Lung Protective Effects of Esketamine in Patients undergoing video-assisted thoracoscopic surgery: A randomized controlled trial

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Research Article

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Abstract

Background

Video-assisted thoracic surgery (VATS) is associated with pulmonary function impairment on account of the specificity of the surgical site. Recent studies have reported that the widespread application of esketamine in general anesthesia. Esketamine acts on multiple receptors but the role in pulmonary protection is indeterminate. Hence, we hypothesized that esketamine exerts protective effects on pulmonary function in patients undergoing VATS and further investigate the possible mechanisms and determine the effects of different dosages.

Methods

Patients with aged 18–65 years scheduled for VATS were included in this study. The patients were assigned randomly to 3 groups as follows: esketamine was administered in group K1 as an initial loading bolus of 0.5 mg/kg before induction and followed by a maintenance infusion of 0.5 mg/kg/h during surgery, patients in group K2 received esketamine as an initial loading bolus of 1.0 mg/kg before induction and followed by 0.5 mg/kg/h during surgery. And group C was received identical amount of normal saline as a placebo.

Results

In total, 85 eligible patients were enrolled in our study. Patients in the placebo group had lower a/A ratio and OI, higher RI and A-aDO2 when discharged from ICU and 24h postoperatively (all p < 0.05), higher incidence of postoperative pulmonary complications (PPCs) (p = 0.017), higher resting and movement numerical rating scale (NRS) at 24h and 48h postoperatively, greater fluctuations of blood pressure and heart rate intraoperatively compared with the esketamine groups. While the time of tracheal extubation, length of intensive care unit stay, the serum levels of procalcitonin (PCT) and the incidence of postoperative adverse events were similar among the 3 groups.

Conclusions

Esketamine administration was effective in protecting pulmonary function in patients undergoing VATS by improving oxygenation, reducing hemodynamic fluctuation and postoperative pain. But the relationship between the optimal dosage and minimal adverse events needed further researches.

1. Introduction

After COVID-19 pandemic, the clinical detective rate of lung cancer is obviously enhanced, which is the second most common cancer with 2 million diagnoses and 1.8 million deaths each year[1]. Video-assisted
thoracoscopic surgery (VATS) as the recommended treatment for patients with early-stage non-small lung cancer which has low complication rate, increased 5-year survival mortality rate, short intercostal drainage duration and less postoperative pain when compared with conventional thoracotomy [2, 3]. Protective lung ventilation strategies, preoperative respiratory function exercises, multi-model analgesia and the application of some anesthetics are usually adopted by anesthetists to prevent the occurrence of lung injury in patients undergoing VATS [4–7]. However, due to the hyperperfusion and ventilator-induced injury of the nonoperative lung, the ischemia-reperfusion injury and shear stress on reventilation of the collapsed lung and inflammatory cytokines or reactive oxygen species of surgery manipulation, the incidence of lung injury still remains high [8]. Acute lung injury caused by these physiological mechanisms is the main cause to affect the rapid recovery after surgery and also closely associated with increased postoperative pulmonary complications (PPCs) and mortality.

Esketamine, a noncompetitive N-methyl-D-aspartic acid (NMDA) receptor antagonist, which is the S-enantiomer of ketamine and has stronger sedative and analgesic effects, fewer adverse events and less cardiorespiratory depression than ketamine [9]. It has been FDA-approved in the United States in 2019 and received wide attention for treating resistant depression as an antidepressants [10]. Some studies have investigated the application of esketamine in pediatric surgery, outpatient gastrointestinal endoscopy, obstetric anesthesia and postoperative assisted analgesia by reducing opioid consumption and opioid-induced cough, prolonging the duration of analgesic action, decreasing induction hypotension through its sympathetic stimulation and antagonism of the NMDA receptor [11–14]. Previous study showed that the use of ketamine could result in lower pain score, higher postoperative SpO₂, anti-inflammatory effect after thoracic surgery because of its remarkably stable hemodynamic conditions, better respiratory parameters and effectively counter opioid-induced respiratory depression [15–17]. Theoretically, esketamine might be promising in postoperative prognosis, yet there is still a lack of research concentrate on whether esketamine can improve lung function and its relationship between dose and effect.

Thus, we propose the hypothesis that intravenous use of esketamine may improve pulmonary function and we further explore the underlying mechanisms and its influence of different dosage of esketamine's pulmonary protective effect in patients undergoing video-assisted thoracoscopic surgery.

2. Materials and methods

2.1 Design and patients

This prospective, randomized, controlled study has been approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (No.2021 – 318) and was also registered in the Chinese Clinical Trials Registry (registration number: ChiCTR2100051518, date: 25/09/2021) https://www.chictr.org.cn/. All patients signed informed consent before surgery and the study was conducted under the guiding principles of the World Medical Association Declaration of Helsinki.
Ninety Patients with American Society of Anesthesiologists (ASA) classification II or III, aged 18–65 years, BMI between 18–30 kg/m², were selected undergoing elective video-assisted thoracoscopic surgery from September 2021 to June 2022. Exclusion criteria were contraindications to esketamine, poorly unregulated or malignant hypertension (systolic/diastolic blood pressure over 180/110 mmHg), increased intracranial pressure, untreated or under-treated hyperthyroidism, severe cardiopulmonary disease, liver or kidney dysfunction, mental illness or substance abuse, impossibility to have a good comprehension of the study, refusal to participate, persistently intraoperative $S_pO_2$ 90% even after fiberoptic bronchoscopy’s adjustment.

2.2 Randomization

Patients were randomly assigned into three groups (n = 30) by a 1:1:1 ratio using a computer-generated randomization table before initiation of the study: low-dose esketamine group (K1 group), high-dose esketamine group (K2 group) and control group (C group). For allocation concealment, group assignments were placed in sealed envelopes. The surgeons and nurses who were involved in perioperative management, postoperative follow-up as well as patients themselves were blinded to the group assignment.

2.3 Anesthetic management and intervention

All patients were fasted for 6-8h. Routine intraoperative monitoring was established, including pulse oxygen saturation, heart rate, electrocardiogram. Radial artery puncture catheter under local anesthesia was placed for measuring arterial blood pressure and sampling arterial blood gas. Anesthesia was induced with midazolam 0.06–0.08 mg/kg, propofol 1.5-2 mg/kg, sufentanil 0.5–0.6 ug/kg, vecuronium 0.08–0.12 mg/kg. After the induction of anesthesia, a endotracheal double-lumen tube (female 32 or 35F, male 35 or 37F) was intubated and was adjusted to the exact position using fiberoptic bronchoscopy. Anesthesia was maintained with remifentanil (0.15–0.3 ug/kg/min), propofol (4–8 mg/kg/h) and combined with inhalation of sevoflurane 1–2% in 100% oxygen. In K1 group, patients received a bolus of 0.5 mg/kg of esketamine intravenously followed by a continuous infusion of 0.5 mg/kg/h during surgery. In K2 group, a loading dose of 1.0 mg/kg of esketamine intravenously before intubation followed by a continuous infusion of 0.5 mg/kg/h during surgery. In C group, the equivalent volume of saline was used.

The ventilation parameters were standardized in all three groups: tidal volume (VT) of 6 ml/kg, FiO2 100%, positive end-expiratory pressure of 5 cmH2O, respiratory rate of 14–16 times/min, inspiratory-to-expiratory ratio of 1:2, and end-tidal carbon dioxide partial pressure (PetCO2) of 35–45 mmHg. The goals of intra-operative haemodynamics were a mean arterial pressure between 70 and 100 mmHg, a heart rate between 50 and 100 beats/min, $S_pO_2$ over 90%, the BIS value was maintained between 40 and 60. After surgery, all patients need to change from a double-lumen tracheal tube into a single-lumen tracheal tube and then transferred to the thoracic surgery intensive care unit (ICU) for observation. The tracheal tube was removed when the patients reached the extubation criteria.

2.4 Measurements
Radial arterial blood collected before induction of anesthesia (T0), after intubation (T1), 30 min of one-lung ventilation (T2) (OLV), 1 h of OLV (T3), after the resumption of bilateral ventilation (T4), admission to ICU (T5), after extubation (T6), discharge from ICU (T7) and 24 h postoperatively (T8). Vein blood was collected 24 h postoperatively to illustrate the levels of white blood cells, neutrophil percentage, and procalcitonin.

Blood pressure and heart rate were recorded from T0 to T4, respiratory parameters such as VT, PetCO2 were recorded from T1 to T4. The arterial-alveolar oxygen partial pressure ratio (a/A ratio), oxygenation index (OI), alveolar arterial partial pressure difference of oxygen (A-aDO2), respiratory index (RI), dynamic lung compliance (Cdyn), static lung compliance (Cst), and dead space volume (Vd/Vt) were recorded and calculated as following:

\[
a/A = \frac{PaO2}{PAO2}
\]

\[
OI = \frac{PaO2}{FiO2}
\]

\[
RI = \frac{A-aDO2}{PaO2}
\]

\[
A-aDO2 = \frac{PAO2-PaO2}{0.8-PaO2} = 713FiO2 - PaCO2
\]

\[
Cdyn = \frac{Vt}{(Ppeak-PEEP)}
\]

\[
Cst = \frac{Vt}{(Pplat-PEEP)}
\]

\[
Vd/Vt = \frac{(PaCO2-PeTCO2)}{PaCO2}
\]

### 2.5 Primary and Secondary Outcomes

In our study, the primary outcome was the a/A ratio. The secondary outcomes included: (1) other variables reflecting pulmonary function (OI, A-aDO2, RI, Cdyn, Cst, Vd/Vt); (2) the ICU and hospital length of stays; (3) the dosage of anesthetics (propofol, sufentanyl, remifentanil, and vasoactive drugs); (4) the incidence of postoperative nausea and vomiting or other adverse effects; (5) the incidence of PPCs 7 days after surgery; (6) the value of pain score at 24 h and 48 h during rest and movement respectively by using the 11-point numerical rating scale (NRS).

### 2.6 Statistical Analysis

A sample size calculation was based on PASS 15.0. According to our pilot trial, the a/A ratio reflecting pulmonary gas exchange function was 0.65 at 24 hours after surgery in patients underwent video-assisted thoracoscopic surgery. Thus, we hypothesized that esketamine could increase a/A ratio by 10%, \( \alpha = 0.05 \) and \( 1-\beta = 0.9 \), a sample of 21 was necessary in each group. Anticipating the cases’ dropout was 30%, a total of 90 cases needed to enroll in our study.

SPSS version 26.0 was used for statistical analysis. The measurement variables of normal distribution were expressed as mean ± standard deviation (\( x \pm SD \)) and were compared using one-way analysis of variance (ANOVA). While non-normally distributed variables were described using the median (interquartile...
range 25th–75th percentiles), and were compared using Kruskal-Wallis H test. Categorical variables were expressed as count and percentage (%), and the Chi-square test or the Fisher’s exact test was used to compare categorical variables among groups, and post-hoc was performed using the least significance difference test (LSD-t). Two-way repeated measures ANOVA was analyzed for repeated measures, testing for a difference between and within the groups, and for Time x Group interaction effect. The P value < 0.05 was considered statistically significant.

3. Results

From September 2021 to June 2022, we evaluated 100 patients for eligibility. Six patients did not meet the inclusion criteria, three refused to participate, and one did not enroll in this study because other reason. Twenty-eight patients were randomly assigned to K1 group, twenty-nine patients were randomly assigned to K2 group and twenty-eight patients were randomly assigned to C group. Two patients in K1 group were excluded due to lost to follow-up and changed to thoracotomy, one patient in K2 group was excluded due to lost to follow-up and two patients in C group were excluded due to lost to follow-up and SpO₂ persistently lower than 90% (Figure 1).

There were no significant differences in the demographic profile and baseline characteristics that we evaluated among the three groups (Table 1).

3.1 The a/A ratio outcome

As shown in Fig. 2a, we observed an obvious decrease about a/A ratio at the beginning of mechanical ventilation and one-lung ventilation in all three groups, and gradually increased at the end of surgery. The a/A ratio of K1 and K2 groups recovered fully to the preoperative level and significantly higher at T7 and T8, but C group was still significantly lower than the preoperative level and lower than the esketamine groups (T7: C vs K1 vs K2=64.5±3.6 vs 83.2±3.6 vs 79.7±3.5, F=7.801, P=0.001 <0.05) (T8: C vs K1 vs K2=64.7±18.2 vs 84.4±18.8 vs 82.6±17.8, F=9.961, P=0.000 <0.05, (ANOVA analysis: P<0.05, P<0.05, P<0.05)). And there was no significant differences between K1 and K2 groups (Fig. 2a).

3.2 Other variables reflecting pulmonary gas exchange function

Compared with K1 and K2 group, the RI of patients in C group at T7 and T8 was significantly higher (T7: C vs K1 vs K2=0.65±0.40 vs 0.27±0.33 vs 0.37±0.47, F=6.103, P=0.003 <0.05) (T8: C vs K1 vs K2=0.67±0.46 vs 0.25±0.35 vs 0.27±0.32, F=10.443, P=0.000 <0.05, (ANOVA analysis: P<0.05, P<0.05, P<0.05)) (Fig.2b).

Compared with K1 and K2 group, the ratio of OI in C group at T7 and T8 was significantly lower (T7: C vs K1 vs K2=391.9±98.5 vs 488.8±107.7 vs 472.6±123.2, F=6.20, P=0.003 <0.05) (T8: C vs K1 vs K2=373.6±97.6 vs 480.5±107.9 vs 470.5±98.6, F=9.531, P=0.000 <0.05, (ANOVA analysis: P<0.05, P<0.05, P<0.05)) (Fig.2c).
Compared with K1 and K2 group, the A-aDO2 ratio in C group was significantly higher at T7 and T8 (T7: C vs K1 vs K2 = 80.8±27.5 vs 43.6±19.9 vs 48.9±24.8, F=19.53, P=0.0000.05) (T8: C vs K1 vs K2 = 78.9±33.1 vs 35.5±13.2 vs 38.5±19.3, F=30.376, P=0.0000.05, (ANOVA analysis: P (group)<0.05, P (time)<0.05, P (group x time)<0.05)). There was no significant difference between K1 and K2 group in RI, OI and A-aDO2 ratio at each time point (all P>0.05) (Fig.2d).

3.3 The Vd/Vt outcome reflecting pulmonary ventilation function

We observed a significant increase in alveolar dead space fraction after OLV and peaked at T4 in K1 group and C group (P<0.05), but we did not observe an obvious change in K2 group, whose alveolar dead space fraction was significantly lower than K1 group and C group (T3: C vs K1 vs K2 = 19.5±4.3 vs 19.4±5.4 vs 15.6±5.4, F=5.454, P=0.0060.05) (T4: C vs K1 vs K2 = 22.7±4.5 vs 20.3±6.7 vs 15.4±5.7, F=12.444, P=0.0000.05, (ANOVA analysis: P (group)<0.05, P (time)<0.05, P (group x time)<0.05)) (Fig.3a).

3.4 The variables reflecting pulmonary respiratory mechanics

Cst and Cdyn decreased significantly in all three groups after OLV, but Cst in C group was no significant difference compared with group K1 and K2 at same time point (P>0.05) (Fig.3b). Cdyn was higher in K2 group than in C and K1 groups at T2 (F=3.667, P=0.03 < 0.05, (ANOVA analysis: P (time)<0.05)) and no significant difference between group C and K1 groups (P>0.05) (Fig.3c).

3.5 Intraoperative haemodynamics

Intraoperative MAP and HR in the all three groups decreased after anesthesia, but K1 and K2 group fluctuated less than group C (p 0.05). Specifically, C group had significant lower MAP and HR at T1-T4 than K2 group (p 0.05). In addition, HR at T2 and T4 in K1 group lower than K2 group (p 0.05), intraoperative hemodynamics had no significant differences between the two esketamine groups (p 0.05) (Table 2).

3.6 Postoperative pain scores

Postoperative pain scores were assessed by patients using the numeric rating scale at 24h and 48h after surgery. Higher postoperative pain scores at rest and movement NRS were reported in C group compared with K1 group at both time points, meanwhile the rest and movement NRS in K2 group were significant higher than group K1 at 48h postoperatively. But at the 24h postoperatively there was no difference (Table 3).

3.7 Incidence of postoperative pulmonary complications

Postoperative pulmonary complications occurred in 15 patients (53.6%) in C group and only 7 patients (25%) in K1 group and 6 patients (20.7%) in K2 group, and the incidence was significantly higher in C group compared with K1 and K2 group (P=0.017<0.05). It was similar between group K1 and K2 (P>0.05). The most common PPCs was postoperative respiratory failure, with incidence rates of
46.4%, 25.0%, and 13.7% in C, K1 and K2 group respectively, and C group was significantly higher than K1 and K2 group (P=0.010<0.05), and no significant difference between K1 and K2 group (P>0.05) (Table 4).

3.8 Postoperative adverse events and inflammatory biomarkers

The postoperative adverse events had shown in table 4. The incidence of postoperative nausea and vomiting in the three groups was similar (P=1.000>0.05). One case in K1 group had a psychiatric adverse reaction manifested as postoperative nightmare with an incidence of 3.6%, and two patients in K2 group had agitation during extubation with an incidence of 6.9%, and there was no significant difference (P>0.05) in the incidence of adverse events among the three groups.

There was no significant differences in the time of tracheal extubation, length of intensive care unit stay, and hospital stay among three groups (P>0.05). Postoperative inflammatory indexes were equally elevated in all three groups (P>0.05) (Table 5).

4. Discussion

In this randomized controlled trial conducted in patients undergoing video-assisted thoracoscopic surgery, we investigated that perioperative esketamine was associated with significant trend of pulmonary protective function especially the improvement of pulmonary gas exchange function. In addition, patients in the esketamine groups had significantly lower postoperative rest and movement pain scores, better stable hemodynamics and lower occurrence of PPCs. However, the different inducting doses of 0.5 mg/kg and 1.0 mg/kg provided similarly beneficial effects in lung protective function.

Ketamine as a noncompetitive, N-methyl-D-aspartate receptor antagonist, showed its bronchodilatatory properties by the mechanisms of direct relaxant effect, histamine and acetylcholine antagonistic effect, calcium influx blockage and membrane-stabilizing effect in some asthma case reports thus further reduced airway resistance, increased lung compliance, and was approved as a rapid intubation induction drug in patients with bronchial asthma[18, 19]. Mehrdad Esmailian[20] found that in mild to moderate asthma patients, administration of 0.4–0.5 mg/kg doses of ketamine can relieve asthma symptom by improving peak expiratory flow rate. In our study, the intraoperative Cst and Cdyn of patients was lower while the alveolar dead space volume was significantly higher in C group than that in K2 group, indicates esketamine can improve respiratory mechanics and lung compliance, which may be one of the esketamine's lung protection mechanisms.

Patients undergoing video-assisted thoracoscopic surgery are potentially prone to hypertension, poor haemodynamic stability, and the unstable hemodynamics adversely affect the oxygenation situation. Esketamine can increase heart rate and cardiac output through its sympathetic stimulation, analgesia and antagonism[21]. Wencai Tu's[9] study suggested combined low-dose esketamine for anaesthesia induction in the elderly undergoing knee arthroplasty reduced the incidence of hypotension and was more hemodynamically stable, which is in accordance with our findings.
Although the mechanism has not been completely clarified, the analgesic effects of esketamine have been confirmed in many studies. Helmar’s study showed minimal-dose esketamine (0.015 mg/kg/h continuous intravenous infusion) for 48h can achieve optimal postoperative analgesia and minimizing the risk of the corresponding complications\[22\]. Helena’s study observed intravenous use of esketamine combined with thoracic paravertebral nerve block reduced pain scores at 48h postoperatively\[23\]. Our study found 0.5 mg/kg esketamine reduced pain scores in thoracoscopic patients for 48h postoperatively, perhaps lower pain had a favorable impact on early activity and sputum removal. Those manifestations further promote the recovery of pulmonary function.

The anti-inflammatory effect of esketamine may be an additional mechanism. Surgical manipulation causes the damaged cells to release cytoplasmic substance which can trigger inflammatory cascade by activating the corresponding receptors. Meanwhile, lung re-expansion after one-lung ventilation led to local neutrophil recruitment, enhanced pulmonary myeloperoxidase activity, increased vascular permeability and pulmonary edema. This causes systemic inflammatory response with elevated levels of inflammatory cytokines such as IL-6 and IL-1\[24, 25\]. Previous studies showed that esketamine can produce systemic anti-inflammatory effects by inhibiting the production of inflammatory factors (including IL-6 and TNF-α) and neutrophil activation\[26\]. Welters’ study showed that the use of esketamine as the only analgesic during coronary artery bypass surgery significantly reduced the pro-inflammatory cytokines IL-6 and IL-8 after aortic opening levels and elevated levels of the anti-inflammatory factor IL-10\[27\]. This suggests that esketamine may act as an immunomodulatory agent in thoracoscopic partial pneumonectomy, mitigating lung injury and protecting lung function by suppressing inflammatory response. Although no significant differences in postoperative inflammatory biomarkers were found among the three groups of patients in our study, this may be related to our small sample size and the fact that we monitored systemic inflammation-related indicators rather than inflammatory indicators associated with lung injury.

The adverse mental events associated with NMDA receptor antagonists are the main reasons for its limited use in the past. Esketamine had fewer adverse reactions than racemic ketamine, and the application of midazolam also reduced the incidence of adverse events. In our study, there were only three patients had esketamine related adverse reactions, and 1 patient presented as postoperative nightmare and the patient’s symptoms soon remissioned spontaneously, and 2 patients showed agitation during extubation and improved after intramuscular injection of morphine.

### 5. Limitations

Our study has some limitations. First, this prospective, randomized, controlled study was performed at a single center with small samples, which needs to be verified by a multicenter and large sample clinical study. Second, the fact that we did not find the differences about lung related indicators in two groups of different dosage. It is possible that those selected measures did not capture the important variations of pulmonary function. Third, we hypothesized that the protective effect of esketamine on lung function may be related to its anti-inflammatory effect, but no discrepancy about inflammatory factors associated with lung injury were observed in this study. The changes in inflammatory factors associated with this study
need to be confirmed by further studies. At last, in the present study, we only observed two different induction dosages of esketamine, further dose stratification will allow for clarifying the relationship between dosage and efficacy.

6. Conclusions

In summary, we observed esketamine can improve oxygenation, alleviate lung injury, provide pulmonary protection and reduce postoperative rest and movement pain scores in patients undergoing video-assisted thoracoscopic surgery. However, there are no difference between two doses of esketamine administered for improving postoperative length of ICU stay and hospital stay. Meanwhile, though the difference did not reach statistical significance about esketamine’s postoperative adverse mental reaction, it should be evaluated in future studies.

Declarations

Ethics approval and consent to participate: Not applicable.

Consent for publication: Consent for publication has been obtained from all persons for the included images.

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

Competing interests: All other authors declare that they have no competing interests.

References


Tables

Tables 1 to 5 are available in the Supplementary Files section

Figures

Figure 1

Flowchart of the study design
Figure 2

Changes about a/A ratio and other variables reflecting pulmonary gas exchange function at various time points in patients undergoing VATS

- **a** a/A ratio
- **b** RI
- **c** OI
- **d** A-aDO2

# means P<0.05 in group K1 versus C.* means P<0.05 in group K2 versus C.

T0, before anesthesia.
T1, after intubation.
T2, 30min of OLV.
T3, 1h of OLV.
T4, after the resumption of bilateral ventilation.
T5, admission to ICU.
T6, after extubation.
T7, discharge from ICU.
T8, 24h postoperatively.
Figure 3

Indicators reflecting pulmonary Vd/Vt, Cst and Cdyn at various time point in patients undergoing VATS.

*a* Vd/Vt, Dead space-to-tidal volume ratio; *b* Cst, Static lung compliance; *c* Cdyn, Dynamic compliance. * means P<0.05 in group K2 versus other two groups.
Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.docx
- Table2.docx
- Table3.docx
- Table4.docx
- Table5.docx