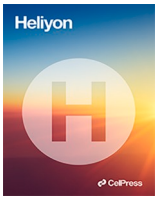
Heliyon 10 (2024) e25100

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Postoperative esketamine improves ventilation after video-assisted thoracoscopic lung resection: A double-blinded randomized controlled trial

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ARTICLE INFO

Keywords:
Video-assisted thoracoscopy
postoperative pulmonary function
Postoperative pulmonary complication
Esketamine
Randomized controlled trial

ABSTRACT

Background: Pain management after lung resection plays a crucial role in reducing postoperative pulmonary complications (PPCs). This study aimed to examine the effect of postoperative esketamine infusion as an adjunct to opioid analgesia on ventilation and pulmonary complications in patients underwent lung resection.

Methods: Patients undergoing video-assisted thoracoscopic lung resection were randomly assigned to either the esketamine group or the control group. The esketamine group received a 24-h infusion of 1.5 mcg/ml sufentanil combined with 0.75 mcg/ml esketamine after surgery, while the control group received 1.5 mcg/ml sufentanil alone. The primary outcome measure was low minute ventilation, and the secondary outcome measures were hypoxemia, PaO2/FiO2 levels, postoperative pulmonary complications, hospital stay duration, ambulation time, Visual Analogue Scale (VAS) score, depression and anxiety levels, sleep quality, and analgesia satisfaction.

Results: 80 patients were randomly divided into two groups: the esketamine group ($n = 40$) and the control group ($n = 40$). The esketamine group exhibited notably reduced incidence of low minute ventilation ($P = 0.014$), lower occurrence of postoperative pulmonary complications (PPCs) compared to the control group ($P = 0.039$), and decreased incidence of hypoxemia ($P = 0.003$). Furthermore, the esketamine group showed improved outcomes with lower VAS scores on the second postoperative day and enhanced sleep quality ($P < 0.001$) after the surgery.

Conclusions: Postoperative esketamine infusion with opioids improved ventilation and reduced PPCs after lung resection, warranting further clinical studies.

Trial registration: This study was registered on ClinicalTrials.gov (Trial ID: NCT05458453, https://clinicaltrials.gov/ct2/show/NCT05458453).

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https://doi.org/10.1016/j.heliyon.2024.e25100
Received 26 November 2023; Received in revised form 19 January 2024; Accepted 19 January 2024
Available online 24 January 2024

1. Introduction

Postoperative pulmonary complications (PPCs) are estimated to occur at a rate of 30 %–50 % after thoracic surgery [1]. Despite advancements in minimally invasive techniques like video-assisted thoracic surgeries (VATS), PPCs remain notably high, ranging from 26.8 % to 29.9 % [2]. One key factor contributing to PPCs is acute postoperative pain, which can lead to reduced minute ventilation (MV), retained secretions, atelectasis, and pneumonia [3,4]. Decreased MV following thoracic surgeries can compromise gas exchange and ventilation distribution, leading to hypoxia, hypercapnia, and potentially respiratory failure.

For postoperative pain management following thoracic surgeries, patients commonly receive opioids such as morphine, fentanyl, and sufentanil. Although these opioids are effective in providing pain relief, their potential to induce respiratory depression could impede the recovery of postoperative pulmonary function in thoracic surgery patients [5]. Esketamine, also known as (S)-ketamine, is the S-enantiomer of ketamine, which can provide both analgesic and sedative effect for patients. Animal studies have provided evidence suggesting that esketamine may stimulate respiration through N-methyl-D-aspartate (NMDA) receptor activation [6]. Human volunteer study has demonstrated that esketamine effectively counters opioid-induced respiratory depression and improves respiration [7]. The underlying mechanism may be attributed to the ability of esketamine to enhance the sensitivity of end-tidal carbon dioxide ($EtCO_2$), while opioids can decrease the sensitivity of $EtCO_2$ by reducing respiratory drive and blunting chemoreceptor response to blood CO2 levels [7,8]. Furthermore, esketamine can relax the airway smooth muscles, increase the activity of the sympathetic nervous system, and elevate the levels of norepinephrine in the synapse, which in turn stimulates respiration [9]. As an analgesic, esketamine can also reduce the opioid consumption and significantly alleviates postoperative pain [10].

While esketamine theoretically could enhance respiratory function after thoracic surgery, limited clinical evidence exists. This study aims to investigate the effect of intravenous esketamine on respiratory function and PPCs in elective thoracic surgery patients.

2. Methods

2.1. Study design

This is a randomized controlled trial, which follows the Consolidated Standards of Reporting Trials (CONSORT) guidelines. The study protocol has been approved by the Ethics Committee of our hospital (Approval No. 2022-101). All patients provided written informed consent prior to their participation in the study. The study has been registered on the ClinicalTrials.gov. Complete study protocol and research data can be obtained from the corresponding authors.

2.2. Patients

We enrolled patients undergoing elective VATS lung resection from July 7, 2022 to Feb 20, 2023 with the following inclusion criteria: age 18–65 years old, American Society of Anaesthesiologists (ASA) physical status classification I-III, willing to receive continuous intravenous analgesia for pain management and completed informed consent. Exclusion criteria included known drug allergy to ketamine and other common anaesthetics, a history of previous thoracic surgery or concomitant chest trauma, uncontrolled hypertension, increased intracranial pressure, comorbid psychiatric disorders, drug abuse, and patients who are unable to communicate. Patients who require conversion to open chest surgery during the operation, or who need to be transferred to the Intensive Care Unit (ICU) for further treatment after surgery, will be withdrawn from the study.

2.3. Randomisation, masking, and allocation concealment

Patients were randomly assigned to either esketamine group or control group using computer-generated random numbers, which were prepared by an independent researcher and concealed in opaque and sealed envelopes with sequential numbers. In this study, both participants and researchers who involved in data collection and input were blinded to their group allocation. The continuous intravenous analgesia pump was prepared by an independent anesthetist who were not involved in data collection, input, or analysis. Patients were enrolled by trained researcher, who also helped connect the infusion pump. Respiratory function assessment, psychological assessment, and relevant postoperative data collection were performed by trained professionals who were not involved in patient care and were blinded to group allocation.

2.4. Anesthetic procedure and intervention

Standardized anesthesia induction was performed using propofol (2–2.5 mg kg^{-1}), sufentanil (0.2–0.5 mcg. kg^{-1}), midazolam (0.05–0.2 mg kg^{-1}), and rocuronium (0.6 mg kg^{-1}) intravenous anesthesia. After intubation with a double-lumen tube, fiberoptic bronchoscopy verified endotracheal tube placement. One lung ventilation (OLV) commenced when surgery started, employing protective lung ventilation: 6–8 mL kg^{-1} predicted body weight, personalized PEEP levels, intermittent recruitment maneuvers, and FiO2 around 50 %–60 %. Anesthesia was maintained by propofol and remifentanil infusion with target bispectral index (BIS) 40–60. Norepinephrine was used to maintain blood pressure within 20 % of baseline values. Ultrasound-guided erector spinae block was conducted using 0.375 % ropivacaine (20 mL) after surgery. After the nerve block, a continuous intravenous analgesia pump was started with a 10 mcg sufentanil loading dose. For the esketamine group, the pump was prepared by combining 1.5 mcg. mL^{-1} of sufentanil and 0.75 mcg. mL^{-1} in 100 mL of normal saline. For the control group, the pump contained only 1.5 mcg. mL^{-1} of sufentanil

in 100 mL of normal saline. The infusion rate was determined based on the body weight of the patients, using a dosage of sufentanil 0.1 mcg. kg^{-1}. $h^{-1}$and esketamine 0.05 mcg kg^{-1} h^{-1} for esketamine group, or sufentanil 0.1 mcg kg^{-1} h^{-1} alone for control group. The infusion rate on the pump could be calculated as body weight divided by 15 for both groups. Infusion was administered for 24 h after the surgery. Paracetamol or flurbiprofen would be given as additional analgesia when patients had VAS >3.

2.5. Outcome measures

The primary outcome measure of our study was the incidence of low minute ventilation (MV) during the 2-day postoperative follow-up period. Low MV was defined as a decrease of more than 40 % from the baseline value of MV [11,12], which was assessed using a non-invasive respiratory monitor (ExSpiron; Respiratory Motion Inc, MA, USA) to measure tidal volume (TV), respiratory rate (RR), and minute ventilation (MV) [13] during quiet breathing for 3 min, before surgery (T0), 5 min after extubation (T1), and at 8:00–10:00 a.m. (T2) and 3:00–5:00 p.m. (T3) on the first and second day after surgery (T4 and T5), and the average values were recorded. The timeline of data collection was shown in Supplemental Fig. 1. The secondary outcomes included incidence of PPCs during hospitalization, hypoxemia and low PaO_2/FiO_2 (PF ratio, PF ratio <300) during the 2-day postoperative follow-up period, length of hospital stay, time to ambulation, pain scores assessed by Visual Analogue Scale (VAS) on the first and second day after surgery, depression and anxiety status, sleep quality, and level of analgesia satisfaction. The presence of PPC was defined by using the Melbourne Group Scale (MGS) [14,15]' which included 8 criteria: chest X-ray findings of atelectasis or consolidation, white cell count >11.2 × 109/L, temperature >38 °C, signs of infection on sputum microbiology, purulent sputum, oxygen saturations <90 % on room air; clinical diagnosis of pneumonia; and prolonged high dependency unit stay for respiratory complications. Patients reached four or more of the 8 criteria would be diagnosed with PPC. Hypoxemia was defined as $SpO_2 \leq 92$ %. Postoperative depression was assessed using the Patient Health Questionnaire-9 (PHQ-9) and anxiety status was assessed using the Generalized Anxiety Disorder-7 (GAD-7) scale on postoperative day 1 (POD1) and postoperative day 2 (POD2). The quality of sleep after surgery was evaluated using the Richards-Campbell Sleep Questionnaire on both POD 1 and POD 2. The questionnaire measures sleep quality using a score ranging from 0 to 100 based on six items. A higher score indicates a better sleep quality. Adverse events, such as nausea, vomiting, pruritus, urinary retention, and cardiovascular system abnormalities, were monitored after surgery.

2.6. Statistical analysis

Based on the pilot study, it was found that the incidence of low minute ventilation was 8 % (1/12) when sufentanil was used in combination with esketamine and increased to 33 % (4/12) when using sufentanil alone. Through PASS 11.0 software with a power of

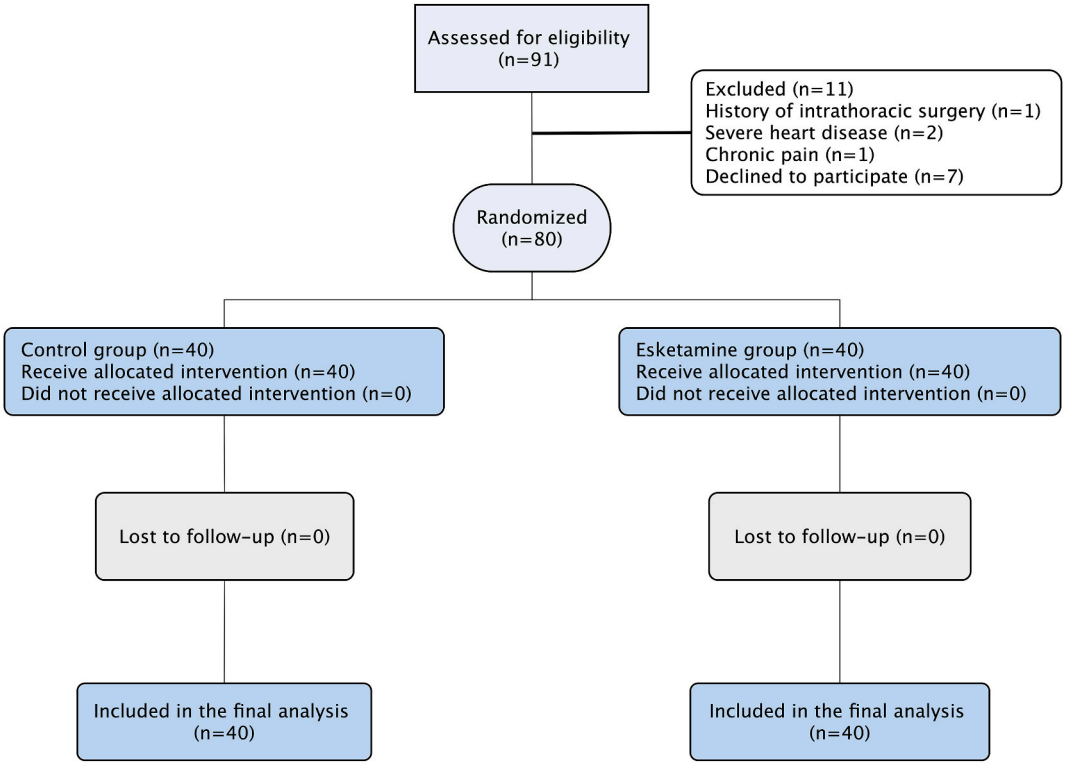

Fig. 1. Flow Chart of the study.

80 % and a significance level of 0.05, the calculated sample size was 38 in each group. Considering a missing follow-up rate of approximately 5 %, the total sample size required for the study would be approximately 80 patients, with 40 patients in each group.

The statistical analysis for this study was performed using the SPSS software (version 26.0; SPSS, Chicago, IL, USA) following the intention-to-treat principle. A two-sided $P < 0.05$ was considered statistically significant. Continuous variables were presented as means ± standard deviations or medians with interquartile ranges depending on the distribution of the data. Qualitative variables were presented as numbers and percentages. Qualitative variables such as incidences of low minute ventilation between the esketamine and sufentanil groups were compared using the chi-square test or Fisher's exact test. The independent *t*-test was used to compare continuous normally distributed data between the esketamine and sufentanil groups, while the Mann-Whitney *U* test was used to compare abnormal distributed data. Risk difference and mean difference with 95 % confidence interval (CI) were calculated for the study outcomes. Cumulative incidences of low minute ventilation and hypoxemia along with time were compared between different groups using Kaplan–Meier analysis. In addition, logistic analysis with enter model was performed to further validate the effects of esketamine on incidence of low minute ventilation through including the potential related factors (≥60 years or <60 years, sex, ASA status, with or without cancer, smoking status, surgery type and surgery duration <2 h or ≥2 h).

3. Results

The final analysis included a total of 80 patients, with 40 patients in each group as shown in Fig. 1. Demographic and baseline parameters of patients in each group are listed in Table 1.

As shown in the graphs of respiratory parameters (Fig. 2), comparisons were made among six time points, including preoperative baseline (T0), 5 min after extubation (T1), postoperative day 1 morning (T2), postoperative day 1 afternoon (T3), postoperative day 2 morning (T4), and postoperative day 2 afternoon (T5), in terms of minute ventilation, tidal volume, and respiratory rate. The tidal volume showed a statistical significance at time points T2 and T3 ($p < 0.05$) as demonstrated in Fig. 2A. Despite the control group having a higher baseline respiratory rate, there was a significant increase in respiratory rate at time points T4 and T5 ($p < 0.01$) in the esketamine group as demonstrated in Fig. 2B. Although the control group had a higher MV at T0, Fig. 2C indicates that MV in esketamine group was significantly higher than control group from T2 to T5.

The incidence of low minute ventilation within 48 h was significantly lower in the esketamine group (Risk difference = 22.5 %; 95

Table 1
Baseline parameters.

	Esketamine group (n = 40)	Control group (n = 40)
Age (year)	54.4 ± 11.5	54.8 ± 9.8
Male, n (%)	18 (45.0 %)	16 (40.0 %)
BMI (kg/m^2)	24.1 ± 2.6	23.5 ± 2.9
ASA physician status		
I, n (%)	0 (0)	0 (0)
II, n (%)	31 (77.5 %)	29 (72.5 %)
III, n (%)	9 (22.5 %)	11 (27.5 %)
Smoker		
Yes, n (%)	6 (15.0 %)	11 (27.5 %)
Quitter, n (%)	6 (15.0 %)	2 (5.0 %)
NO, n (%)	28 (70.0 %)	27 (67.5 %)
COPD, n (%)	0 (0)	0 (0)
Asthma, n (%)	0 (0)	0 (0)
OSAS, n (%)	0 (0)	0 (0)
Coronary artery disease, n (%)	0 (0)	1 (2.5)
Hypertension, n (%)	2 (5.0)	4 (10.0)
Diabetes, n (%)	2 (5.0)	2 (5.0)
Procedure		
Lobectomy, n (%)	9 (22.5 %)	18 (45.0 %)
Wedge resection, n (%)	23 (57.5 %)	16 (40.0 %)
Segmentectomy, n (%)	8 (20.0 %)	6 (15.0 %)
Surgery duration (min)	146.90 ± 58.64	155.12 ± 66.94
Blood loss (mL)	30.50 ± 13.95	32.38 ± 17.65
Arterial Blood Gas		
PO_2 (mmHg)	93.93 ± 9.25	90.03 ± 12.86
PCO2 (mmHg)	36.30 ± 3.57	38.80 ± 10.53
PF ratio	449.53 ± 44.48	436.74 ± 45.64
Depression, n (%)[a]	2 (5.0 %)	0 (0.0 %)
Anxiety, n (%)[b]	5 (12.5 %)	1 (2.5 %)
Richards-Campbell sleep score	56.99 ± 19.13	75.65 ± 12.07
Cancer diagnosis n (%)	30 (75.0 %)	32 (80.0 %)

BMI, body mass index; ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; OSAS, obstructive sleep apnea syndrome; PF ratio, PaO2/FiO2 ratio.

[a] Defined as Patient Health Questionnaire-9 (PHQ-9) score≥5.

[b] Defined as Generalized Anxiety Disorder-7 (GAD-7) score≥5.

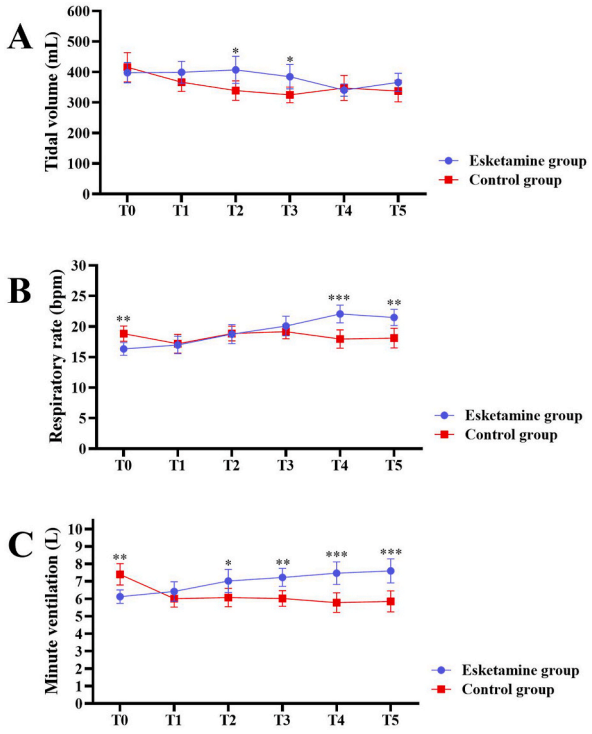

Fig. 2. Respiratory data from T0 to T5, including tidal volume (A), respiratory rate (B), and minute ventilation (C). (Data are presented as mean with 95 % confidence interval, *P < 0.05, **P < 0.01, ***P < 0.001).

% CI, 5.3 %–40.0 %; P = 0.014). The overall occurrence of hypoxemia was also significantly lower in the esketamine group (Risk difference = 42.5 %; 95 % CI, 22.7 %–62.3 %; P = 0.003) as shown in Table 2. By further calculating the cumulative incidence of low MV as shown in Fig. 3A and hypoxemia ($SpO_2 \leq 92$ %) as shown in Fig. 3B along with time from T0 to T5, statistically significant difference was found between two groups. The incidence of low PF ratio was significantly lower in the esketamine group than in the control group (Risk difference = 27.5 %; 95 % CI, 10.6 %–44.4 %; P = 0.010). The incidence of PPCs in the esketamine group during hospitalization was significantly lower than that in the control group (Risk difference = 20.0 %; 95 % CI, 1.5 %–38.5 %; P = 0.039) as shown in Table 2 and Fig. 4A. In the set of eight evaluation criteria within the MGS, the group treated with esketamine exhibited a reduced occurrence of postoperative chest X-ray results indicating atelectasis or consolidation (P = 0.029). Additionally, lower occurrences of postoperative purulent sputum (P = 0.003) were observed in the same group, as illustrated in Fig. 4B.

In addition, this study found that the VAS scores of esketamine were not significantly different from the control group in the time periods of T1-T3 (P = 0.602, P = 0.316, P = 0.071), but in T4 and T5, the VAS scores were significantly better than the control group (P = 0.003, P = 0.001). The incidence of inadequate pain control (defined as VAS≥4) in the esketamine group had no difference from the control group (P = 0.16), while the analgesic satisfaction of the esketamine group was better than the control group (P = 0.002) (Table 2).

Patients' Richards-Campbell sleep score in esketamine group was higher than the control group on POD1 (P < 0.001) and POD2 (P < 0.001). Additionally, there was no significant difference in the incidence of PONV between two groups as well as the time to ambulance and length of hospital stay. Lastly, there was no significant difference in postoperative anxiety and depression between the esketamine group and the control group as shown in Table 2.

Results of multiple logistic regression analysis for affecting postoperative low minute ventilation were shown in Table 3. Only Esketamine (Yes *vs.* No) was identified as independent effective factor forx occurring of low minute ventilation with OR 0.21 (95 % CI, 0.05–0.90).

4. Discussion

The results of this study showed that the incidence of low MV and the incidence of PPCs during hospitalization after VATS lung resection were significantly lower in the esketamine group compared to the control group. There was no significant difference in the incidence of postoperative nausea and vomiting (PONV), length of hospital stays, time to ambulation and the incidence of postoperative depression and anxiety between the esketamine group and the control group. Although both groups received adequate pain control, esketamine group had lower VAS score after the analgesic infusion.

Esketamine, a chiral derivative of ketamine, can increase minute ventilation, which is consistent with previous research on its

Table 2
Postoperative outcome measures.

	Esketamine group (n = 40)	Control group (n = 40)	P	Mean difference or risk difference	95 % CI
Low MV, n (%)[a]	4 (10.0 %)	13 (32.5 %)	0.014	22.5 %	5.3 %–40.0 %
Low PF ratio, **n (%)**[a]	3 (7.5 %)	14 (35.0 %)	0.010	27.5 %	10.6 %–44.4 %
Hypoxemia, n (%)[a]	11 (27.5 %)	28 (70.0 %)	0.003	42.5 %	22.7 %–62.3 %
PPCs during hospitalization, n (%)	6 (15.0 %)	14 (35.0 %)	0.039	20.0 %	1.5 %–38.5 %
VAS at T1	1.60 ± 1.02	1.70 ± 0.70	0.602	0.10	−0.29 to 0.49
VAS at T2	2.55 ± 1.02	2.75 ± 0.75	0.316	0.20	−0.20 to 0.60
VAS at T3	2.58 ± 0.82	2.89 ± 0.65	0.071	0.30	−0.26 to 0.63
VAS at T4	2.66 ± 0.68	3.14 ± 0.70	0.003	0.48	0.17 to 0.79
VAS at T5	2.58 ± 0.83	3.16 ± 0.67	0.001	0.58	0.25 to 0.92
VAS >3 within 48 h, n (%)	11 (27.5 %)	17 (42.5 %)	0.160	15.0 %	−5.6 %–35.6 %
Level of Analgesia satisfaction[b], **n**	0//0/0/6/34	0/0/1/20/19	0.002		
Anxiety POD1, n (%)[c]	2 (5.0 %)	0 (0.0 %)	0.474	−5.0 %	−11.8 %–1.8 %
Anxiety POD2, n (%)[c]	2 (5.0 %)	0 (0.0 %)	0.474	−5.0 %	−11.8 %–1.8 %
Depression POD1, n (%) [d]	1 (2.5 %)	3 (7.5 %)	0.608	5.0 %	−4.5 %–14.5 %
Depression POD2, n (%) [d]	1 (2.5 %)	6 (15.0 %)	0.113	12.5 %	0.4 %–24.6 %
Richards-Campbell sleep score at POD1	81.26 ± 13.97	56.63 ± 15.75	0.000	−24.63	−31.25 to −18.00
Richards-Campbell sleep score at POD2	81.96 ± 13.33	55.36 ± 18.76	0.000	−26.60	−33.84 to −19.35
PONV, n (%)	10 (25.0 %)	10 (25.0 %)	1.000	0.0 %	−19.0 %–19.0 %
Time to Ambulation (Hour)	18.64 ± 2.74	18.85 ± 3.53	0.764	−0.21	−1.62 to 1.19
Incidence of flurbiprofen use, (%)	1 (2.5 %)	13 (32.5 %)	0.001	30.0 %	14.7 %–45.3 %
Cumulative consumption of flurbiprofen, (mg)	0.0 (0.0–0.0)	0.0 (0.0–50.0)	0.004	21.25	7.02 to 35.48
Incidence of paracetamol use, (%)	2 (5.0 %)	3 (7.5 %)	0.603	2.5 %	−8.2 %–13.2 %
Cumulative consumption of paracetamol, (mg)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.473	0.01	−0.02 to 0.04
Length of Hospital stays (day)	10.85 ± 5.01	10.33 ± 2.83	0.565	0.53	−1.29 to 2.34

PPC, postoperative pulmonary complication; MV, minute ventilation; PF ratio, PaO2/FiO2 ratio; VAS, visual analogue scale; T1, 5 min after extubation; T2, postoperative day 1 morning; T3, postoperative day 1 afternoon; T4, postoperative day 2 morning; T5, postoperative day 2 afternoon; PONV, postoperative nausea and vomiting; POD1, postoperative day 1; POD2, postoperative day 2.

[a] Incidence during the 2-day postoperative follow-up period.

[b] Level of satisfaction was divided into five options: very dissatisfied/dissatisfied/neutral/satisfied/very satisfied.

[c] Defined as Generalized Anxiety Disorder-7 (GAD-7) score≥5.

[d] Defined as Patient Health Questionnaire-9 (PHQ-9) score≥5.

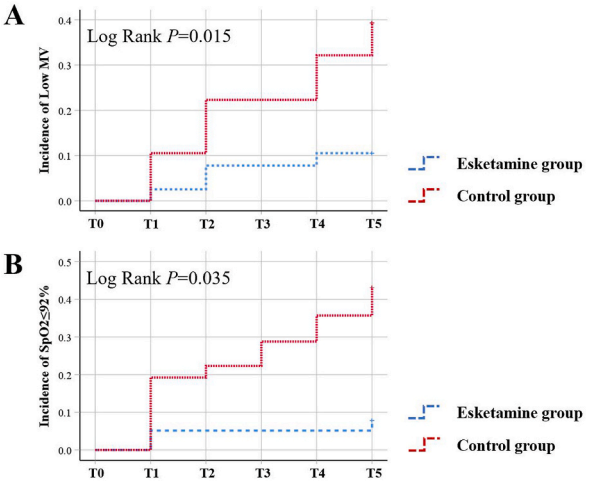

Fig. 3. Cumulative incidence of low minute ventilation (MV) (A) and hypoxemia (SpO_2≤92 %) (B) along with time from T0 to T5 by using Kaplan–Meier analysis.

ventilatory effect and also in line with the research of ketamine [6,16,17]. For opioids induced respiratory depression, the decreased respiratory rate was a main component of ventilation reduction, while the decrease in tidal volume was dose dependent. At low doses, the tidal volume usually remains unaffected, as dose increase the tidal volume decreases [18]. In our study, the increase in MV was

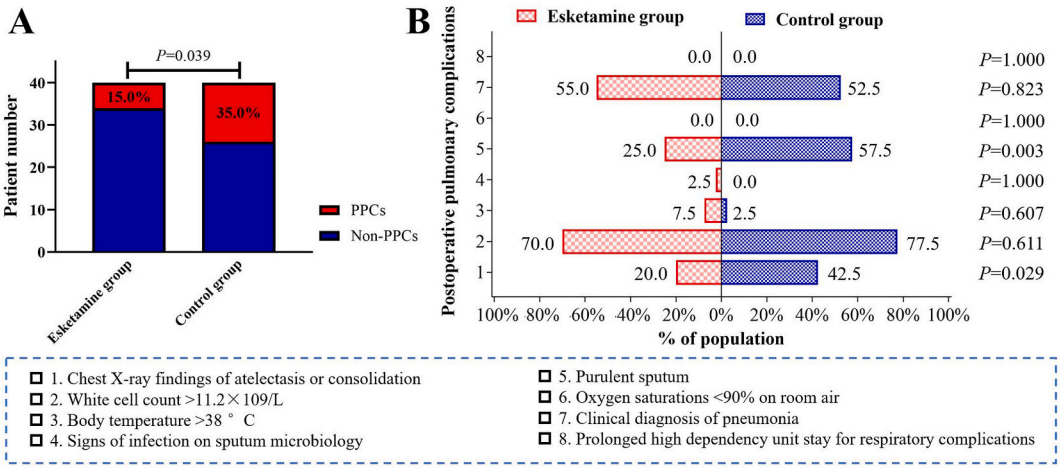

Fig. 4. The presence of postoperative pulmonary complications (PPCs) was defined by using the Melbourne Group Scale (MGS). (A) Incidence of PPCs in esketamine group and control group. (B) Detailed comparisons of MGS criteria.

Table 3
Enter model of multiple logistic regression analysis for affecting postoperative low minute ventilation.

Variables	Wald x^2	*P* value	OR (95 % CI)
Age group (≥60 years *vs.* <60 years)	0.747	0.387	1.91 (0.45–8.30)
Sex (Male *vs.* Female)	0.661	0.416	0.45 (0.07–3.05)
ASA status (III *vs.* II)	2.385	0.122	4.82 (0.66–35.40)
Cancer (Yes *vs.* No)	1.759	0.185	0.29 (0.05–1.80)
Smoker	0.968	0.616	
No *vs.* Yes	0.968	0.325	0.38 (0.05–2.65)
Quit *vs.* Yes	0.056	0.813	0.72 (0.05–11.05)
Surgery type	2.2385	0.319	
Segmentectomy *vs.* Wedge resection	1.912	0.167	0.14 (0.01–2.26)
Lobectomy *vs.* Wedge resection	0.062	0.803	0.75 (0.08–7.02)
Surgery duration (<2 h *vs.*≥2 h)	0.158	0.691	0.67 (0.09–4.91)
Esketamine (Yes *vs.* No)	4.411	0.036	0.21 (0.05–0.90)

ASA, American Society of Anesthesiologists; OR, odds ratio; CI, confidence interval.

mainly attributed to an increase in tidal volume during esketamine infusion, while after the analgesic infusion finished, the increase in MV was mainly due to an increase in RR. During the period of continuous infusion of esketamine, esketamine may potentially antagonize the reduction in tidal volume caused by opioids through increasing ventilatory CO_2 chemosensitivity [6]. Ventilatory response to activation of chemoreceptor include elevation in both tidal volume and respiratory rate [19,20]. In our study, we used sufentanil as the primary analgesic, and it was reported consistently causing an immediate and dose-dependent decrease in tidal volume [21]. Respiratory rate depression caused by sulfentanil would become evident with higher doses [21,22]. Hypoventilation is one of the leading factors that causes hypoxemia. In our study, the incidence of hypoexemia was lower in the esketamine group, aligning with the respiratory impact of this intervention. Following discontinuation of the infusion, esketamine may have an anti-hyperalgesic effect [23], which could lead to a decrease in the VAS score and facilitate the effort of breathing, resulting in an increase in minute ventilation.

Reported interventions for reducing PPCs include the enhanced recovery after surgery (ERAS) protocol, lung-protective ventilation, prophylactic use of mucolytics, respiratory physiotherapy, epidural analgesia, and goal-directed hemodynamic therapy [24,25]. Effective management of postoperative pain holds significant importance within ERAS protocols, as pain stands out as a primary factor capable of diminishing minute ventilation and impairing the capacity to effectively expel secretions and sputum through coughing. In our study, both groups had received adequate pain control, while the esketamine group has a lower VAS score after analgesia infusion. Esketamine, an NMDA receptor blocker, has agonistic action towards the delta and mu-opioid receptors. It serves as an anesthetic agent, offering analgesia and preventing hyperalgesia [26]. In addition, esketamine is a potential bronchodilator [27], which may facilitate the pulmonary function improvement promote the clearance of airway secretions and mucus. The reduction in PPCs observed in the esketamine group within our study can be attributed, as per the MGS criteria, to a decrease in coughing with purulent sputum and the presence of atelectasis or consolidation evident in chest X-ray findings. However, no difference was observed on the incidences of pneumonia, which is probably because that clinical diagnosis of pneumonia is based on a combination of signs, symptoms, and diagnostic tests. The diagnostic criteria may vary slightly depending on the guidelines or clinical practice followed. In our study we did not standardize the diagnosis criteria for pneumonia.

The esketamine group demonstrated an improvement in postoperative sleep quality, which is in line with previous study by Di Qiu et al. [28], suggesting that esketamine has a prophylactic effect on postoperative sleep disorder. Although previous research has confirmed the rapid antidepressant effect of esketamine [29], this study showed no significant difference between the esketamine group and the control group, possibly because depression and anxiety were secondary outcomes in this study, and the sample size was insufficient to draw conclusions on mood improvement. Furthermore, the patients recruited for this study were not considered high-risk for depression or anxiety, nor had they been diagnosed with mood-related disorders, which may have limited the ability to fully reflect the potential antidepressant and anxiolytic effects of esketamine in this study. Esketamine group had significantly higher satisfaction level compared to the control group. This may be attributed to the significant improvement in VAS score and postoperative respiratory function in the esketamine group, which may have reduced the occurrence of PPCs.

There are several limitations in this study. Firstly, although this study suggests that esketamine can improve postoperative respiratory function in patients undergoing VATS lung resection, it should be noted that this was a single-center trial and there were baseline differences in ventilation-related parameters, such as respiratory rate and MV. Further multicenter trials with larger sample sizes are needed to confirm the efficacy of esketamine. Secondly, this study did not explore different dosages of esketamine, so further research is needed to determine the optimal dosage and whether the improvement effect is dose dependent. Lastly, both groups were given the fixed dose of opioids to exclude the difference in respiratory depression caused by different doses of opioids. It is necessary to further evaluate esketamine in patients using patient control analgesia (PCA). Opioid-sparing effect of esketamine [30] may have additional benefits for respiratory function and postoperative prognosis following lung surgery.

5. Conclusion

This prospective double-blinded randomized trial provides evidence that the continuous intravenous administration of esketamine as an adjuvant of postoperative analgesia can effectively improve postoperative respiratory function and decrease PPCs in patients undergoing VATS lung resection. Our results suggest that esketamine is a promising option for postoperative pain management. However, further multicenter clinical studies are needed to confirm its efficacy.

Funding information

The corresponding author Yuanjing Chen is supported by the Chongqing Municipal Education Commission (KJQN202000409) as a non-restricted educational grant.

CRediT authorship contribution statement

Mengyue Fu: Writing – original draft, Formal analysis, Data curation. **Rui Xu:** Methodology, Investigation, Formal analysis. **Guizhen Chen:** Resources, Investigation. **Xuemei Zheng:** Investigation, Data curation. **Bin Shu:** Validation, Supervision. **He Huang:** Validation, Project administration. **Guangyou Duan:** Project administration, Methodology. **Yuanjing Chen:** Writing – review & editing, Project administration, Methodology, Funding acquisition.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Yuanjing Chen reports was provided by Chongqing Municipal Education Commission. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

We would like to express our sincere gratitude to Dr. Li Li and Dr. Bin Zhu from the Thoracic Surgery Department for providing us with tremendous support throughout the trial. Many thanks are owed to Mr. Qiangting Deng, a brilliant statistician who provided us with invaluable advice on statistics.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e25100.

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