]. Hemodynamic parameters (MAP and HR), arterial blood gas values [partial pressure of oxygen (PaO_2) and carbon dioxide ($PaCO_2$)], and the cumulative consumption of opioids and norepinephrine during surgery were also monitored.

Postoperative outcome metrics included time to LMA removal, length of post-anesthesia care unit (PACU) stay, numerical rating scale (NRS)-quantified patient pain intensity at 30 min, 6, 12, 24, and 48 h after LMA removal, time to first postoperative compression of the PCIA device, total number of compressions, and number of effective compressions; and the systematic assessment of the incidence of postoperative complications (including PONV, excessive sedation [Ramsay score ≥4], dizziness, drowsiness, delirium [CAM-assessed], nightmares, and hallucinations).

Statistical Analysis and Data Management

Following the intention-to-treat principle, statistical analyses and figure generation were performed using SPSS 25.0 (IBM Corp., USA) and GraphPad Prism 10.0 (GraphPad Software, USA). The normality of continuous variables was assessed using the Shapiro–Wilk test. Normally distributed data were presented as mean ± standard deviation (x ± s) and compared using independent Student's t-tests. On the other hand, non-normally distributed data were reported as median (interquartile range [IQR]) and analyzed using Mann–Whitney *U*-tests. Categorical variables were expressed as counts (n) and percentages and compared using χ^2 or Fisher's exact tests, as appropriate. Odds ratios (OR) with 95% confidence intervals (CIs) were calculated for dichotomous safety indicators, rescue analgesia requirements, and postoperative adverse events (AEs). Between-group differences in repeated measures were evaluated using mixed-effects models, with Bonferroni correction employed for multiple comparisons.

Sample size determination was performed using data from a pre-test involving 16 NIVATS patients from our institution. The key measure was MPT at 6 h postoperatively. The difference in mean MPT between the two groups was 0.72 kgf/cm² (standard deviation = ±0.68). Using G Power 3.1 and a two-tailed independent Student's *t*-test, an effect size (Cohen's d) of 0.82 was derived from the pre-experimental data. Considering a significance level (α) of 0.05, a power (1-β) of 0.80, and a 1:1 allocation ratio, a minimum of 35 patients was required per group, which rose to 41 (82 patients in total) after accounting for a potential loss rate of 15%. The sensitivity analysis confirmed that the adjusted sample size maintained a power of 0.80. Furthermore, a post hoc power analysis using effect sizes observed in the pre-experiment and the final analyzable cohort (n = 79) confirmed a power of 84.3% (α = 0.05), validating the adequacy of the sample size. Missing data (<5% of all observations) were addressed via multiple imputation by chained equations (MICE).

Two independent investigators performed double data entry and validation, and protocol deviations and dropouts were documented and analyzed via the intention-to-treat approach. All analyses adhered to CONSORT guidelines. All tests were two-sided, and results or differences with $P < 0.05$ were considered statistically significant.

Results

Participant Flow and Baseline Characteristics

A total of 97 patients were initially enrolled, among whom 8 were excluded as they did not meet the criteria, 5 declined to participate, and 2 refused to receive PICA. The remaining 82 patients were randomized and assigned to two groups (N=41/group). Three patients were further excluded post-randomization (1 in the esketamine group due to conversion to thoracotomy and 2 in the control group for hypercapnia [$ETCO_2$ > 80 mmHg] and refractory severe mediastinal swing); hence, only 79 participants were included in the final analysis [Esketamine Group (n=40) and Control Group (n=39)]. (Figure 1). Demographic and perioperative data, including age, gender, BMI, smoking status, history of hypertension and diabetes mellitus, surgical procedure type, operative duration (min), anesthesia time (min), time to LMA removal postoperatively (min), PACU stay (min), postoperative hospitalization duration (days), and hospitalization expenses (CNY), were systematically collected (Table 1). There were no significant intergroup differences in these baseline characteristics (all $P > 0.05$).

Primary Outcomes

Esketamine + PVB significantly reduced postoperative hyperalgesia. Compared to the control group, the esketamine group demonstrated a higher MPT on the non-dominant forearm at 6 h (2.77 ± 0.80 vs 2.17 ± 0.59 kgf/cm², $P < 0.001$) and 24 h (2.43 ± 0.68 vs 2.10 ± 0.54 kgf/cm², $P < 0.05$) postoperatively (Figure 2a), and similarly showed higher MPT in the peri-incisional area at 6 h (2.95 ± 0.89 vs 2.17 ± 0.62 kgf/cm², $P < 0.001$) and 24 h (2.32 ± 0.62 vs 1.93 ± 0.61 kgf/cm², $P < 0.01$) (Figure 2b).

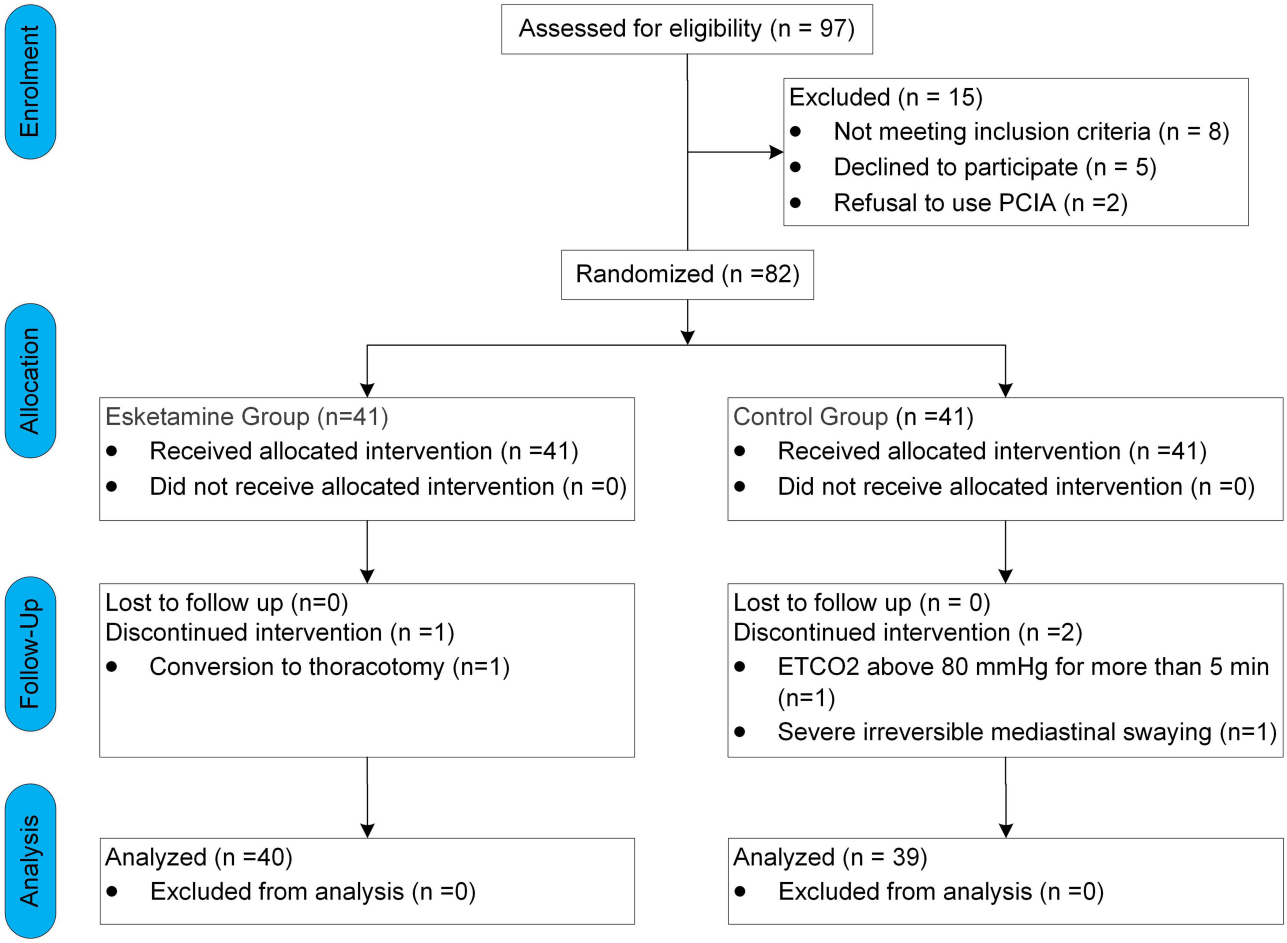

Figure 1 CONSORT 2010 flow diagram illustrating patient enrollment.

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Table 1 Baseline Characteristics of Patients

	All Patients (n=79)	Esketamine Group (n=40)	Control Group (n=39)	*P*-Value
Age (years)	56 (45.0–62.0)	55.5 (45.0–62.8)	56.0 (46.0–60.0)	0.735
Gender (male)	31 (39.2%)	16 (40.0%)	15 (38.5%)	0.889
BMI (kg/m²)	23.5 (21.9–24.4)	23.5 (21.8–24.3)	23.4 (21.9–24.4)	0.780
ASA I/II	18 (22.8%)/61 (77.2%)	11 (27.5%)/29 (72.5%)	7 (17.9%)/32 (82.1%)	0.312
Ever smoked	21 (26.6%)	10 (25.0%)	11 (28.2%)	0.591
Hypertension	14 (17.7%)	6 (15.0%)	8 (20.5%)	0.521
Diabetes	9 (11.4%)	5 (12.5%)	4 (10.3%)	0.754
Surgical procedure				0.708
Wedge resection	52 (65.8%)	28 (70.0%)	24 (61.5%)	
Segmentectomy	17 (21.5%)	8 (20.0%)	9 (23.1%)	
Lobectomy	10 (12.7%)	4 (10.0%)	6 (15.4%)	
Surgery time (min)	90.2 (34.2)	85.2 (35.4)	95.4 (32.7)	0.186
Anaesthesia time (min)	128.8 (33.1)	124.3 (33.3)	133.5 (32.6)	0.218
Time to LMA removal (min)	7 (5–15)	6 (5–10)	10 (5–15)	0.194
Length of stay PACU (min)	55 (45–60)	55 (45–60)	55 (45–70)	0.471
Norepinephrine consumption (μg)	305.0 (178.0)	219.1 (124.7)	393.7 (182.3)	<0.001[a]
Remifentanil consumption (μg)	334.9 (119.0)	314.9 (118.2)	355.4 (118.0)	0.132
Sufentanil consumption (μg)	12.5 (5.0–17.5)	5.0 (0.0–9.5)	17.5 (15.0–20.0)	<0.001[a]
Postoperative hospitalization duration (d)	5 (4–6)	5 (4–5)	5 (4–7)	0.191
Postoperative hospitalization expenses (CNY)	4944.7 (4166.9–6145.6)	4948.6 (4260.4–6039.0)	4900.0 (4060.8–6178.5)	0.875

Notes: Data are presented as mean ± SD, median with IQR, or number (percentage). [a]$P < 0.001$.
Abbreviations: ASA, American Society of Anesthesiologists; LMA, laryngeal mask airway; BMI, Body Mass Index; PACU, Post-anesthesia Care Unit; CNY, Chinese Yuan.

Secondary Outcomes

Compared to the control group, the esketamine group demonstrated significantly lower NRS scores at 12 and 24 h post-LMA removal (median: 2 vs 3, $P < 0.01$) (Figure 2c). The esketamine group also showed significantly improved hemodynamic stability, required less intraoperative norepinephrine administration (219.1 ± 124.7 vs 393.7 ± 182.3 μg, $P < 0.001$). The benefits of blood flow stabilization in terms of MAP were observed at multiple vital perioperative stages, including at 1 min after LMA insertion (89 ± 9.8 mmHg vs 82 ± 7.9 mmHg, $P < 0.01$) and at the end of the procedure (84 ± 7.5 mmHg vs 78 ± 6.4 mmHg, $P < 0.001$). In contrast, HR was consistently comparable between groups at all measured points (Figures 3a and b). Additionally, the esketamine group showed improved intraoperative respiratory stability, as evidenced by lower $PaCO_2$ levels at various critical time points. At 30 min post-LMA removal, $PaCO_2$ was significantly lower in the esketamine group than in the control group (58.2 ± 6.0 vs 63.4 ± 8.0 mmHg, $P < 0.01$), suggesting improved alveolar ventilation and reduced respiratory depression. In

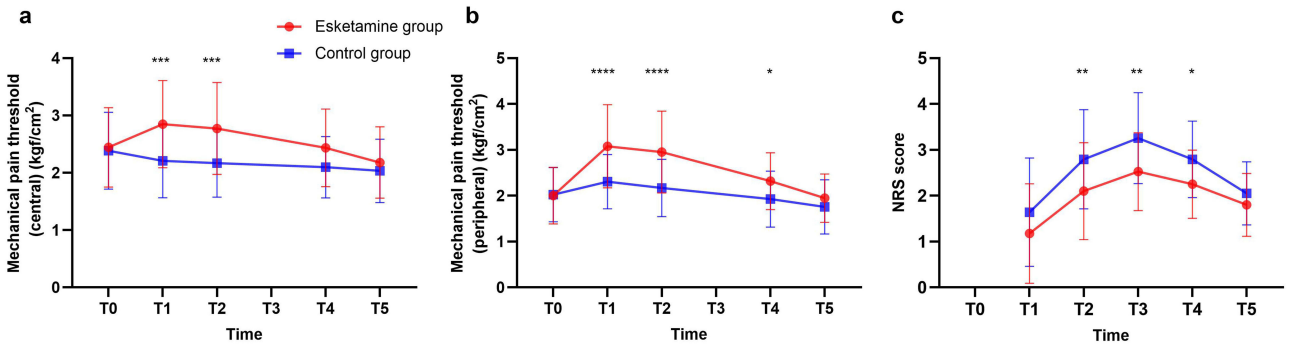

Figure 2 Mechanical pain threshold (MPT) and numeric rating scale (NRS) scores. (**a**) Central MPT (nondominant forearm); (**b**) Peripheral MPT (peri-incisional area); (**c**) NRS scores. Time points (T0: pre-induction; T1–T5: 30 min, 6, 12, 24, 48 h after laryngeal mask airway (LMA) removal). Data are represented as mean ± SD. Compared with the control group, *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$ (two-way repeated-measures ANOVA with Bonferroni correction).

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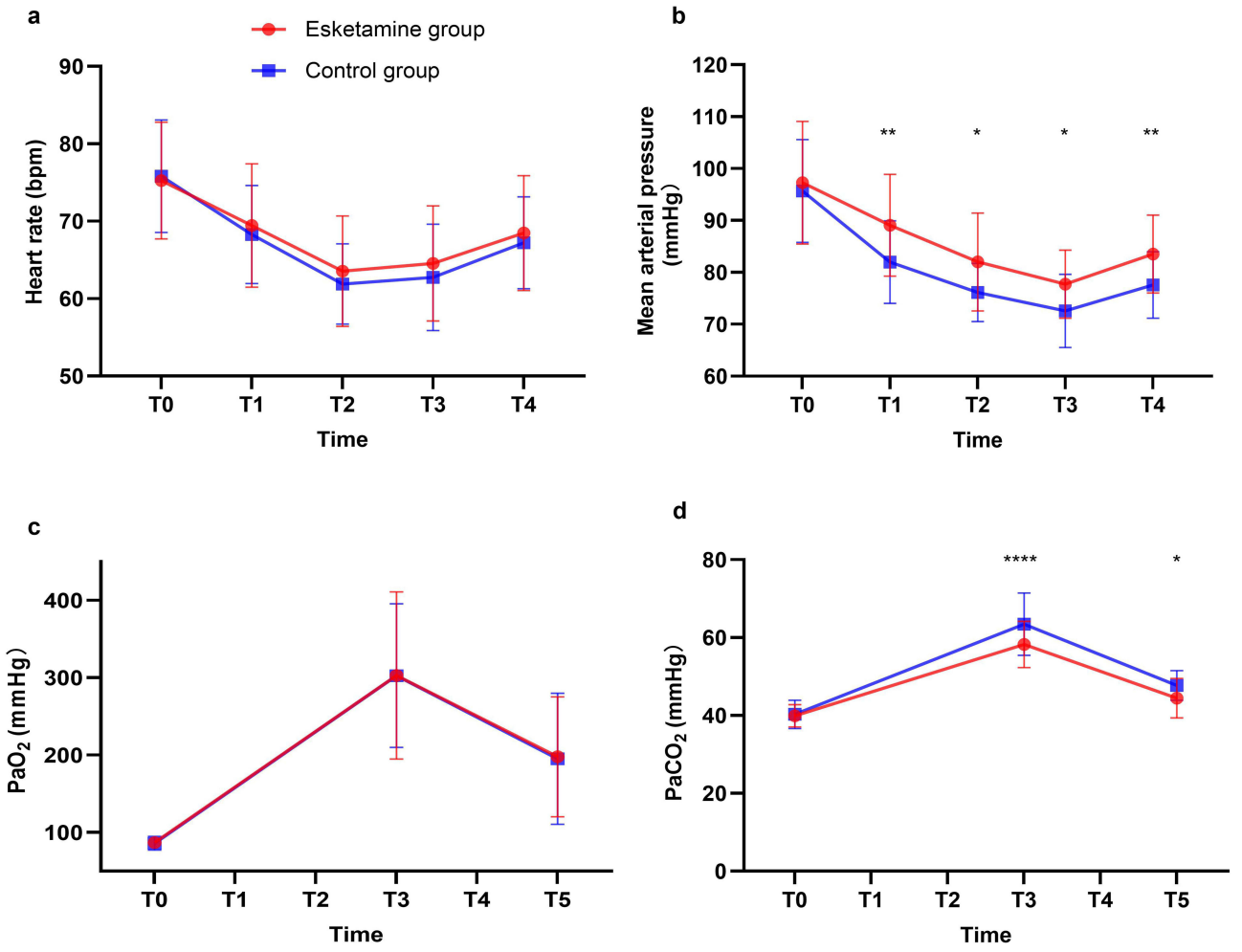

Figure 3 Intraoperative hemodynamic and blood gas profiles. (**a**) Heart rate; (**b**) Mean arterial pressure; (**c**) PaO_2 (arterial partial pressure of arterial oxygen); (**d**) $PaCO_2$ (arterial partial pressure of carbon dioxide). Time points: T0 (pre-induction), T1 (post-LMA insertion), T2 (surgical incision), T3 (skin closure), T4 (end of surgery), T5 (30 minutes post-LMA removal). Data are presented as mean ± SD. Compared with the control group, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{****}P < 0.0001$ (two-way repeated-measures ANOVA with Bonferroni correction).

contrast, PaO_2 levels remained comparable between two groups (Figures 3c and d). Furthermore, the esketamine group showed superior recovery on POD1 (QoR-40 score: 182.3 ± 6.0 vs 175.8 ± 7.2, $P < 0.001$) and POD3 (QoR-40 score: 190.3 ± 2.9 vs 186.8 ± 3.6, $P < 0.001$) (Table 2). Critically, intraoperative sufentanil consumption was 71.4% lower in the esketamine group (median 5.0 μg, IQR 0.0–9.5) than in the control group (median 17.5 μg, IQR 15.0–20.0; $P < 0.001$). Additionally, the need for rescue analgesia within 48 h postoperatively was significantly lower in the esketamine group than in the control group (20.0% vs 43.6%, $P < 0.05$). Although the two groups showed no significant differences in postoperative length of hospital stay and costs, an expanded sample size will be required to further validate the effect of potential confounders. Similarly, no significant differences were observed in PCIA device use and postoperative sleep quality. We also found that routine 24 h postoperative continuous ECG monitoring and nocturnal infusion therapy may affect the objectivity of sleep quality scores. It is also noteworthy that the esketamine group showed a lower rate of postoperative complications, with reductions in PONV (0% vs 15.4%, $P < 0.05$) and dizziness (2.5% vs 12.8%) incidences (Table 3). Finally, there were no cases of hallucinations, delirium, or nightmares in either group.

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Table 2 Postoperative Recovery, Sleep Quality and PCIA Use

	All patients (n=79)	Esketamine Group (n=40)	Control Group (n=39)	*P*-value
QoR-40				
POD1	179.1 (7.4)	182.3 (6.0)	175.8 (7.2)	<0.001[a]
POD3	188.5 (3.7)	190.3 (2.9)	186.8 (3.6)	<0.001[a]
PSQI				
Preoperative Day 1	5.0 (4.0–8.3)	5.0 (4.0–8.0)	5.5 (4.0–9.3)	0.466
POD3	7.2 (3.3)	7.2 (3.4)	7.3 (3.4)	0.828
PCIA device first press time (hr)	4.3 (1.25–11.5)	7.0 (1.5–12.6)	2.3 (1.3–8.0)	0.19
Total number of PCIA device presses	7 (3–11)	7 (3–10)	6 (3–16)	0.482
Effective number of PCIA device presses	7 (3.0–9.0)	7 (2.3–9.0)	5 (3.0–12.0)	0.516

Notes: Data are presented as mean ± SD, median with IQR, or number (percentage). [a]$P < 0.001$.
Abbreviations: QoR-40, quality of recovery 40-item score; POD, postoperative day; PSQI, Pittsburgh Sleep Quality Index; PCIA, Patient-Controlled Intravenous Analgesia.

Table 3 Safety Indicators, Rescue Analgesia and Adverse Events

	Esketamine Group (n=40)	Control Group (n=39)	OR (95% CI)	*P*-Value
Accidental cough	1 (2.6%)	1 (2.5%)	0.97 (0.06–16.20)	1.000
Mediastinal swing				0.092
Mild	37 (92.5%)	31 (79.5%)		
Moderate	3 (7.5%)	7 (17.9%)		
Severe	0 (0.0%)	1 (2.6%)		
Rescue analgesia (≥1 time)	8 (20.0%)	17 (43.6%)	0.23 (0.08–0.67)	0.025[b]
PONV	0 (0.0%)	6 (15.4%)	0.06 (0.003–1.12)	0.012[b]
Dizziness	1 (2.5%)	5 (12.8%)	0.18 (0.02–1.62)	0.108
Drowsiness	2 (5.0%)	3 (7.7%)	0.63 (0.10–4.06)	0.675
Delirium	0 (0.0%)	1 (2.6%)	0.33 (0.01–8.26)	0.494

Notes: Data are presented as number (percentage), odds ratio (OR), and 95% confidence interval (CI).
[b]$P < 0.05$.
Abbreviation: PONV, Postoperative Nausea and Vomiting.

Discussion

In this randomized trial, low-dose esketamine combined with PVB significantly attenuated postoperative hyperalgesia, achieved 71.4% reduction in intraoperative sufentanil use, and enhanced early recovery in NIVATS patients. These outcomes directly address the unmet need for balanced analgesia-respiration management in spontaneous ventilation thoracoscopy, while aligning with ERAS-recommended multimodal strategies.[16] Subsequent sections contextualize these findings within existing evidence and discuss clinical implications.

At 24 h postoperatively, the more pronounced improvement in MPT was observed at peripheral sites (20.2% increase) compared to central locations (15.7% increase) provides mechanistic support for the synergistic dual-action effects of esketamine and PVB. These differential improvements mechanistically validate the dual-action interplay of both esketamine and PVB. Esketamine, an NMDA receptor antagonist, was found to attenuate remifentanil-induced hyperalgesia by suppressing spinal dorsal horn sensitization.[17] On the other hand, PVB blocks nociceptive signal transmission from thoracic spinal nerve roots, providing targeted somatic and visceral analgesia.[18] This is consistent with findings from a previous study on cesarean sections, where ketamine combined with epidural analgesia reduced pain scores by 30%.[19] This study represents a pioneering effort to apply dual-mechanism analgesia within the context of NIVATS, a spontaneous ventilation setting that requires precise analgesia and sedation management, thereby addressing

a significant gap in thoracic ERAS protocols. Central sensitization reduction observed herein highlights esketamine's systemic antinociceptive hypersensitivity, a phenomenon consistent with preclinical studies that showed that NMDA receptors regulate ascending pain pathways.[20] It could also explain the significant increase in MPT observed at 6 and 24 h postoperatively.

Regarding reduced opioid use and hemodynamic stabilization, we found a 71.4% reduction in intraoperative sufentanil use in the esketamine group, implying that esketamine significantly reduced the risk of opioid-associated respiratory depression and intestinal paralysis, which aligns with ERAS goals. Similarly, norepinephrine requirements were reduced, potentially attributable to the stabilizing effect of esketamine's sympathomimetic properties of intraoperative circulation in NIVATS—a finding that aligns with the results of a previous study involving elderly patients who underwent gastrointestinal endoscopy.[21] Furthermore, Chen et al recently compared the sedative and analgesic effects of dexmedetomidine and esketamine in liposuction anesthesia and found that the esketamine group exhibited more stable hemodynamics, a phenomenon consistent with our findings.[22] However, it did not address the synergistic effects of regional anesthesia, whereas this study further optimized the analgesia-sedation balance via PVB integration. Although conventional epidural analgesia has been established as the "gold standard" for thoracic surgical analgesia, it has been associated with multiple drawbacks such as hypotension (15–30% incidence), motor blockade, and operative complexities.[23] Conversely, in this study, no severe hypotensive events were reported in the esketamine+PVB regimen. It is also noteworthy that Allegaert et al's concept of "individualized analgesia" was extended in this study.[24] By dynamically adjusting esketamine's infusion rate (0.15 mg/kg/h) and the number of postoperative PCIA presses, continuous pain management from the intraoperative to postoperative periods was achieved, potentially offering a reference for the refined design of ERAS pathways in the future. Moreover, the stable PaO_2 and $PaCO_2$ (58.2 ± 6.0 vs 63.4 ± 8.0 mmHg, $P < 0.05$) levels observed during suturing further validated esketamine's safety in maintaining gas exchange during spontaneous ventilation.

Regarding the quality of recovery and safety, the QoR-40 scores (POD1 and POD3; $P < 0.001$) were higher in the esketamine group, reflected in improvements across five dimensions, encompassing physical comfort, emotional state, and independence—core ERAS goals. Regarding safety, consistent with the findings of a recent RCT on spinal stenosis among the elderly, no hallucination or delirium cases were reported.[25] Notably, they used low-dose esketamine (0.2 mg/kg induction, 0.125 mg/kg/h infusion) as in this trial, allaying concerns about esketamine's psychotomimetic effects. Transient procedure-related events were observed, with 12 patients (15.2%) experiencing mild discomfort at the PVB site within 12 h postoperatively. In four patients, this discomfort persisted for up to 24 h but resolved fully by 48 h. These findings likely reflect local anesthetic dissipation or fascial irritation during needle placement. This self-limiting phenomenon is consistent with prior reports investigating ultrasound-guided PVB,[26] which warrants mechanistic follow-up but requires no clinical intervention or extended hospitalization. Moreover, PONV incidence was significantly reduced ($P < 0.05$), further highlighting esketamine's clinical potential in NIVATS.

Overall, this study supports the use of low-dose esketamine in the accelerated recovery pathway of NIVATS patients. Reduced opioid dependence might allow clinicians to minimize sedation-related respiratory risks and promote early postoperative pulmonary function exercises and out-of-bed activities for patients.[27] Furthermore, combined PVB protocols could offer a practical and scalable approach for promoting non-intubation techniques, especially in resource-limited healthcare settings lacking advanced analgesic techniques such as thoracic segmental epidural anesthesia.

Despite its valuable insights, this study had several notable limitations. First, although the consistency of the study protocol was assured, additional multicenter trials will be required to verify the generalizability of the results. Second, the 72-hour observation window precluded the assessment of the incidence of chronic pain, an omission that might affect the comprehensiveness of the study's conclusions. This shortcoming is particularly echoed by the fact that chronic pain is a major clinical problem after thoracic surgery that correlates strongly with central sensitization.[28] Third, the study's exclusion of obese (BMI > 25) and elderly patients might limit the extrapolation of its findings to a wider population.[29] Although patients classified as ASA I–II were selected to reduce cardiopulmonary confounding factors, future research should evaluate the efficacy and safety of this regimen in higher-risk populations (eg, ASA III), where the benefits of NIVATS may be more pronounced. To further elucidate the mechanism of central sensitization to esketamine + PVB, while ensuring protocol consistency, future studies should focus on long-term clinical outcomes, including chronic pain

rates at 3–6 months postoperatively. Functional magnetic resonance imaging (MRI) should also be incorporated, with clarity on key brain regions (eg, thalamus, anterior cingulate cortex, and insula), imaging time points (1 week, 1 month, and 3 months postoperatively), and control group designs.[30]

Conclusion

This randomized trial demonstrates that low-dose esketamine combined with PVB in ASA I–II NIVATS patients significantly attenuated postoperative hyperalgesia, reduced intraoperative sufentanil by 71.4% and norepinephrine by 44.3%, while improving early recovery and reducing PONV. The strategy provides high-level evidence for ERAS pathway standardization, particularly benefiting patients without major comorbidities. Validation in broader populations is warranted.

Data Sharing Statement

The datasets generated and analyzed during the current study are not publicly available due to institutional privacy policies. However, de-identified data supporting the findings of this study are available from the corresponding author upon reasonable request. Data access requires a formal proposal outlining the intended use and compliance with ethical standards.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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