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ORIGINAL RESEARCH

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Low-dose esketamine improves acute postoperative pain in patients undergoing thoracoscopic surgery

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Abstract

Purpose The current study was designed to investigate the analgesic effect of esketamine on patients underwent thoracoscopic surgery and the underlying mechanism.

Methods In this randomized, double blind, placebo-controlled study, 60 patients scheduled to undergo thoracoscopic lobectomy or segmentectomy were randomized to two groups to receive esketamine (group ESK) or saline (group SAL), respectively. 0.25 $mg{\cdot}kg^{-1}$ esketamine was given in group ESK for induction of anesthesia, and 0.12 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ esketamine for intraoperative maintenance. Group SAL received an equal volume of saline. The primary outcomes were the visual analogue scale (VAS) pain scores at rest and deep cough state which evaluated at departure from post-anesthesia care unit (PACU) (T1), 6 h, 24 h and 48 h after surgery (T2–T4). The secondary outcomes included the levels of white blood cell (WBC) count, absolute neutrophil count (ANC), interleukin-6 (IL-6), procalcitonin (PCT), anxiety/depression scores at T3, oxygen saturation (SpO2), and adverse reactions.

Results Esketamine significantly decreased both rest and cough VAS pain scores at T1, and rest pain scores at T1, T2 and T4. Patients in ESK group had significantly lower WBC and ANC levels than SAL group, while the alteration of IL-6 and PCT levels between groups showed no significance. The anxiety scores of patients in both groups were significantly decreased after surgery. However, the depression scores of patients in ESK group did not decrease after surgery when compared with the preoperation. The postoperative SpO2 and the incidence of adverse reaction including postoperative nausea, vomiting, dizziness and dissociative symptom showed no significant difference between two groups ($p > 0.05$).

Conclusion Esketamine can alleviate the acute postoperative pain of patients undergoing thoracoscopic surgery without increasing adverse reactions, and the underlying mechanism may be associated with the reduction of postoperative inflammation.

Trial registration Registered at Chinese Clinical Trial Registry on February 7, 2022 (ChiCTR 2200056524).

Keywords Esketamine, Thoracic surgery, Analgesia, Inflammatory response

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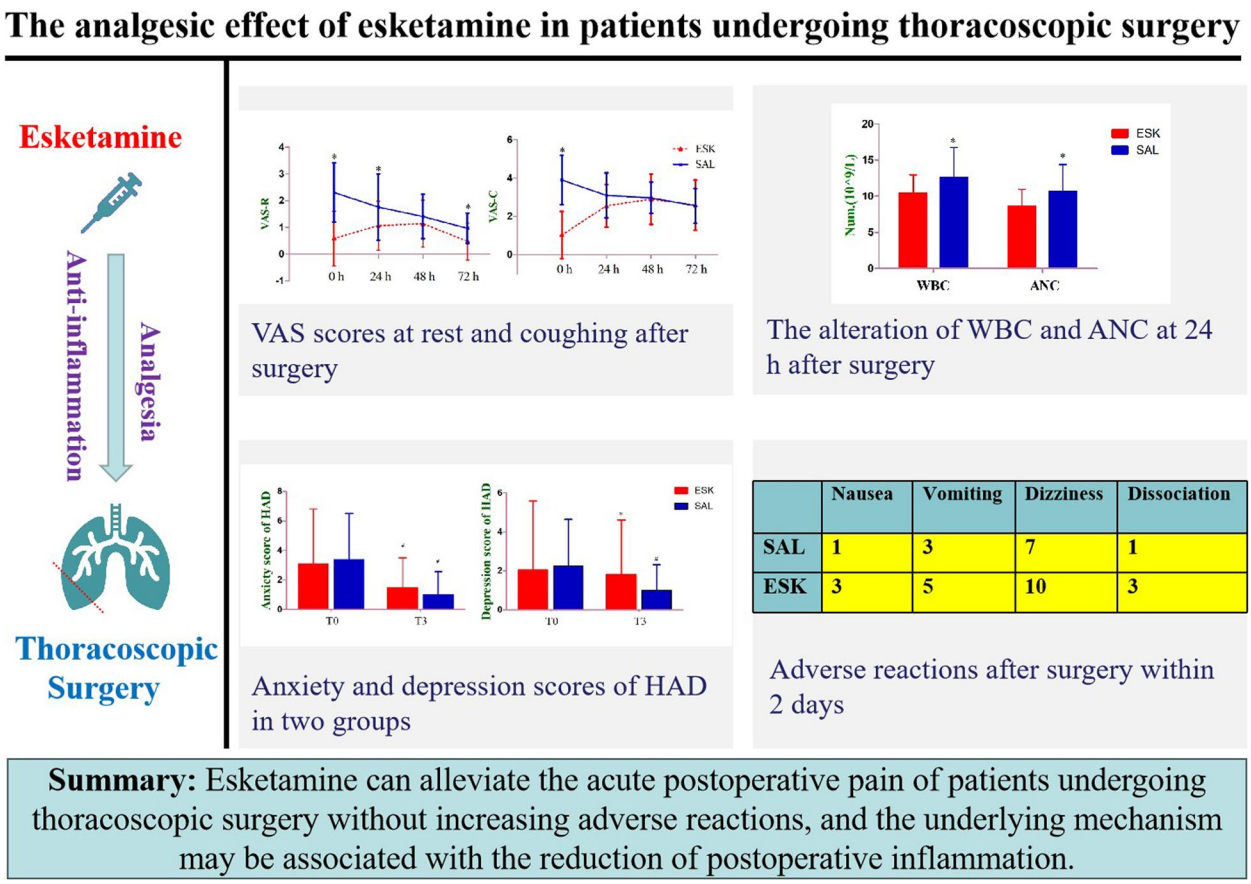
Graphical Abstract



	Nausea	Vomiting	Dizziness	Dissociation
SAL	1	3	7	1
ESK	3	5	10	3

1 Introduction

Video-assisted thoracic surgery (VATS) is the primary and minimally invasive therapy for thoracic tumors in clinical practice. However, VATS still induces moderate to severe postoperative pain in patients as a result of incision damage, tissue traction or drainage tube stimulus [1, 2]. Invasive operation often induces inflammatory cascade, which leads to enhanced and prolonged postoperative pain. Moreover, chronic inflammatory stimulation can decrease excitation threshold of nociceptive nerve endings, resulting in hyperalgesia and even spontaneous pain in corresponding areas [3]. Epidural or para-vertebral nerve block, as the gold standard for thoracic analgesia, has strict application restrictions and a certain rate of failure. Perioperative application of opioids may induce critical adverse effects including respiratory depression or atelectasis, which could be profoundly unbeneficial for patients after VATS. Thus, it has become a critical issue to find a safe and convenient resolution to alleviate postoperative pain in patients undergoing VATS.

Esketamine (S-ketamine) is the dextral isomer of ketamine and provides favorable sedation, analgesia and anti-anxiety effects. Previous studies suggest that the esketamine has a stronger affinity for N-methyl-D-aspartate receptor (NMDAR) and its analgesic efficacy is twice as effective as ketamine, while its adverse reactions especially the dissociative and psychotomimetic side effects are still argument. It has been also reported that the analgesic effects of ketamine was mediated by inhibiting the production of inflammatory factors such as interleukin- 6 (IL-6) and tumor necrosis factor-α (TNF-α) [4]. However, there lacks relevant studies as regard to the analgesic effect of esketamine in patients undergoing thoracoscopic lobectomy.

To determine whether intraoperative administration of low-dose esketamine relieves postoperative pain in patents following thoracoscopic surgery and whether the analgesic effect is associated with its anti-inflammatory effect, we conducted this randomised, double blind, placebo-controlled study.

2 Methods

This trial has been registered at Chinese Clinical Trial Registry (ChiCTR 2200056524) and approved by the ethics committee of the first affiliated hospital of nanjing medical university (2021-SR-281). Written informed consent was obtained from all participants before enrollment. All study procedures were conducted according to good clinical practice guidelines and adhered to the tenets of the Declaration of Helsinki.

2.1 Subjects

Patients scheduled for thoracoscopic lobectomy or segmentectomy under general anesthesia, aged 18–75 years, American Society of Anesthesiologists (ASA) I–III, were enrolled in this study. Exclusion criteria included: allergy for used drugs; preexisting neurological or psychiatric illnesses; difficulties in cooperation; and severe unexpected surgical complications.

2.2 Study intervention

A total of 60 patients were enrolled in this randomized controlled double-blind study. Patient grouping and medication preparation were completed by one person. Anesthesia implementation and postoperative data collection were completed by two other individuals who were not aware of the patient grouping.

Eligible patients were randomized and equally divided into esketamine group (ESK group) or saline group (SAL group) according to the randomization table.

Peripheral vein access of the upper limb of patients was established after they entered the operating room, and electrocardiogram, invasive (intra-arterial) blood pressure (IBP), heart rate and oxygen saturation (SpO2) were monitored continuously. Double lung ventilation parameters were set as 8 $ml \cdot kg^{-1}$ of tide volume, 10–14 breaths/min and I:E = 1:2. During one-lung ventilation, tide volume was set 6 $ml \cdot kg^{-1}$, 12–16 breaths/min and I:E = 1:1.5, maintaining $P_{ET}CO_2$ 35–45 mmHg, and inspired oxygen fraction as needed up to 100%. After surgery, patients were sent to PACU and the tracheal tube would be removed after consciousness and spontaneous breath recovery. When vital signs stabilization for more than 15 min under air and modified Aldrete sore ≥ 9, the patients were allowed return to ward.

2.2.1 Drug administration

Patients in ESK group were administrated with esketamine at anesthesia induction (0.25 $mg \cdot kg^{-1}$, i.v.) and maintained at the rate of 0.12 $mg \cdot kg^{-1} \cdot h^{-1}$ until the beginning of thoracic closure. SAL group was given the same volume of saline. General anesthesia was induced with midazolam (0.5 $mg \cdot kg^{-1}$), etomidate (0.2 $mg \cdot kg^{-1}$) and fentanyl (4 $\mu g \cdot kg^{-1}$) and cisatracurium (0.15 $mg \cdot kg^{-1}$) with additional fentanyl of 2 $\mu g \cdot kg^{-1}$ before incision. A double-lumen tracheal catheter was inserted under a visual laryngoscope and positioned under fibrobronchoscopy. Anesthesia was maintained with propofol(2–4 $mg \cdot kg^{-1} \cdot h^{-1}$), remifentanil (0.1–0.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$), and cisatracurium (0.15 $mg \cdot kg^{-1} \cdot h^{-1}$). Sevoflurane (1%–3%) was adjusted accordingly to maintain a stable IBP within 20% of baseline blood pressure and bispectral index (40–60).

Endoscopic assisted intercostal nerve block were applied in all patients with 0.375% ropivacaine 20 ml before suturing the incision. Parecoxib 40 mg was titrated intravenously, if postoperative visual analogue scale (VAS) > 3. Meanwhile, Dezocine or tramadol was used as a rescue measure when the patient was not satisfied with the analgesic effect or the VAS score was still greater than 3.

2.3 Measurements

VAS (scores from 0 = no pain to 10 = worst pain imaginable) at rest (VAS-R) and cough state (VAS-C) were recorded at departure from PACU (T1), 6 h (T2), 24 h (T3) and 48 h (T4) after surgery. SpO_2 was recorded at T0–T4 as assessment of respiratory function. Intravenous blood collection was performed at preoperative visit (T0) and T3, and then the white blood cell (WBC), absolute neutrophil count (ANC), IL-6 and procalcitonin (PCT) were examined at T3 to estimate the systemic inflammatory response. The Hospital Anxiety and Depression (HAD) scale (scores from 0 = not anxiety nor depression to 18 = severe anxiety and depression) were investigated before and 24 h after surgery. Overall satisfaction with pain therapy was assessed at 8 h after surgery (1 = very satisfied, 2 = satisfied, 3 = unsatisfied, and 4 = very unsatisfied). Adverse reactions including nausea, vomiting, dizziness and psychiatric symptoms (involuntary language or body movements) were documented. As regard to patients' recovery, extubation time, PACU retention time, chest tube extraction time and discharge time were recorded.

2.4 Data analysis

Statistical analysis was performed using the IBM SPSS Statistics 25.0 software. Numerical variables were expressed as mean ± standard deviation, and comparisons between groups were performed using two independent sample T tests or Mann-Whitney test. Categorical variables were expressed in percentage or number of cases and compared by χ^2 test or Fisher's exact test. Repeated measurement data were analyzed by repeated measures

Analysis of Variance (ANOVA). *P*-values < 0.05 were considered statistically significant.

2.5 Sample size calculation

In this study, we assumed that compared with the SAL group, the decrease of average VAS scores in the ESK group achieve more than 2 points is defined as clinical significance. According to the preliminary experimental results, the standard deviation of postoperative cough VAS score was 1.5 which was evaluated at departure from PACU. The probability of making class I errors should not exceed 1% and the probability of making class II errors should not exceed 10%. When the freedom of the T-boundary value table was infinite, the bilateral t0.01 = 2.5758, t0.1 = 11.6449, the sample size of each group was calculated to be 20 cases. Therefore, there were 30 patients in each group of this experiment in case of dropping during the trial.

3 Results

Sixty patients were recruited in the study (Fig. 1). Two patients were excluded from this study, including one patient in ESK group refused postoperative trial and the other one in SAL group had severe bronchial residual terminus leakage and chylothorax comorbidly after surgery. Therefore, data from 58 patients were analyzed.

3.1 Patient characteristics and operative data

Patients in two groups had similar demographic and health data (Table 1). No difference was found in surgery duration, extubation time and discharge time between groups ($P > 0.05$). However, esketamine efficiently reduced the PACU retention time and chest tube extraction time ($P < 0.05$), which indicated a relatively faster recovery of patients. In addition, there were no significant differences in the incidence of hypertension, hypotension, tachycardia, and bradycardia during the operation between groups, which indicates that esketamine did not increase the incidence of hemodynamic disturbances.

3.2 Analgesic effect of esketamine

Patients in ESK group had lower VAS-R than SAL group at all time points, and the difference was statistically significant at T1, T2 and T4 ($P < 0.05$) (Fig. 2A). In cough state, VAS-C of ESK group was significantly

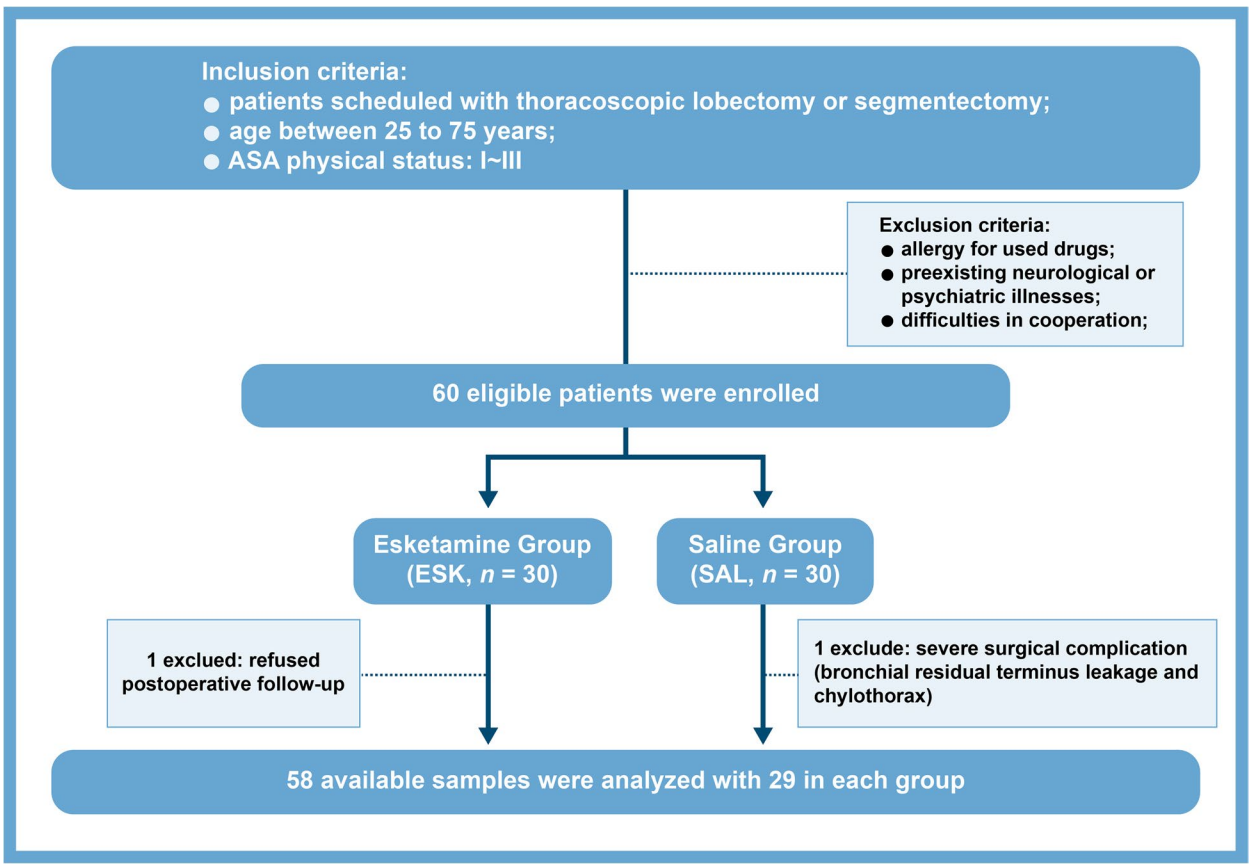


Fig. 1 The flow diagram of this study

Table 1 Demographics and clinical characteristics

	SAL group ($n=29$)	ESK group ($n=29$)	*P*-value
Ages (years)	58.34 ± 9.14	58.83 ± 10.94	0.182
Gender (M/F)	10/13	6/23	0.379
Height (cm)	163.71 ± 7.10	162.07 ± 7.49	0.874
Weight (kg)	65.86 ± 11.37	63.62 ± 9.62	0.123
Hypertension (%)	27.59% (8)	20.69% (6)	0.76
Diabetes (%)	6.90% (2)	10.34% (3)	0.22
History of MA[a]	17.24% (5)	6.90% (2)	0.423
Types of surgery			
Lobectomy	18	18	0.292
Segmentectomy	11	11	0.429
Intraoperative data			
Duration of surgery (min)	104.69 ± 30.3	104.40 ± 28.35	0.373
Hypertension	44.83%(13)	37.93%(11)	0.790
Hypotension	55.17%(16)	48.28%(14)	0.793
Tachycardia	6.90%(2)	10.34%(3)	0.999
Bradycardia	3.45%(1)	0	0.999
Postoperative data			
Extubation time (min)	34.28 ± 15.59	25.34 ± 14.97	0.672
Length of stay in PACU (min)	39.14 ± 9.69	36.90 ± 13.22	0.023*
Extubation time of thoracic tube (d)	2.42 ± 2.63	1.96 ± 0.52	0.019*
Discharge time (d)	4.12 ± 2.77	3.37 ± 0.84	0.186

Data are provided as means ± standard deviation or percent (numbers). *P* value represents two-tailed unpaired value or Fisher's exact test with two-tailed *P* value

* *P* < 0.05

[a] MA: Cardiovascular accident

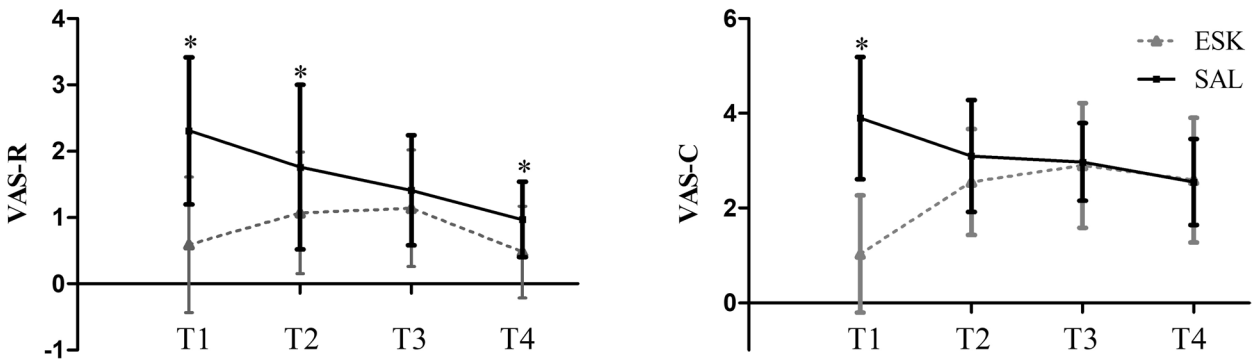


Fig. 2 VAS score of patients at different time points after operation in two groups. **A** VAS-R: the VAS scores of patients at rest. **B** VAS-C: the VAS scores of patients at deep cough. Compared with ESK group, $^{*}P < 0.05$. The date was expressed as mean ± SD and analyzed by repeated measures ANOVA or T tests

lower than that of SAL group at T1 ($P < 0.05$), but there was no statistical significance at other time points (Fig. 2B).

The number of patients using decocine as a rescue analgesic measure after surgery in ESK group was significantly lower than that in SAL group ($P < 0.05$), while there was no statistical difference in the number of patients using tramadol or paricoxib between the two groups ($P > 0.05$) (Table 2).

3.3 Effect of esketamine on respiratory function

The preoperative and postoperative SpO2 had no meaningful difference between two groups ($P < 0.05$) (Fig. 3), and SpO2 declined significantly after surgery in

Table 2 The number of patients receiving rescue analgesics

	SAL group ($n=29$)	ESK group ($n=29$)	*P*-value
Parecoxib	15	15	1
Dezocine	16	7	0.016*
Tramadol	7	4	0.315

Data are provided as number of cases. *P* value represents by χ^2 test or Fisher's exact test

* $P<0.05$

both groups. This result indicates that, unlike opioids, esketamine does not inhibit postoperative respiratory competence.

3.4 Effect of esketamine on systematic inflammation

At T0, two groups showed equivalent pre-operative WBC and ANC levels ($P>0.05$) (Fig. 4A, B). Compared with T0, WBC and ANC levels at T3 increased significantly in both groups. Meanwhile, patiens in ESK group had significantly lower WBC and ANC levels at T3 when compared with SAL group ($P<0.05$). However, the difference of IL-6 and PCT levels in two groups had no statistic significance at T3 (Fig. 4C, D).

3.5 Anti-anxiety and anti-depression effect of esketamine

Patients had close anxiety and depression level before surgery (Fig. 5). The HAD anxiety scores of patients in both groups decreased significantly 24 h after surgery when compared to the preoperative, but had no significant diffference between two groups. Likewise, the HAD depression scores in SAL group decreased significantly after surgery. However, the depression score of patients in ESK group was higher than the SAL groups at T3, with no significant difference with preoperative depression score.

3.6 Overall satisfaction of patients

The overall satisfied percent (very satisfied + satisfied) had no statistical difference between the two groups (Table 3). However, the percent of very satisfied patients in the ESK group was significantly higher than the SAL group ($P<0.05$).

3.7 Adverse reaction

No significant difference was found in the incidence of adverse reactions including postoperative nausea, vomiting, dizziness, and psychotic dissociation symptoms in the two groups ($P>0.05$) (Table 4), which further confirmed the safety of clinical use of esketamine for analgesia.

4 Discussion

Postoperative acute pain can increase complications such as respiratory inhibition, pulmonary infection and even chronic pain, which delaying the enhanced recovery after surgery [5]. Opioids are commonly used in clinic to relief postoperative pain, but it also accompanied with some unexpected adverse effects including respiratory depression, nausea and vomiting, constipation, itchiness and vertigo. It has been reported that the noncompetitive NMDAR antagonist ketamine can increase the analgesic efficacy of opioids and inhibit the transformation from acute pain to chronic pain [6]. However, the side effects of ketamine, for example hallucinations, dizziness, nausea, nightmares, blurred vision and others [7], also lead clinicians to be more cautious when using it. Recent

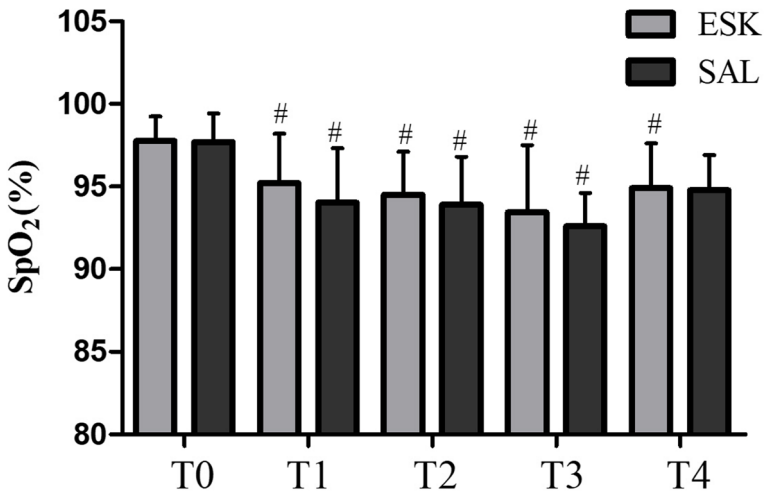


Fig. 3 The SpO2 alteration of patients in two groups. Compared with T0, #$P<0.05$. The date was expressed as mean ± SD and analyzed by repeated measures ANOVA or T tests

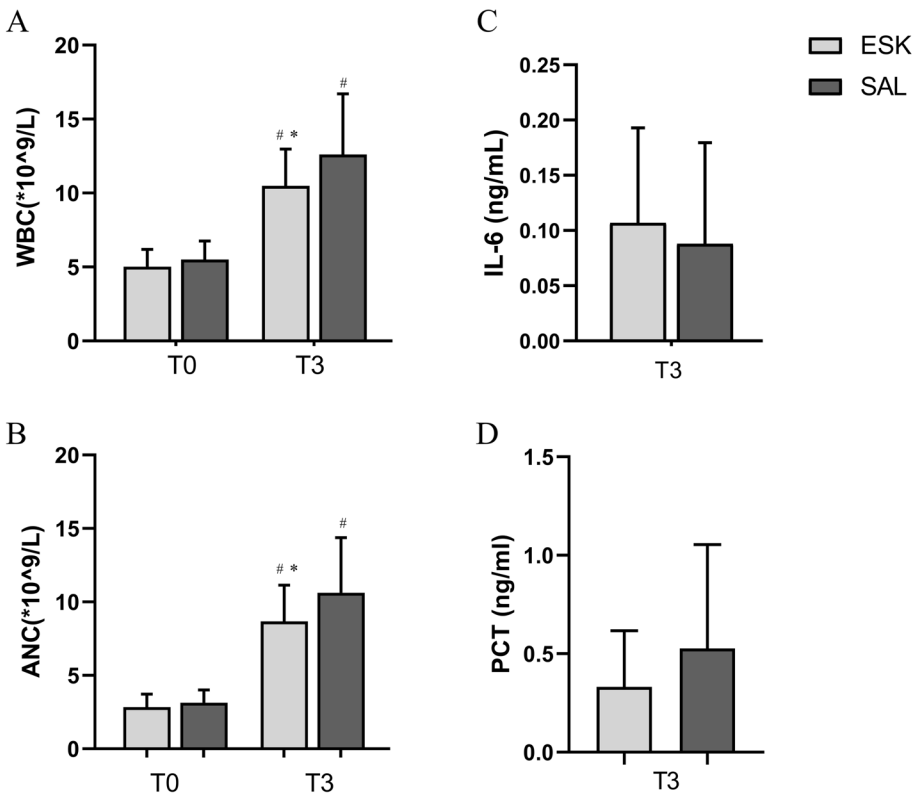


Fig. 4 The levels of inflammatory factors, including (**A**) WBC, (**B**) ANC, (**C**) IL-6 and (**D**) PCT in two groups. Compared with T0, $^{\#}P < 0.05$; Compared with ESK group, $^{*}P < 0.05$. The date was expressed as mean ± SD and analyzed by T tests

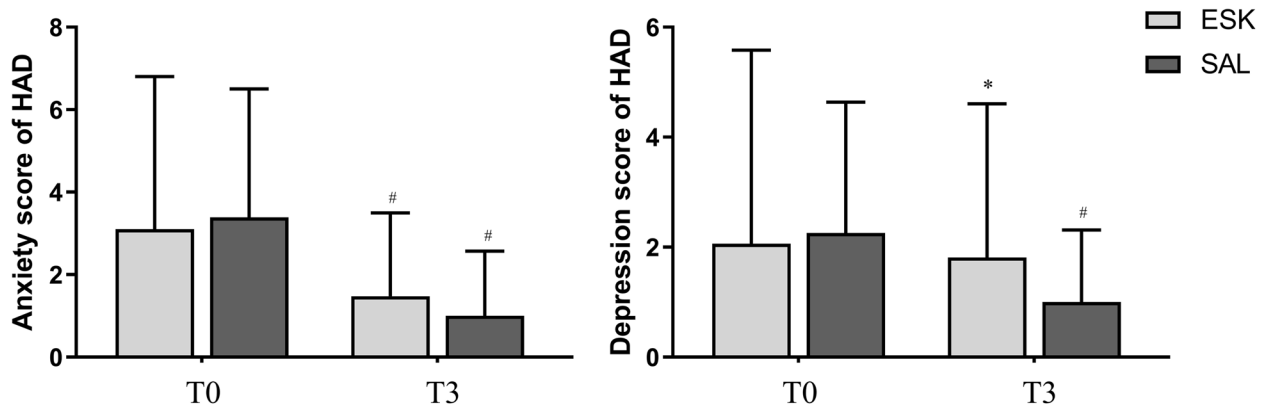


Fig. 5 The hospital self-rating anxiety and depression scale, HAD. Compared with T0, $^{\#}P < 0.05$; Compared with ESK group, $^{*}P < 0.05$. The date was expressed as mean ± SD and analyzed by T tests

studies find that esketamine, the dextral isomer of racemic ketamine, has a higher affinity for NMDA receptor and other receptors, meanwhile, a lower dosage of esketamine can achieve same favorable sedative and analgesic effects with ketamine [8].

In previous trials, pre-incisional injection of esketamine 0.5 $mg{\cdot}kg^{-1}$ followed by an infusion of 0.2 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ can relieve postoperative pain effectively in traumatic abdominal surgery [9]. Meanwhile, ketamine has approved efficiency in alleviating postoperative pain up to 72 h in patients of thoracic surgery, with initial dosage at 0.5 $mg{\cdot}kg^{-1}$ and maintenance at 0.25 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ for 48 h [10]. Esketamine is assumed to have twice potency than ketamine in analgesia [11],

Table 3 Overall satisfaction of patients

	Very satisfied	Satisfied	Unsatisfied	Very unsatisfied
SAL group	5 (17.24%)	20 (68.97%)	3 (10.34%)	1 (3.45%)
ESK group	19 (65.52%)*	8 (27.59%)	2 (6.90%)	0 (0%)

Data are provided as number of cases. *P* value represents by χ^2 test or Fisher's exact test

* $P < 0.05$

Table 4 Adverse reactions

	SAL group ($n = 29$)	ESK group ($n = 29$)	*P*-value
Nausea	1	3	0.611
Vomiting	3	5	0.706
Dizziness	7	10	0.565
Dissociation	1	3	0.611

Data are provided as number of cases. *P* value represents by χ^2 test or Fisher's exact test

therefore we administrate 0.25 $mg{\cdot}kg^{-1}$ esketamine at induction with an infusion rate of 0.12 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ until the beginning of thoracic closure.

Feltracco et al. [12] found that the epidural application of esketamine can decrease the consumption of intraoperative fentanyl and has lower postoperative VAS score than epidural ropivacaine. Although ketamine has been reported to prevent the transition from acute pain to chronic pain by inhibiting the phosphorylation of NMDAR, some studies found no improvement in chronic pain but only acute pain relief with perioperative use of ketamine in thoracic surgery [7, 13]. In present study, we observed significant lower VAS-R and VAS-C score in ESK group at the departure from PACU, suggesting that esketamine can significantly relieve acute pain in patients with thoracic surgery, which is consistent with previous studies. Besides, VAS-R in ESK group was also lower than SAL group at other time points, and the difference was statistically significant at 6 h and 48 h after surgery, indicating that postoperative pain in the esketamine group was significantly relieved in most of time. The difference in VAS-C between the two groups showed no significance at other time points other than T1, which may resulted from the relatively small dose of esketamine used in our study. Nevertheless, some studies reported that intravenous ketamine did not reduce postoperative pain nor improve pulmonary dysfunction following thoracic surgery, which may owe to the low pain scores adjusted by the optimized patient-controlled epidural analgesia mode [14, 15].

Inflammatory factors can act on nociceptive nerve endings and cause hyperalgesia by reducing the excitation threshold of nociceptive receptor on afferent nerves [16, 17]. After surgical tissue injury, white blood cells increase and the release of following cytokines were activated, such as IL-6 and TNF-α, which can in turn to regulate inflammation and immune response. Hence, WBC is one of the indicators to reflect the degree of inflammation in the body. In cardio-thoracic surgery, ketamine produces analgesia effect by reduce the expression of leukocyte surface adhesion molecules CD11b and CD16, and proinflammatory factor like IL-6 and TNF-α [18, 19]. In vitro, esketamine can inhibit neutrophil activation and reduced the production of superoxide anion [20]. Our study indicates that WBC and ANC increased dramatically in both groups at 24 h after surgery when compared with the preoperation, while the postoperative WBC and ANC in the ESK group was significantly lower than the SAL group. These results suggest that esketamine partially inhibited the postoperative systemic inflammatory response. The correlation of reduced VAS score along with lower WBC and ANC level in ESK group implies that the pain-reliving effect of esketamine might due to its influence in alleviating inflammation. However, it should be noted that this causal relationship needs more evidence.

It was documented that IL-6 can modulate the immune response and stimulates neutrophil formation in the bone marrow. In present study, mild inflammation in patients was detected by the IL-6 level at 24 h after surgery, but there was no statistically significant difference between the two groups. This may count on the fact that the non-infectious inflammation after thoracic surgery was not severe enough and IL-6 could have already been largely cleared within 24 h postoperatively. Besides, leukocyte and its downstream inflammatory factors are also involved in the body postoperative inflammatory reactions, and further studies are needed to investigate the effects of esketamine on the expression of other inflammatory factors in thoracic surgery.

Esketamine exerts rapid antidepressant effect at an intravenous dose of 0.2 $mg{\cdot}kg^{-1}$, and its nasal spray formulation has been approved for clinical use in patients with depression [21, 22]. It has also been reported that 0.25 $mg{\cdot}kg^{-1}$ racemic ketamine improve the anxiety score of patients with anxiety disorder, and this effect can be enhanced with a higher dose of 1.0 $mg{\cdot}kg^{-1}$ [23]. However, there still lacks solid evidence on the improving effect of esketamine on anxiety. It's worth noting that a large number of studies suggested the relationship between emotional disorders and inflammatory response. For instance, the probability of anxiety or depression in patients with inflammatory bowel disease is more than 16.4% and 21.6%, respectively [24]. In this

study, the HAD scale was used to evaluate the degree of anxiety and depression before and after surgery. Statistical analysis showed that esketamine did not play an obvious anti-anxiety effect. In addition, the postoperative depression score in the esketamine group was significantly higher than that in the control group. These findings were inconsistent with previous findings, possibly contribute to the research subjects who were combined with psychiatric disorders or not and the relatively larger subjective factors in scale scores evaluation and small sample size. However, recent studies from Zarate et al. group suggest that antidepressant effects of intranasal esketamine are less potent than intravenous racemic ketamine which is consistent with our study, and more and more studies document the effective antidepressant effect of arketamine [25, 26]. This contradictory research findings may be due to the the different routine of drug administration or the classification and severity of basic psychiatric disorders. This still require more detailed further research.

Patients in both groups obtained favorable analgesia in general, with relatively high score as regard to satisfaction with pain therapy. Interestingly, compared with SAL group, the number of very satisfied patients in the ESK group obviously increased, suggesting that esketamine can significantly improve patients' postoperative satisfaction.

Compared with the preoperative, SpO2 declined significantly after operation in both groups, which strongly indicated the profound influence of thoracic surgery on respiration. Esketamine does not inhibit postoperative respiratory competence as we observed a similar SpO2 after surgery in two groups at all time points.

Previous studies document that the subanesthetic S-ketamine can improve short-term depression and pain for patients after surgery, and the effects were better than with the same dose of racemic ketamine [8, 27]. However, there are also studies found intravenous racemic ketamine demonstrated more significant overall response and remission rates of depression, as well as lower dropouts due to adverse effects, when compared with intranasal esketamine [25]. These inconsistent research results may be due to differences in the underlying diseases of the study subjects. In this study, we found no statistical differences in nausea, vomiting dizziness and mental separation disorder between two groups within 2 d after surgery, suggesting esketamine doesn't increase the adverse effects after surgery. Remarkably, the 3 cases with mental separation disorder in ESK group all occurs in patients older than 70 yr, prompting that the dosage and injection speed of esketamine should be selected more carefully when applied to elder patients. In addition, although there is no statistical difference between two groups, we noticed larger number of patients with adverse effects in ESK group.

In conclusion, intraoperative application of low-dose esketamine added to general anesthesia regimen improves pain relief after thoracoscopic surgery without respiratory depression nor augment in the incidence of adverse reactions. Esketamine is an ideal option for postoperative analgesia in patients with thoracoscopic surgery, and is worth clinical promotion and application. Further research is still needed to clarify the optimal application dosage and specific mechanism of the esketamine.

5 Conclusion

Low dosage esketamine improves acute trauma-induced pain in patients undergoing thoracoscopic surgery, which may be mediated by alleviating the production of WBC and ANC, without inhibiting the respiratory function and increasing advent reactions.

Abbreviations

ANC	Absolute neutrophil count
HAD	Hospital Anxiety and Depression
IBP	Invasive (intra-arterial) blood pressure
IL-6	Interleukin-6
NMDAR	N-methyl-D-aspartate receptor
PACU	Post-anesthesia care unit
PCT	Procalcitonin
S-ketamine	Esketamine
SpO2	Oxygen saturation
TNF-α	Tumor necrosis factor-α
VAS	Visual analogue scale
VAS-C	Visual analogue scale cough state
VAS-R	Visual analogue scale at rest
VATS	Video-assisted thoracic surgery
WBC	White blood cell

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Not applicable.

Authors' contributions

Qing-wei Zhang helped conduct the study, analyse the data, and write the manuscript. Xin Wang collected original study data and write the manuscript. Zhong-yun Wang helped design the study and conduct the study. He-liang Sun helped design the study, analyse the data, and approved the final manuscript.

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Availability of data and materials

All authors ensure the authenticity and validity of data in the article and you can obtain the original data by email to the corresponding author.

Declarations

Ethics approval and consent to participate

This study has been approved by the ethics committee of the First Affiliated Hospital of Nanjing Medical University (2021-SR-281). Written informed consent was obtained from all participants before enrollment. All study

procedures were conducted according to good clinical practice guidelines and adhered to the tenets of the Declaration of Helsinki.

Consent for publication
All authors gave their consent for publication.

Competing interests
The authors declare that they have no conflicts of interest.

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References

1. Rodriguez-Aldrete D, Candiotti KA, Janakiraman R, Rodriguez-Blanco YF. Trends and New Evidence in the Management of Acute and Chronic Post-Thoracotomy Pain-An Overview of the Literature from 2005 to 2015. J Cardiothorac Vasc Anesth. 2016;30(3):762–72.
2. Yie JC, Yang JT, Wu CY, Sun WZ, Cheng YJ. Patient-controlled analgesia (PCA) following video-assisted thoracoscopic lobectomy: comparison of epidural PCA and intravenous PCA. Acta Anaesthesiol Taiwan. 2012;50(3):92–5.
3. Matsuda M, Huh Y, Ji R-R. Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain. J Anesth. 2019;33(1):131–9.
4. Moyse DW, Kaye AD, Diaz JH, Qadri MY, Lindsay D, Pyati S. Perioperative Ketamine Administration for Thoracotomy Pain. Pain Physician. 2017;20(3):173–84.
5. Elmore B, Nguyen V, Blank R, Yount K, Lau C. Pain Management Following Thoracic Surgery. Thorac Surg Clin. 2015;25(4):393–409.
6. Beaudoin FL, Lin C, Guan W, Merchant RC. Low-dose ketamine improves pain relief in patients receiving intravenous opioids for acute pain in the emergency department: results of a randomized, double-blind, clinical trial. Acad Emerg Med. 2014;21(11):1193–202.
7. Laskowski K, Stirling A, McKay WP, Lim HJ. A systematic review of intravenous ketamine for postoperative analgesia. Can J Anaesth. 2011;58(10):911–23.
8. Wang J, Huang J, Yang S, Cui C, Ye L, Wang SY, et al. Pharmacokinetics and safety of esketamine in Chinese patients undergoing painless gastroscopy in comparison with ketamine: a randomized, open-label clinical study. Drug Des Devel Ther. 2019;13:4135–44.
9. Argiriadou H, Himmelseher S, Papagiannopoulou P, Georgiou M, Kanakoudis F, Giala M, et al. Improvement of pain treatment after major abdominal surgery by intravenous S+-ketamine. Anesth Analg. 2004;98(5):1413–8.
10. Tena B, Gomar C, Rios J. Perioperative epidural or intravenous ketamine does not improve the effectiveness of thoracic epidural analgesia for acute and chronic pain after thoracotomy. Clin J Pain. 2014;30(6):490–500.
11. Himmelseher S, Durieux ME. Ketamine for perioperative pain management. Anesthesiology. 2005;102(1):211–20.
12. Feltracco P, Barbieri S, Rizzi S, Ori C, Groppa F, De Rosa G, et al. Brief report: perioperative analgesic efficacy and plasma concentrations of S+ -ketamine in continuous epidural infusion during thoracic surgery. Anesth Analg. 2013;116(6):1371–5.
13. Dualé C, Sibaud F, Guastella V, Vallet L, Gimbert YA, Taheri H, et al. Perioperative ketamine does not prevent chronic pain after thoracotomy. Eur J Pain. 2009;13(5):497–505.
14. Joseph C, Gaillat F, Duponq R, Lieven R, Baumstarck K, Thomas P, et al. Is there any benefit to adding intravenous ketamine to patient-controlled epidural analgesia after thoracic surgery? A randomized double-blind study. Eur J Cardiothorac Surg. 2012;42(4):e58-65.
15. Mendola C, Cammarota G, Netto R, Cecci G, Pisterna A, Ferrante D, et al. S(+)-ketamine for control of perioperative pain and prevention of post thoracotomy pain syndrome: a randomized, double-blind study. Minerva Anestesiol. 2012;78(7):757–66.
16. Muley MM, Krustev E, McDougall JJ. Preclinical assessment of inflammatory pain. CNS Neurosci Ther. 2016;22(2):88–101.
17. Ronchetti S, Migliorati G, Delfino DV. Association of inflammatory mediators with pain perception. Biomed Pharmacother. 2017;96:1445–52.
18. Welters ID, Hafer G, Menzebach A, Mühling J, Neuhäuser C, Browning P, et al. Ketamine inhibits transcription factors activator protein 1 and nuclear factor-kappaB, interleukin-8 production, as well as CD11b and CD16 expression: studies in human leukocytes and leukocytic cell lines. Anesth Analg. 2010;110(3):934–41.
19. Bartoc C, Frumento RJ, Jalbout M, Bennett-Guerrero E, Du E, Nishanian E. A randomized, double-blind, placebo-controlled study assessing the anti-inflammatory effects of ketamine in cardiac surgical patients. J Cardiothorac Vasc Anesth. 2006;20(2):217–22. Retraction in: J Cardiothorac Vasc Anesth. 2014;28(5):1435.
20. Lu HW, He GN, Ma H, Wang JK. Ketamine reduces inducible superoxide generation in human neutrophils in vitro by modulating the p38 mitogen-activated protein kinase (MAPK)-mediated pathway. Clin Exp Immunol. 2010;160(3):450–6.
21. Singh JB, Fedgchin M, Daly E, Xi L, Melman C, De Bruecker G, et al. Intravenous esketamine in adult treatment-resistant depression: a double-blind, double-randomization, placebo-controlled study. Biol Psychiatry. 2016;80(6):424–31.
22. Kim J, Farchione T, Potter A, Chen Q, Temple R. Esketamine for treatment-resistant depression - first FDA-approved antidepressant in a new class. N Engl J Med. 2019;381(1):1–4.
23. Glue P, Neehoff S, Sabadel A, Broughton L, Le Nedelec M, Shadli S, et al. Effects of ketamine in patients with treatment-refractory generalized anxiety and social anxiety disorders: exploratory double-blind psychoactive-controlled replication study. J Psychopharmacol. 2020;34(3):267–72.
24. Neuendorf R, Harding A, Stello N, Hanes D, Wahbeh H. Depression and anxiety in patients with Inflammatory bowel disease: a systematic review. J Psychosom Res. 2016;87:70–80.
25. Bahji A, Vazquez GH, Zarate CA Jr. Comparative efficacy of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. J Affect Disord. 2021;278:542–55.
26. Zhang J-C, Yao W, Hashimoto K. Arketamine, a new rapid-acting antidepressant: a historical review and future directions. Neuropharmacology. 2022;218:109219.
27. Han Y, Li P, Miao M, Tao Y, Kang X, Zhang J. S-ketamine as an adjuvant in patient-controlled intravenous analgesia for preventing postpartum depression: a randomized controlled trial. BMC Anesthesiol. 2022;22(1):49.

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