中国临床研究 Chin J Clin Res, December 2024, Vol.37, No.12

Cite as: Li WY, Zhang Y, Zhang C, Shi L. Effects of esketamine combined with thoracic paravertebral block on postoperative early sleep in patients undergoing thoracoscopic lobectomy [J]. Chin J Clin Res, 2024, 37(12): 1834-1838.
DOI: 10.13429/j.cnki.cjcr.2024.12.004

Effects of esketamine combined with thoracic paravertebral block on postoperative early sleep in patients undergoing thoracoscopic lobectomy

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Abstract: Objective To observe the effects of continuous intravenous infusion of esketamine combined with paravertebral nerve block on early postoperative sleep, analgesia, and recovery quality in patients undergoing thoracoscopic lobectomy. **Methods** A total of 76 patients scheduled for elective thoracoscopic lobectomy at Nanjing First Hospital from January 2023 to January 2024 were randomly divided into two groups: the control group (C group) and the esketamine group (E group). Patients in the E group received intravenous injection of 0.2 mg/kg esketamine during anesthesia induction, followed by a continuous infusion of 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$ esketamine until the end of the surgery. Patients in the C group received an equal volume of normal saline. Multichannel sleep monitoring was conducted on the day before surgery, the first day after surgery, and the third day after surgery to assess patients' sleep conditions. The Pittsburgh Sleep Quality Index (PSQI) was used to evaluate sleep quality on the same days. Visual Analog Scale (VAS) scores were recorded at 2, 6, 12, 24, and 48 hours postoperatively, along with patient-controlled intravenous analgesia (PCIA) pressing times and rescue analgesia rates. The Hospital Anxiety and Depression Scale (HADS) was used to assess anxiety and depression scores one day before surgery, the first and third days after surgery. Recovery quality was assessed using the Quality of Recovery-15 (QoR-15) on the first and third days after surgery, and the time of flatus was recorded. **Results** Compared with the C group, the total sleep time, sleep efficiency index, proportion of rapid eye movementwere higher, while PSQI score was lower in the E group on the first and third postoperative days (P<0.05). VAS seores at 24 hours and 48 hours after surgery were significantly lower in the E group than those in the C group (P<0.05), and the PCIA pressing times at 48 hours postoperatviely were significantly lower than those in the E group[(16.2±3.7) times *vs* (13.8±4.3) times, t=2.556, P=0.013]. Compared with the C grup, the HADS-A and HADS-D scores were lower, the QoR-15 seores were higher (P<0.05) on the first and third days ater surgery , and the fatus time occurring significantly earlier [(18.3±2.1) h *vs* (17.1±2.0) h, t=2.646, P=0.010] in the E group. **Conclusion** Intraoperative intravenous infusion of esketamine combined with TPVB can improve early postoperative sleep, anxiety, and depression, and promote recovery in patients undergoing thoracoscopic lobectomy to a certain extent.

Keywords: Esketamine; Thoracic paravertebral block; Sleep; Depression; Quality of recovery

Thoracoscopic lobectomy accounts for a large proportion of thoracic surgery, and some studies have shown that patients undergoing thoracic surgery are prone to postoperative sleep disturbances (POSD) [1]. POSD refers to changes in the structure and quality of patients' sleep after surgery, which are mainly manifested by increased wakefulness, shortened rapid eye movement (REM) time and sleep fragmentation, etc. POSD may exacerbate acute postoperative pain and delay postoperative recovery [2-4]. In addition, the anxiety and depression that often accompany surgical patients are also high-risk factors for developing postoperative sleep and postoperative recovery. Postoperative sleep disturbances often occur in conjunction with postoperative depression [5-7]. Esketamine, the more potent dextro structure of ketamine, is a novel N-methyl-D-aspartate (NMDA) receptor antagonist, which has been widely used in clinical anesthesia. Some studies have shown that esketamine can reduce postoperative depressive symptoms in breast cancer patients [8]. In addition to its antidepressant effects, esketamine has been shown to improve sleep disturbances in patients, suggesting a potential role in POSD [9-10]. Given these characteristics of esketamine, it is of interest whether perioperative application of esketamine can improve postoperative sleep and postoperative recovery in patients undergoing thoracoscopic lobectomy. Therefore, this study intends to investigate the effects of intravenous infusion of esketamine during thoracoscopic lobectomy on patients' postoperative sleep and recovery.

1 Materials and methods

1.1 General data

A total of 76 patients, aged 18-65 years, with body mass index (BMI) of 18-25 kg/m^2, American Society of Anesthesiologists (ASA) I-II, who underwent

thoracoscopic lobectomy from January 2023 to January 2024 in Nanjing First Hospital were selected.

Exclusion criteria: Contraindication or allergy to esketamine; presence of central nervous system and psychiatric disorders; preoperative sleep disorders; suffering from sleep apnea syndrome.

Elimination criteria: Intraoperative change of surgical procedure; postoperative admission to intensive care unit; reoperation during follow-up; serious complications; patient request to withdraw from the study.

All patients were randomly divided into two groups: control group (C group) and esketamine group (E group) with 38 patients in each group. The study was approved by the Ethics Committee of the hospital (Ethics No. KY20220825-09). Patients were enrolled after signing an informed consent form.

1.2 Sample size calculation

Sample size estimation was conducted using PASS 15, based on the results of the pre-test, the main outcome index was total sleep time (TST) at 1 day postoperatively, and the data of two groups were obtained, C group (5.2±0.4) h and E group (5.5±0.5) h. Assuming bilateral α=0.05 and test efficacy 1-β=0.80, a total of 70 patients were required. A total of 78 patients were included, taking into account a shedding rate of 10%.

1.3 Methods

After the patients entering the preanesthesia room, they were inhaled oxygen and opened the peripheral veins of the upper limbs, and routine cardiac monitoring was performed. The patients were placed in the lateral position to perform the thoracic paravertebral block (TPVB), disinfected and toweling was done, and the two points of T4 and T6 were selected for the block, and the needles were inserted to the paravertebral space by ultrasound-guided puncture, and after the withdrawal of blood and air, 15 mL of 0.375% ropivacaine (AstraZeneca AB, lot number: LBVM) were injected. The success of the block was verified by the detection of skin warmth and tactile sensation in the corresponding area by means of alcohol-infiltrated cotton balls [11]. After 30 min of observation without adverse effects, the patients were admitted to the operating room. Thoracic paravertebral nerve block was performed by the same experienced anesthesiologist.

Heart rate (HR), ambulatory blood pressure (ABP), electrocardiogram (ECG), oxygen saturation (SpO_2) and bispectral index (BIS) were routinely monitored after admission. Patients in E group were injected intravenously with 0.2 mg/kg esketamine (Jiangsu Hengrui Pharmaceuticals, batch no. 220922BL) at the time of anesthesia induction, followed by continuous pumping of 0.1 $mg\cdot kg^{-1}\cdot h^{-1}$ esketamine until the end of the operation. Patients in C group were given an equal amount of saline. Anesthesia was induced by intravenous injection of sufentanil (Yichang Renfu Pharmaceuticals, batch no. AB40101621) 0.4 μg/kg, midazolam (Jiangsu Enhua Pharmaceuticals, batch no: TMZ23A01) 0.05 mg/kg, propofol (Fresenius Kabi Warui Pharmaceuticals, batch no: 16SL9251) 1-2 mg/kg and rocuronium bromide (Zhejiang Xianju Pharmaceuticals, batch no: EB1916) 0.6 mg/kg , double-lumen bronchial intubation was performed, and mechanical ventilation was performed to maintain the end-expiratory carbon dioxide partial pressure of 35-45 mmHg. Anesthesia was maintained by intravenous pumping of propofol 2-5 $mg\cdot kg^{-1}\cdot h^{-1}$, remifentanil (Yichang Renfu Pharmaceuticals, lot no: 20A02131) 8-10 $mg\cdot kg^{-1}\cdot h^{-1}$, and rocuronium bromide 0.3 mg/kg intermittently. During the operation, the anesthetic dose was regulated according to the BIS value, and the BIS value was maintained between 40 and 60. The patient's HR and blood pressure were kept within 20% of the baseline during the operation. Anesthesia maintenance drugs were discontinued at the end of surgery and the patient was admitted to the postanesthesia care unit (PACU). Aldrete score ≥ 9 was transferred out of the PACU and then transferred to a single room. At the end of the operation, patient controlled intravenous analgesia (PCIA) was performed, formulated as sufentanil 150 μg + tropisetron 8.96 mg + saline 250 mL, continuous infusion of 3 mL/h, self-controlled dose of 5 mL, locking time of 8 min. If the patient's visual analogue scale (VAS) exceeded 4, 50 mg of flurbiprofenate would be injected intravenously for remedial analgesia. Surgery was performed by the same group of experienced thoracic surgeons, and all patients were operated before 4 pm.

1.4 Observation indexes

The anesthesia and adverse reactions of the two groups were recored. Polysomnography (Polypro YH-2000A, Shanghai Hanfei Medical Instrument) was used to monitor patients' sleep 1 d before, 1 d after and 3 d after surgery. TST, sleep efficiency index (SEI), and REM percentage in TST (REM%) were recorded, and sleep quality was assessed by using the Pittsburgh sleep quality index (PSQI) scale at 1 d before, 1 d after, and 3 d after surgery. VAS scores at 2, 6, 12, 24, and 48 h postoperatively and the number of PCIA compressions and remedial analgesia rate at 48 h postoperatively were recorded. Anxiety and depression scores were recorded on 1 d before, 1 d after, and 3 d after surgery using the Hospital Anxiety and Depression Scale (HADS). The HADS scale includes two subscales, HADS-A and HADS-D, with higher scores indicating more severe symptoms of anxiety or depression. The 15-item Quality of Recovery-15 (QoR-15), was performed on 1 d and 3 d postoperatively, and the time of the patient's exhaustion was recorded.

1.5 Statistical analysis

Statistical analysis was performed using SPSS 22.0. Normally distributed measurements were expressed as $\bar{x}$

±*s*, and two independent samples t-test was used for comparison between groups. Skewed distribution measurements were expressed as *M* (*IQR*), and Mann-Whitney *U* test was used for comparison between groups; and χ^2 test was used for comparison of counting data. Data with multiple measurements (≥3 times) were analyzed using ANOVA for repeated measurements and *LSD-t* test for two-by-two comparisons. If the data were severely skewed, the Mann-Whitney *U* test was used for between-group comparisons, and Friedman's test was used for within-group comparisons. Differences were considered statistically significant when $P < 0.05$.

2 Results

2.1 Comparison of the general conditions of patients in the two groups

A total of 78 patients were initially included in this study, and 76 patients were finally included due to intraoperative change of the surgical method in 2 cases. No significant adverse reactions were seen in both groups. The differences between the two groups of patients in terms of age, gender, BMI, ASA classification, single-lung ventilation time, operation time, anesthesia time and bleeding volume were not statistically significant ($P > 0.05$). **[Table 1]**

2.2 Comparison of sleep-related indexes between the two groups

There was no statistically significant difference between the TST, SEI, REM% and PSQI scores of the two groups in the preoperative 1 day. The TST, SEI and REM% of the patients in E group were significantly higher than those in C group in the 1st and 3rd postoperative days (P<0.05). By Friedman test, the difference between PSQI scores within groups C and E was statistically significant (χ^2 =75.510, P<0.001; χ^2 =75.040, P<0.001). The PSQI scores of patients in E group were significantly lower than those in C group on postoperative days 1 and 3 (P<0.05). **[Table 2-3]**

Tab.1 Comparison of general data of the two groups of patients (n= 38, $\overline{x}$ ±*s*)

Groups	Age (years)	Gender (case, m/f)	BMI (kg/m^2)	ASA grading (case, I/II)	Single-lung ventilation time(min)	Surgical time (min)	Anesthesia time (min)	Hemorrhage (mL)
C group	45.7±5.3	14/24	21.2±1.3	13/25	85.9±22.6	97.5±27.0	118.5±31.9	150.5±39.8
E group	46.8±5.1	12/26	21.1±1.4	11/27	88.1±21.1	99.7±28.2	123.6±36.7	158. 9±35.2
t/χ^2 value	0.956	0.234	0.138	0.244	0.430	0.353	0.644	0.978
P value	0.342	0.629	0.891	0.622	0.668	0.725	0.522	0.331

Tab.2 Comparison of sleep related indexes between the two groups of patients (*n*= 38, $\overline{x}$ ±*s*)

Groups	TST (h)			SEI (%)			REM% (%)		
	Preoperative 1d	Postoperative 1d	Postoperative 3d	Preoperative 1d	Postoperative 1d	Postoperative 3d	Preoperative 1d	Postoperative 1d	Postoperative 3d
C group	6.3±0.8	5.2±0.5[a]	5.6±0.5[a]	82.5±5.6	70.3±4.0[a]	78.1±3.6[a]	23.1±2.2	16.1±2.0[a]	18.9±2.1[a]
E group	6.3±0.7	5.5±0.5[ab]	5.8±0.4[ab]	83.2±5.0	74.6±3.9[ab]	80.8±4.1[ab]	22.7±2.3	19.4±1.9[ab]	20.4±2.1[ab]
F/P (group)		8.682/0.004			20.960/<0.001			31.518/<0.001	
F/P (time)		50.373/<0.001			105.476/<0.001			109.082/<0.001	
F/P (interaction)		1.515/0.225			3.050/0.056			14.307/<0.001	

Note:[a] P<0.05 compared with 1 d preoperatively in this group;[b] P<0.05 compared with the same time point in C group.

Tab.3 Comparison of PSQI between the two groups in patients [n=38, point, *M* (*Q1, Q3*)]

Groups	1 d preoperativly	1 d postoperatively	3 d postoperatively
C group	2 (2, 3)	6 (5, 8)	5 (4, 6)
E group	3 (2, 3)	5 (4, 6)	4 (3, 4)
Z value	0.152	3.815	4.075
P value	0.879	<0.001	<0.001

2.3 Comparison of postoperative VAS scores and analgesia-related indexes between the two groups

The difference between the VAS scores of the two groups of patients at 4 h and 12 h postoperatively was not statistically significant (P>0.05). Compared with C group, the VAS scores of patients in E group were significantly lower at 24 h and 48 h postoperatively (P<0.05). By Friedman's test, the difference in VAS scores within groups C and E was statistically significant when compared within groups (χ^2 =101.853, P<0.001; χ^2 =94.144, P<0.001) **[Table 4]**. The difference in the rate of remedial analgesia at 48 h postoperatively was not statistically significant when comparing groups C and E [18.4% (7/38) *vs* 10.5% (4/38), χ^2 =0.957, P=0.328]. The number of PCIA compressions at 48 h postoperatively was lower in C group than in E group and the difference was statistically significant [(16.2±3.7) *vs* (13.8±4.3), t=2.556, P=0.013].

Tab.4 Comparison of postoperative VAS scores between the two groups of patients [n=38, point, *M* (*Q1, Q3*)]

Groups	4 h postoperatively	12 h after surgery	24 h after surgery	48 h after surgery
C group	1 (0, 1)	3 (3, 4)	4 (3, 5)	4 (3, 4)
E group	0 (0, 1)	3 (2, 4)	4 (3, 4)	3 (3, 3)
Z value	1.182	1.342	2.465	2.741
P value	0.237	0.179	0.014	0.006

2.4 Comparison of postoperative recovery-related indexes between the two groups

There was not significant statistical difference in the HADS-A and HADS-D scores of the patients between the two groups on the 1 d preoperatively (P>0.05). Compared with C group, patients in E group had significantly lower HADS-A and HADS-D scores and higher QoR-15 scores on postoperative days 1 and 3 (P<0.05). By Friedman's test, for HADS-A scores, the difference was statistically significant for within-group comparisons in C group (χ^2 =63.762, P<0.001); and within-group comparisons in E group (χ^2 =68.709, P<0.001). For HADS-D scores, the difference was statistically significant for within-group comparisons in C group (χ^2 =26.000, P<0.001). The difference within E group was statistically significant for intra-group comparison (χ^2 =69.378, P<0.001) **[Table 5]**. The postoperative venting time of C group was earlier than that of E group, and the difference was statistically significant [(18.3±2.1)h *vs* (17.1±2.0)h, t=2.646, P=0.010] .

Tab.5 Comparison of the indexes related to postoperative recovery between the two groups [n=38, point, M(IQR)]

Groups	QoR-15		HADS-A			HADS-D		
	1 d postoperatively	3 d postoperatively	1 d preoperative	1 d postoperatively	3 d postoperatively	1 d preoperative	1 d postoperatively	3 d postoperatively
C group	83 (79, 87)	106 (104, 112)	7(5,8)	6(5,6)	5(4,6)	6(5,8)	6(5,8)	5(4,7)
E group	86(82,90)	113 (108, 116)	7(6,8)	5(4,5)	4(4,5)	6(5,7)	5(4,6)	4(3,6)
Z value	2.508	3.155	0.301	3.471	2.719	0.279	2.895	3.538
P value	0.012	0.002	0.763	0.001	0.007	0.78	0.004	<0.001

3 Discussion

Sleep disorders are a common but easily overlooked problem in cancer patients. Sleep can be categorized into two major processes, REM and non-rapid eye movement (NREM). REM is an active stage in the physiological cycle of sleep, which is crucial for brain function recovery and emotional health [12]. Surgical trauma, general anesthesia, and intraoperative bleeding may be important factors that lead to POSD in patients [13-14]. It has been suggested that general anesthesia interferes with the normal sleep-wake cycle, disrupts melatonin metabolism, and affects the biological clock in the supraoptic nucleus [15-16]. In addition, the oxidative stress caused by surgical trauma may disrupt the neuroendocrine system, affect hormone levels and immune function, and may cause an inflammatory response. Studies have shown that patients undergoing video-assisted thoracoscopic surgery are prone to sleep disturbances, which are manifested by a reduced distribution of each sleep stage and a decrease in sleep efficiency [1], which may lead to prolonged recovery and increased hospitalization costs. Therefore, it is important to improve anesthetic factors to prevent POSD in patients and improve the quality of postoperative recovery.

The results of this study showed that the TST of patients in E group was significantly longer than that of C group on postoperative days 1 and 3, and the SEI and REM% were significantly higher than that of C group. In addition, the PSQI scores of patients in E group were lower than that of C group on postoperative days 1 and 3. It is suggested that intraoperative intravenous continuous infusion of esketamine can improve patients' sleep in the early postoperative period. It has been shown that esketamine can increase the expression of synapse-related proteins, promote the activation of related pathways in the prefrontal cortex, nourish the nerves and increase the synaptic strength in order to increase neuroplasticity, activate gene molecules related to the biological clock and regulate the circadian rhythms, thus improving the quality of sleep [17-18]. Therefore, the beneficial effects of Eketamine on PSD may be related to the regulation of the circadian system. It has been suggested that inflammatory responses are involved in the onset of sleep deprivation [19]. Ketamine has a unique pleiotropic anti-inflammatory effect, which inhibits the release of pro-inflammatory factors by inducing anti-inflammatory mediators such as adenosine [20], and inhibits leukocyte activation and recruitment, and promotes apoptosis of inflammatory cells [21-22]. Recent studies have shown that esketamine inhibits the release of inflammatory cells stimulated by oxygen free radicals and reduces the secretion of pro-inflammatory factors by leukocytes, thereby reducing the inflammatory response [23-24]. These results suggest that the anti-inflammatory effect of esketamine may also contribute to its preventive effect on POSD.

A recent study further indicated that perioperative use of esketamine in thoracic surgery patients relieves early postoperative pain and improves postoperative depression [25]. This is consistent with the results of the present study, which showed that patients in E group had significantly lower VAS scores at 24 h and 48 h postoperatively and fewer PCIA compressions at 48 h postoperatively compared with C group. The results of the present study are consistent with the results of the present study. The VAS scores at 4 h and 12 h postoperatively and the rate of remedial analgesia at 48 h postoperatively were not significantly different between the two groups, which may be due to the fact that the multimodal analgesic regimen used in the present study included thoracic paravertebral nerve block and PCIA, which may mask the analgesic effect of esketamine in the first 12 h postoperatively. It was demonstrated that esketamine relieved patients' anxiety and depression, probably because it increased the number and function of synapses, activated neurotrophic factors, and induced neuroplasticity [17,26]. Similarly, the results of the present study showed that patients in E group had significantly lower HADS-A and HADS-D scores on postoperative days 1 and 3 compared to C group. The results of the present study showed that patients in E

group had significantly lower HADS-A and HADS-D scores on postoperative days 1 and 3. Both pain and sleep have an impact on patients' postoperative recovery; therefore, improvement of postoperative pain and sleep would be beneficial to patients' postoperative recovery. The results of this study showed that patients in E group had significantly higher QoR-15 scores and decreased time to exhaustion on postoperative days 1 and 3 compared with C group. The results of this study showed that patients in E group had significantly lower QoR-15 scores on postoperative days 1 and 3 compared with C group. This suggests that intraoperative intravenous infusion of esketamine can improve the quality of postoperative recovery in patients undergoing thoracoscopic lobectomy. In addition, there are some limitations in this study: this study is a single-center study with a relatively small sample size, which should be further verified by a multicenter study in the future. This study only followed up the patients for 3 days after the operation, and the long-term effects of esketamine on the patients are not yet clear. This study only designed a single dose of esketamine, and did not explore the other dosages, so whether this dose is the optimal dose still needs further Research.

In conclusion, this study found that intraoperative intravenous infusion of esketamine combined with thoracic paravertebral nerve block can somewhat improve early postoperative sleep, anxiety and depression and promote postoperative recovery in patients undergoing thoracoscopic lobectomy.

Conflict of interest None

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Submission received: 2024-06-12 / **Revised:**2024-08-05

·论　著·

艾司氯胺酮联合胸椎旁神经阻滞对胸腔镜肺叶切除术后患者早期睡眠的影响

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摘要：目的　观察胸腔镜肺叶切除术中持续静脉输注艾司氯胺酮并联合胸椎旁神经阻滞（TPVB），对患者术后早期睡眠、镇痛及恢复质量的影响。**方法**　选择 2023 年 1 月至 2024 年 1 月于南京市第一医院择期行胸腔镜下肺叶切除术的患者 76 例，随机分成对照组（C 组）和艾司氯胺酮组（E 组），每组各 38 例。E 组患者在麻醉诱导时静脉注射 0.2 mg/kg 艾司氯胺酮，随后持续泵注 0.1 mg·kg^{-1}·h^{-1}艾司氯胺酮，直至手术结束。C 组患者给予等量生理盐水。于术前 1 d、术后 1 d 和术后 3 d，采用多导睡眠监测仪监测患者睡眠情况并采用匹兹堡睡眠质量指数（PSQI）量表评估睡眠质量。记录术后 2、6、12、24、48 h 的视觉模拟评分（VAS）和术后 48 h 患者静脉自控镇痛（PCIA）按压次数以及补救镇痛率。于术前 1 d、术后 1 d 和术后 3 d 采用医院焦虑抑郁量表（HADS）记录焦虑（HADS-A）和抑郁（HADS-D）评分。于术后 1、3 d 行 15 项恢复质量评分（QoR-15）评分，并记录患者排气时间。**结果**　E 组患者术后第 1、3 天的总睡眠时间长于 C 组、睡眠效率指数和快速动眼睡眠占比高于 C 组（$P<0.05$）；另外，术后 1、3 d 的 PSQI 得分，E 组患者明显低于 C 组（$P<0.05$）。两组患者术后 4 h、12 h 的 VAS 评分以及术后 48 h 补救镇痛率差异无统计学意义（$P>0.05$）；然而 E 组患者术后 24 h、48 h 的 VAS 评分明显低于 C 组（$P<0.05$），并且术后 48 h PCIA 按压次数明显少于 C 组[（13.8±4.3）次 *vs*（16.2±3.7）次，$t=2.556$，$P=0.013$]。与 C 组相比，E 组患者术后 1、3 d 的 HADS-A 和 HADS-D 评分较低、QoR-15 评分较高（$P<0.05$），且排气时间明显提早[（17.1±2.0）h *vs*（18.3±2.1）h，$t=2.646$，$P=0.010$]。**结论**　术中静脉输注艾司氯胺酮联合 TPVB 可以一定程度改善胸腔镜肺叶切除术患者术后早期睡眠、焦虑抑郁并促进术后恢复。

关键词：艾司氯胺酮；胸椎旁神经阻滞；睡眠；抑郁；焦虑

中图分类号：R614.2　**文献标识码：**A　**文章编号：**1674-8182（2024）12-1834-05

Effects of esketamine combined with thoracic paravertebral block on postoperative early sleep in patients undergoing thoracoscopic lobectomy

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Abstract: Objective　To observe the effects of continuous intravenous infusion of esketamine combined with thoracic paravertebral nerve block (TPVB) on postoperative early sleep, analgesia, and recovery quality in patients undergoing thoracoscopic lobectomy. **Methods**　A total of 76 patients scheduled for elective thoracoscopic lobectomy at Nanjing First Hospital from January 2023 to January 2024 were randomly divided into two groups: the control group (C group) and the esketamine group (E group), with 38 patients in each group. Patients in the E group received intravenous injection of 0.2 mg/kg esketamine during anesthesia induction, followed by a continuous infusion of 0.1 mg·kg^{-1}·h^{-1} esketamine until the end of the surgery. Patients in the C group received an equal volume of normal saline. Multichannel

DOI: 10.13429/j.cnki.cjcr.2024.12.004

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出版日期：2024-12-20

QR code for English version

sleep monitoring was conducted on the day before surgery, the first day after surgery, and the third day after surgery to assess patients' sleep conditions. The Pittsburgh Sleep Quality Index (PSQI) was used to evaluate sleep quality on the same days. Visual Analog Scale (VAS) scores were recorded at 2, 6, 12, 24, and 48 hours postoperatively, along with patient-controlled intravenous analgesia (PCIA) pressing times and rescue analgesia rates within 48 hours after surgery. The Hospital Anxiety and Depression Scale (HADS) was used to assess anxiety (HADS-A) and depression (HADS-D) scores on one day before surgery, the first and third days after surgery. Recovery quality was assessed using the Quality of Recovery-15 (QoR-15) on the first and third days after surgery, and the time of flatus was recorded. **Results** Compared with the C group, the total sleep time, sleep efficiency index, proportion of rapid eye movement were higher, while PSQI score was lower in the E group on the first and third postoperative days (P<0.05). VAS scores at 24 hours and 48 hours after surgery were significantly lower in the E group than those in the C group (P<0.05), and the PCIA pressing times at 48 hours postoperatively were significantly lower than those in the E group [(13.8±4.3) times *vs* (16.2±3.7) times, t=2.556, P=0.013]. Compared with the C group, the HADS-A and HADS-D scores were lower, the QoR-15 scores were higher (P<0.05) on the first and third days after surgery, and the flatus time occurring significantly earlier [(17.1±2.0) h *vs* (18.3±2.1) h, t=2.646, P=0.010] in the E group. **Conclusion** Intraoperative intravenous infusion of esketamine combined with TPVB can improve early postoperative sleep, anxiety, and depression, and promote recovery in patients undergoing thoracoscopic lobectomy to a certain extent.

Keywords: Esketamine; Thoracic paravertebral block; Sleep; Depression; Anxiety

胸腔镜肺叶切除术在胸科手术中占很大比例,有研究表明胸科手术的患者术后容易出现睡眠障碍[1]。术后睡眠障碍(postoperative sleep disturbances, POSD)是指患者术后睡眠结构和质量的改变,主要表现为清醒时间增加、快速动眼睡眠(rapid eye movement, REM)时间缩短和睡眠片段化等。POSD 可能会加剧术后急性疼痛,并延迟术后恢复[2-4]。另外,手术患者常伴随的焦虑抑郁情绪也是影响患者术后睡眠以及术后恢复的高危因素。术后睡眠障碍通常与术后抑郁同时出现[5-6]。艾司氯胺酮是氯胺酮中效价更强的右旋结构,是一种新型的 N-甲基-D-天冬氨酸(N-methyl-D-aspartate, NMDA)受体拮抗剂,目前已广泛应用于临床麻醉。有研究表明艾司氯胺酮能减轻乳腺癌患者术后抑郁症状[7]。此外,艾司氯胺酮已被证明可以改善患者的睡眠障碍,提示对 POSD 的潜在作用[8-9]。鉴于艾司氯胺酮这些特点,本研究拟探究在胸腔镜肺叶切除术中静脉输注艾司氯胺酮对患者术后睡眠及恢复的影响。

1　资料与方法

1.1　*一般资料*　选择 2023 年 1 月至 2024 年 1 月于南京市第一医院择期行胸腔镜肺叶切除术的患者 76 例。纳入标准:年龄 18~65 岁,身体质量指数(boely mass index, BMI)18~25 kg/m^2,美国麻醉医师协会(American Society of Anesthesiologists, ASA)分级Ⅰ~Ⅱ级。排除标准:艾司氯胺酮禁忌或过敏;存在中枢神经系统和精神疾病;术前存在睡眠障碍;患有睡眠呼吸暂停综合征。剔除标准:术中改变手术方式,术后入重症监护室,随访期间再次手术,出现严重并发症,患者要求退出研究。根据密封信封中的随机数字进行分组,所有患者分为两组,即对照组(C 组)和艾司氯胺酮组(E 组)。本研究已获得医院伦理委员会批准(伦理号:KY20220825-09)。患者均在签署知情同意书后入组。

1.2　*样本量计算*　采用 PASS 15 进行样本量估算,根据预试验结果,主要结局指标为术后 1 d 总睡眠时间(total sleep time, TST),获取两组数据 C 组(5.2±0.4)h 和 E 组(5.5±0.5)h。假设双侧 α=0.05,检验效能 1-β=0.80,共需要患者 70 例。考虑到脱落率 10%,共纳入 78 例患者。

1.3　*方法*　患者入预麻室后吸氧并开放上肢外周静脉,常规心电监护,患者取侧卧位行胸椎旁神经阻滞(thoracic paravertebral block, TPVB),消毒铺巾,选择 T_4 和 T_6 两点进行阻滞,在超声引导下穿刺进针至椎旁间隙,回抽无血无气后注射 15 mL 0.375%罗哌卡因(阿斯利康,批号:LBVM)。通过酒精浸润的棉球在相应区域进行皮肤温触觉的检测以验证阻滞的成功性[11]。观察 30 min 无不良反应后入手术室。TPVB 由同一经验丰富的麻醉医师进行。

入室后常规监测心率、动态血压(ambulatory blood pressure, ABP)、心电图、脉搏血氧饱和度(saturation of peripheral oxygen, SpO_2)和脑电双频指数(bispectral index, BIS)。E 组患者在麻醉诱导时静脉注射 0.2 mg/kg 艾司氯胺酮(江苏恒瑞医药,批号:220922BL),随后持续泵注 0.1 mg·kg^{-1}·h^{-1}艾司氯胺酮,直至手

术结束。C 组患者给予等量生理盐水。以下方法两组相同。麻醉诱导：静脉注射舒芬太尼（宜昌人福药业，批号：AB40101621）0.4 μg/kg、咪达唑仑（江苏恩华药业，批号：TMZ23A01）0.05 mg/kg、丙泊酚（费森尤斯卡比，批号：16SL9251）1～2 mg/kg 和罗库溴铵（浙江仙琚制药，批号：EB1916）0.6 mg/kg 后进行双腔支气管插管，并行机械通气，维持呼气末二氧化碳分压 35～45 mmHg。麻醉维持：静脉泵注丙泊酚 2～5 mg · kg^{-1} · h^{-1}、瑞芬太尼（宜昌人福药业，批号：20A02131）8～10 mg · kg^{-1} · h^{-1}，并间断追加罗库溴铵 0.3 mg/kg。术中根据 BIS 值调控麻醉药量，将 BIS 值维持在 40～60 之间。术中将患者心率和血压保持在基线的 20% 以内。术毕停用麻醉维持药物，送入麻醉后监测治疗室（postanesthesia care unit，PACU）。Aldrete 评分≥9 则可转出 PACU，然后转移至单人病房。术毕行患者静脉自控镇痛（patient controlled intravenous analgesia，PCIA），配方为舒芬太尼 150 μg+托烷司琼8.96 mg+生理盐水 250 mL，连续输注 3 mL /h，自控剂量5 mL，锁定时间 8 min。若患者视觉模拟评分（Visual Analogue Scale，VAS）>4，则静脉注射 50 mg 氟比洛芬酯行补救镇痛。手术由同一组经验丰富的胸外科医生进行，所有患者的手术均在下午 4 时前完成。

1.4　观察指标　记录两组患者手术麻醉情况及不良反应情况。于术前 1 d、术后 1 d 和术后 3 d 采用多导睡眠监测仪（Polypro YH-2000A 型，上海涵飞医疗器械）监测患者睡眠情况，记录患者的 TST、睡眠效率指数（sleep efficiency index，SEI）以及 REM 在 TST 中所占的百分比（REM%），同时于术前 1 d、术后 1 d 和术后 3 d 采用匹兹堡睡眠质量指数（Pittsburgh sleep quality index，PSQI）量表评估睡眠质量。记录术后 2、6、12、24、48 h 的 VAS 评分和术后 48 h PCIA 按压次数以及补救镇痛率。于术前 1 d、术后 1 d 和术后 3 d 采用医院焦虑抑郁量表（Hospital Anxiety and Depression Scale，HADS）记录焦虑和抑郁评分。HADS 包括 HADS-A 和 HADS-D 两个亚量表，得分越高表示焦虑或抑郁症状越严重。于术后第 1、3 d 行 15 项恢复质量评分（Quality of Recovery-15，QoR-15），并记录患者排气时间。

1.5　统计学方法　采用 SPSS 22.0 进行统计分析。正态分布的计量资料以 $\bar{x}\pm s$ 表示，组间比较采用两独立样本 t 检验；多次测量（测量次数≥3 次）的数据使用重复测量的方差分析及两两比较的 LSD-t 检验。偏态分布的计量资料以 $M(Q_1, Q_3)$ 表示，组间比较采用 Mann-Whitney U 检验，组内比较采用 Friedman 检验；计数资料比较采用 χ^2 检验。以 $P<0.05$ 为差异有统计学意义。

2　结　果

2.1　两组患者一般情况比较　本研究初始纳入患者共 78 例，因术中改变手术方式 2 例，最终纳入 76 例，C 组和 E 组各 38 例。两组患者均未见明显不良反应。两组患者年龄、性别、BMI、ASA 分级、单肺通气时间、手术时间、麻醉时间及出血量等指标差异均无统计学意义（$P>0.05$）。见表 1。

2.2　两组患者睡眠相关指标比较　术前 1 d 两组患者的 TST、SEI、REM% 和 PSQI 得分差异无统计学意义（$P>0.05$）。E 组患者术后第 1、3 天的 TST、SEI 和 REM% 明显高于 C 组（$P<0.05$）。PSQI 得分 C 组和 E 组组内比较差异均有统计学意义（$\chi^2=75.510$，$P<0.001$；$\chi^2=75.040$，$P<0.001$）。术后第 1、3 天 E 组患者的 PSQI 得分明显低于 C 组（$P<0.05$）。见表 2、表 3。

表 1　两组患者一般情况比较　（$n=38$，$\bar{x}\pm s$）

Tab. 1　Comparison of general data of the two groups of patients　（$n=38$，$\bar{x}\pm s$）

组别	年龄（岁）	性别（男/女，例）	BMI（kg/m^2）	ASA 分级（Ⅰ/Ⅱ，例）	单肺通气时间（min）	手术时间（min）	麻醉时间（min）	出血量（mL）
C 组	45.7±5.3	14/24	21.2±1.3	13/25	85.9±22.6	97.5±27.0	118.5±31.9	150.5±39.8
E 组	46.8±5.1	12/26	21.1±1.4	11/27	88.1±21.1	99.7±28.2	123.6±36.7	158.9±35.2
t/χ^2 值	0.956	0.234	0.138	0.244	0.430	0.353	0.644	0.978
P 值	0.342	0.629	0.891	0.622	0.668	0.725	0.522	0.331

表 2　两组患者睡眠相关指标比较　（$n=38$，$\bar{x}\pm s$）

Tab. 2　Comparison of sleep related indexes between the two groups of patients　（$n=38$，$\bar{x}\pm s$）

组别	TST（h）			SEI（%）			REM%（%）		
	术前 1 d	术后 1 d	术后 3 d	术前 1 d	术后 1 d	术后 3 d	术前 1 d	术后 1 d	术后 3 d
C 组	6.3±0.8	5.2±0.5[a]	5.6±0.5[a]	82.5±5.6	70.3±4.0[a]	78.1±3.6[a]	23.1±2.2	16.1±2.0[a]	18.9±2.1[a]
E 组	6.3±0.7	5.5±0.5[ab]	5.8±0.4[ab]	83.2±5.0	74.6±3.9[ab]	80.8±4.1[ab]	22.7±2.3	19.4±1.9[ab]	20.4±2.1[ab]
$F_{组间}/P_{组间}$ 值	8.682/0.004			20.960/<0.001			31.518/<0.001		
$F_{时间}/P_{时间}$ 值	50.373/<0.001			105.476/<0.001			109.082/<0.001		
$F_{交互}/P_{交互}$ 值	1.515/0.225			3.050/0.056			14.307/<0.001		

注：与本组术前 1 d 比较，[a]$P<0.05$；与 C 组同时间点比较，[b]$P<0.05$。

2.3　两组患者术后 VAS 评分及镇痛相关指标比较　两组患者术后 4 h、12 h 的 VAS 评分差异无统计学意义($P>0.05$)。与 C 组相比,E 组患者术后 24 h、48 h 的 VAS 评分明显降低($P<0.05$)。C 组和 E 组 VAS 评分组内比较差异均有统计学意义($\chi^2=101.853$, $P<0.001$; $\chi^2=94.144$, $P<0.001$)。见表 4。C 组和 E 组术后 48 h 补救镇痛率比较差异无统计学意义[18.4%(7/38) *vs* 10.5%(4/38), $\chi^2=0.957$, $P=0.328$]。术后 48 h PCIA 按压次数 C 组高于 E 组,且差异有统计学意义[(16.2±3.7)次 *vs* (13.8±4.3)次, $t=2.556$, $P=0.013$]。

2.4　两组患者术后恢复相关指标比较　两组患者术前 1 d 的 HADS-A 和 HADS-D 评分未见明显差异($P>0.05$)。与 C 组相比,E 组患者术后 1、3 d 的 HADS-A 和 HADS-D 评分明显较低,而 QoR-15 评分较高($P<0.05$)。HADS-A 评分,C 组组内($\chi^2=63.762$, $P<0.001$)和 E 组组内($\chi^2=68.709$, $P<0.001$)比较差异有统计学意义。HADS-D 评分,C 组组内($\chi^2=26.000$, $P<0.001$)和 E 组组内($\chi^2=69.378$, $P<0.001$)比较差异有统计学意义。见表 5。另 C 组术后排气时间晚于 E 组[(18.3±2.1)h *vs* (17.1±2.0)h, $t=2.646$, $P=0.010$]。

表 3　两组患者 PSQI 得分比较　[$n=38$, 分, $M(Q_1,Q_3)$]

Tab. 3　Comparison of PSQI between the two groups of patients　[$n=38$, point, $M(Q_1,Q_3)$]

组别	术前 1 d	术后 1 d	术后 3 d
C 组	2(2,3)	6(5,8)	5(4,6)
E 组	3(2,3)	5(4,6)	4(3,4)
Z 值	0.152	3.815	4.075
P 值	0.879	<0.001	<0.001

表 4　两组患者术后 VAS 评分比较　[$n=38$, 分, $M(Q_1,Q_3)$]

Tab. 4　Comparison of postoperative VAS scores between the two groups of patients　[$n=38$, point, $M(Q_1,Q_3)$]

组别	术后 4 h	术后 12 h	术后 24 h	术后 48 h
C 组	1(0,1)	3(3,4)	4(3,5)	4(3,4)
E 组	0(0,1)	3(2,4)	4(3,4)	3(3,3)
Z 值	1.182	1.342	2.465	2.741
P 值	0.237	0.179	0.014	0.006

表 5　两组患者术后恢复相关指标比较　[$n=38$, 分, $M(Q_1,Q_3)$]

Tab. 5　Comparison of the indexes related to postoperative recovery between the two groups　[$n=38$, point, $M(Q_1,Q_3)$]

组别	QoR-15		HADS-A			HADS-D		
	术后 1 d	术后 3 d	术前 1 d	术后 1 d	术后 3 d	术前 1 d	术后 1 d	术后 3 d
C 组	83(79,87)	106(104,112)	7(5,8)	6(5,6)	5(4,6)	6(5,8)	6(5,8)	5(4,7)
E 组	86(82,90)	113(108,116)	7(6,8)	5(4,5)	4(4,5)	6(5,7)	5(4,6)	4(3,6)
Z 值	2.508	3.155	0.301	3.471	2.719	0.279	2.895	3.538
P 值	0.012	0.002	0.763	0.001	0.007	0.78	0.004	<0.001

3　讨　论

睡眠障碍在癌症患者中是一个常见但容易被忽视的问题。REM 是睡眠生理周期中一个活跃的阶段,对大脑功能恢复和情绪健康至关重要[11]。手术创伤、全身麻醉、术中出血等可能是导致患者发生 POSD 的重要因素[12]。有研究认为全身麻醉干扰了正常的睡眠-觉醒周期,破坏褪黑素代谢,并影响在视交叉上核中的生物钟[13]。此外,手术创伤引起的氧化应激反应可能破坏神经内分泌系统、影响激素水平以及免疫功能,并可能引起炎症反应。研究表明,接受视频辅助胸腔镜手术的患者容易出现睡眠障碍,表现为每个睡眠阶段的分布减少、睡眠效率降低等[1],这可能导致患者恢复期延长及住院费用增多。因此改善麻醉因素来预防患者 POSD 并提高术后恢复质量意义重大。

本研究结果显示,E 组患者术后 1、3 d 的 TST 明显长于 C 组,SEI 和 REM%明显高于 C 组;另外,术后第 1、3 天 E 组患者的 PSQI 得分低于 C 组。提示术中静脉持续输注艾司氯胺酮可以改善患者术后早期的睡眠情况。有研究表明艾司氯胺酮能增加突触相关蛋白的表达,促进前额叶皮质中相关通路激活营养神经并增加突触强度,以增加神经可塑性,激活与生物钟相关的基因分子并调节昼夜节律,从而改善睡眠质量[14]。有研究认为炎症反应参与了睡眠剥夺的发生[15]。氯胺酮具有独特的多效抗炎作用,它通过诱导腺苷等抗炎介质来抑制促炎因子的释放[16],并且能抑制白细胞的激活和募集,促进炎症细胞的凋亡[17]。最近的研究表明,艾司氯胺酮可以抑制由氧自由基刺激的炎症细胞释放,减少白细胞分泌促炎因子,从而降低炎症反应[18]。这些结果提示艾司氯胺酮的抗炎作用也可能有助于其对 POSD 的预防作用。

有研究指出,胸科手术患者围术期使用艾司氯胺酮可以缓解术后早期疼痛并改善术后抑郁[19]。本研究结果与其一致。本研究中与 C 组相比,E 组患者术后 24 h、48 h 的 VAS 评分明显降低并且术后 48 h

PCIA 按压次数明显减少。两组患者术后 4 h、12 h 的 VAS 评分以及术后 48 h 补救镇痛率未见明显差异，这可能是因为本研究采用了多模式镇痛方案，包括 TPVB 和 PCIA，这可能会掩盖艾司氯胺酮在术后前 12 h 的镇痛效果。研究证明艾司氯胺酮可以缓解患者的焦虑和抑郁情绪，可能是由于它增加了突触的数量和功能，激活了神经营养因子，诱导神经可塑性[20]。同样，本研究结果表明，与 C 组相比，E 组患者术后第 1、3 天的 HADS-A 和 HADS-D 评分明显降低。疼痛和睡眠均会对患者术后恢复产生影响，因此，改善术后疼痛和睡眠，均会有利于患者术后恢复。本研究结果显示，与 C 组相比，E 组患者术后第 1、3 天的 QoR-15 评分明显增高并且排气时间明显提早。这表明术中静脉输注艾司氯胺酮可以提高胸腔镜肺叶切除术患者术后恢复质量。另外，存在一些局限性：本研究为单中心研究，样本量相对较小，未来应进行多中心研究来进一步验证；仅对患者进行术后 3 d 的随访，艾司氯胺酮对患者的长期影响尚不明确；仅设计了单一剂量的艾司氯胺酮，并未对其他剂量进行探讨，该剂量是否为最佳剂量仍有待进一步研究。

综上所述，本研究发现，术中静脉输注艾司氯胺酮联合 TPVB 可以一定程度改善胸腔镜肺叶切除术患者术后早期睡眠、焦虑抑郁并促进术后恢复。

利益冲突　无

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收稿日期：2024-06-12　**修回日期**：2024-08-05　**编辑**：叶小舟