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Effect of different administration methods of esketamine on postoperative pain after thoracoscopic lung surgery

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Abstract: Objective To investigate the effect of different administration methods of esketamine on postoperative pain in patients undergoing thoracoscopic lung surgery. **Methods** A total of 90 patients who underwent elective thoracoscopic lung surgery in Qingdao Municipal Hospital from January to June 2023 were selected and randomly divided into three groups. Esketamine group 1 (EK1 group, 0.25 mg/kg of Esketamine was administered intravenously after endotracheal intubation); Esketamine group 2 (EK2 group, intravenous infusion of esketamine at a rate of 0.125 $mg \cdot kg^{-1} \cdot h^{-1}$ for 2 hours after tracheal intubation); Control group (Group C, No administration of esketamine). All three groups were treated with intravenous rapid induction, double lumen tracheal intubation, and ultrasound guided surgical incision intercostal nerve block. When the postoperative pain NRS score≥4 points, dezocine was given intravenously for rescue analgesia, with a single dose of 5 mg. The NRS pain score, hemodynamic indexes and blood gas indexes at different time points after operation were recorded. The rescue analgesia and adverse reactions of the three groups were compared. **Results** There was significant difference in NRS scores among the three groups ($P < 0.05$), and NRS scores of esketamine group (EK1 group and EK2 group) at each time point were lower than those of group C ($P < 0.05$). The number of cases of rescue analgesia within 48 h after operation in EK1 group, EK2 group and C group were 2, 3 and 13 cases respectively. The rescue analgesic rate and dezocine dosage of esketamine group (EK1 group and EK2 group) were lower than those of group C ($P < 0.05$), and the time of first pressing analgesic pump was later than that of group C ($P < 0.05$). There was no significant difference in the incidence of postoperative adverse reactions among the three groups ($P > 0.05$). **Conclusion** Intraoperative use of flaxseed intoxicating dose of esketamine, single intravenous injection, and continuous intravenous pump injection can achieve the goal of reducing postoperative acute pain in patients undergoing thoracoscopic lung surgery, without increasing postoperative adverse reactions. Pre-operative single intravenous injection is more convenient to operate than continuous intravenous infusion, and there is no concern of delayed recovery. It is more recommended for pain relief in thoracoscopic lung surgery.

Keywords: Esketamine; Thoracoscopy; Postoperative pain; Administration method; Blood pressure; Dezocine

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Although thoracoscopic-assisted lung surgery is less invasive than traditional open chest surgery, the retraction of intercostal muscles and nerves at the surgical site can cause significant postoperative pain. Improper management of acute postoperative pain may lead to chronic pain, making effective perioperative analgesia crucial for promoting postoperative recovery. NMDA receptor antagonist ketamine has been shown to have preventive analgesic effects, and esketamine is the *S*-enantiomer. Currently, reports on the use of esketamine in thoracic surgery are limited. Therefore, this study aims to investigate the effects of different administration methods of esketamine on postoperative pain in patients undergoing thoracoscopic lung surgery, providing references for pain management in thoracoscopic procedures.

1 Materials and methods

1.1 General information

The study was approved by the hospital's Medical Ethics Committee (KTLL202306127), and informed consent was obtained from patients or their families. A total of 90 patients scheduled for elective thoracoscopic lung surgery at Qingdao Municipal Hospital from January to June 2023 were included.

Inclusion criteria: age < 65 years; ASA classification I-III; body mass index (BMI) 18-30 kg/m^2; estimated surgery time ≤ 3 hours. Exclusion criteria: surgery time > 3 hours; infusion of esketamine during surgery < 2 hours; conversion to open surgery during the procedure; occurrence of severe adverse events (e.g., massive bleeding).

1.2 Study groups

Patients were randomly divided into three groups using a random number table: (1) Esketamine 1 group (EK1 group, n=30), receiving a 0.25 mg/kg intravenous bolus of esketamine after tracheal intubation; (2) Esketamine 2 group (EK2 group, n=30), receiving a continuous intravenous infusion of esketamine at 0.125

mg·kg^{-1}·h^{-1} for 2 hours after tracheal intubation; (3) Control group (C group, n=30), without esketamine.

1.3 Study methods

After admission, a peripheral vein was opened, and routine monitoring of blood pressure (BP), heart rate (HR), pulse, blood oxygen saturation (SpO_2), and electrocardiogram (ECG) was performed. Invasive blood pressure (IBP) was measured via radial artery cannulation under local anesthesia. Groups C, EK1, and EK2 all received intravenous rapid induction with sufentanil 0.4–0.5 μg/kg, propofol 1.5–2.0 mg/kg, and rocuronium 0.9 mg/kg. A double-lumen endotracheal tube was inserted orally under direct vision, and its position was confirmed with a fiberoptic bronchoscope.

After confirming the tube position, mechanical ventilation was connected. In the EK1 group, 0.25 mg/kg esketamine was administered intravenously, followed by a 10 mL/h infusion of normal saline. In the EK2 group, after bolus administration of the same volume of normal saline, esketamine was infused at 0.125 mg·kg^{-1}·h^{-1} for 2 hours. The C group did not receive esketamine. During surgery, IBP, HR, SpO_2, ECG, and BIS were monitored, maintaining BIS values between 40 and 60, with adjustments to anesthesia depth based on BIS values. After positioning the patient in a lateral decubitus position, ultrasound-guided intercostal nerve blocks were performed at the incision site with 0.375% ropivacaine, totaling 25 mL. Anesthesia was maintained with intravenous infusion of propofol 4–8 mg·kg^{-1}·h^{-1} and remifentanil 0.1 – 0.2 μg·kg^{-1}·min^{-1} for analgesia, with intermittent intravenous boluses of rocuronium 0.3 mg/kg.

At the end of the surgery, propofol and remifentanil infusions were stopped, and ketorolac 30 mg was administered intravenously. Postoperative analgesia was managed with a patient-controlled analgesia (PCA) pump, containing sufentanil 2 μg/kg + tropisetron 5 mg, with a total volume of 100 mL and an infusion rate of 2 mL/h. If the postoperative NRS pain score was ≥4, rescue analgesia with dexmedetomidine 5 mg was administered intravenously.

1.4 Observation indicators

(1) NRS pain scores at 6, 12, 24, and 48 hours postoperatively.

(2) Hemodynamic indicators: systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and HR at skin incision (T1), 30 minutes (T2), 60 minutes (T3), and 90 minutes (T5) during surgery.

(3) Blood gas indicators: oxygen partial pressure (PaO_2), carbon dioxide partial pressure ($PaCO_2$), lactate levels, and blood glucose levels before surgery (T0), at 60 minutes of single-lung ventilation (T4), and 30 minutes postoperatively (T6).

(4) Rescue analgesia: the time of the first PCA pump activation for each group, the number of rescue analgesia instances within 48 hours, and total dexmedetomidine dosage.

(5) Recovery time and extubation time.

(6) Adverse reactions: the incidence of delirium, nausea and vomiting, agitation, and delayed recovery within 48 hours postoperatively for each group.

1.5 Statistical methods

Data were analyzed using SPSS 27.0 software. For quantitative data, normality was tested using the S-W test. Data with normal distribution were expressed as $\bar{x}\pm s$, and between-group comparisons were performed using one-way ANOVA. Repeated measures data were analyzed using repeated measures ANOVA. Non-normally distributed data are expressed as M (Q1, Q3), and between-group comparisons were made using the rank sum test. Categorical data are presented as case (%), with between-group comparisons performed using the chi-square test. A P-value < 0.05 was considered statistically significant.

2 Results

2.1 General characteristics

In this study, one patient was excluded from the EK1 group due to surgery time > 3 hours, and two patients were excluded from the EK2 group due to conversion to open surgery. There was no statistically significant difference in age, gender, height, weight, BMI, anesthesia time, and surgery time among the three groups ($P > 0.05$). **See Table 1.**

Tab. 1 Comparison of general conditions among three groups ($\bar{x}\pm s$)

Indicator	EK1 group (n=29)	EK2 group (n=28)	C group (n=30)	F/χ^2	P
Age(year)	49.03±5.08	52.11±5.59	51.63±6.47	2.384	0.098
Male/female	16/ 13	14/14	14/16	0.432	0.806
Height(cm)	168.21±7.17	168.04±6.45	168.63±5.95	0.065	0.937
Weight (kg)	66.48±8.69	66.82±7.55	65.60±9.52	0.155	0.856
BMI (kg/m^2)	23.38±1.84	23.61±2.28	22.93±2.52	0.687	0.506
Analgesia time(min)	181.10±10.16	185.04±6.10	183.80±9.09	1.482	0.233
Operative time (min)	132.55±8.99	136.50±6.76	134.57±10.16	1.330	0.270

2.2 NRS Pain scores

Postoperative NRS pain scores at 6, 12, 24, and 48 hours were: EK1 group: 1.69 ± 0.47, 2.38 ± 0.56, 3.10 ± 0.31, 2.93 ± 0.26; EK2 group: 1.57 ± 0.63, 2.43 ± 0.63, 3.04 ± 0.43, 2.93 ± 0.26; C group: 2.07 ± 0.58, 3.00 ± 0.83, 3.70 ± 1.21, 3.33 ± 0.71. Differences in NRS scores at different time points were statistically significant (F = 105.774, $P < 0.05$), with peak pain occurring at 24 hours

postoperatively in all groups. There were statistically significant differences in NRS scores among the three groups (F = 20.490, P < 0.05). Esketamine groups (EK1 and EK2) had lower NRS scores at each time point compared to the C group (P < 0.05), with no significant difference between EK1 and EK2 groups (P > 0.05).

2.3 Hemodynamic indicators

There were statistically significant differences in DBP and MAP at different time points (T1, T2, T3, T5) (P < 0.05). However, there were no statistically significant differences in hemodynamic indicators among the three groups (P > 0.05). **See Table 2.**

Tab. 2 Comparison of hemodynamic indicators among three groups （$\bar{x}\pm s$）

Group	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (/min)
EK1 group				
T_1	112.48±4.70	74.07±1.96	86.87±2.50	70.52±4.76
T_2	112.31±4.48	70.07±4.17	84.15±3.97	69.55±3.79
T_3	111.93±4.56	69.28±3.05	83.49±2.67	68.07±4.26
T_5	110.76±3.97	68.21±2.85	82.38±2.89	70.31±3.88
EK2 group				
T_1	113.82±5.22	74.39±4.68	87.54±4.72	70.96±3.65
T_2	111.07±3.77	67.68±3.15	82.14±2.77	67.96±4.05
T_3	111.25±3.59	71.00±4.33	84.42±3.31	70.50±3.85
T_5	112.57±5.02	68.89±5.81	83.43±5.32	68.82±4.07
C group				
T_1	109.93±2.12	71.93±2.61	84.60±1.64	68.17±3.23
T_2	112.10±5.17	68.70±5.66	83.17±5.22	68.13±4.07
T_3	111.87±4.52	68.80±5.62	83.16±3.97	68.70±3.63
T_5	112.20±4.44	70.63±4.26	84.40±4.12	68.13±4.20
F/P_{time}	0.126/0.944	27.118/<0.001	15.075/<0.001	1.500/0.227
F/P_{group}	0.595/0.554	0.282/0.755	0.464/0.631	1.606/0.207
$F/Pi_{interaction}$	2.596/0.019	3.885/0.002	3.483/0.004	0.874/0.477

2.4 Blood gas indicators

There were statistically significant differences in PaO_2, $PaCO_2$, blood glucose levels at different time points (T0, T4, T6) (P < 0.05). However, there were no statistically significant differences in blood gas indicators among the three groups (P > 0.05). **See Table 3.**

2.5 Rescue analgesia

The number of cases requiring rescue analgesia within 48 hours postoperatively were 2, 3, and 13 for EK1, EK2, and C groups, respectively. The rescue analgesia rate and total dosage of dexmedetomidine were lower in the esketamine groups (EK1 and EK2) compared to the C group (P < 0.05), and the time of first PCA pump activation was later in the esketamine groups (P < 0.05). However, there were no statistically significant differences between EK1 and EK2 groups (P > 0.05). **See Table 4.**

2.6 Recovery Time, Extubation Time, and Adverse Reaction Incidence

There was no statistically significant difference in the awakening time, extubation time, and incidence of postoperative adverse reactions among the three groups (P>0.05). **See Table 5.**

Tab. 3 Comparison of blood gas indicators among three groups ($\bar{x}\pm s$)

Group	PaO_2 （mmHg）	$PaCO_2$ （mmHg）	Lactate （mmo/L）	Blood glucose （mmo/L）
EK1 group				
T_0	92.89±4.03	42.81±3.14	0.43±0.57	5.95±0.98
T_4	196.48±8.94	48.32±2.59	0.48±0.55	5.59±0.51
T_6	194.29±21.52	47.95±2.62	0.29±0.48	5.32±0.36
EK2 group				
T_0	92.88±4.13	41.95±3.42	0.21±0.46	5.78±0.92
T_4	196.18±7.66	48.29±1.63	0.25±0.49	5.82±0.48
T_6	200.71±8.66	46.68±2.87	0.32±0.51	5.38±0.28
C group				
T_0	91.28±7.20	42.83±3.14	0.25±0.46	5.94±0.73
T_4	195.23±8.59	47.99±2.24	0.26±0.49	6.12±0.43
T_6	194.52±11.30	46.49±3.05	0.27±0.49	5.47±0.24
F/P_{time}	3192/<0.001	103.394/<0.001	0.164/0.849	20.696/<0.001
F/P_{group}	1.556/0.217	1.524/0.224	2.054/0.135	2.898/0.061
$F/Pi_{interaction}$	1.138/0.337	0.921/0.453	0.722/0.578	1.991/0.115

Tab. 4 Comparison of remedial analgesia among three groups

Group	Rescue analgesia [case （%）]	Time of first PCA pump [M （Q_1,Q_3）]	Dexmedetomidine use[M （Q_1,Q_3）]
EK1 group	2（6.9）[a]	13（12，14）[a]	0（0，0）[a]
EK2 group	3（10.7）[a]	13（12，15）[a]	0（0，0）[a]
C group	13（43.3）	10（9，12）	0（0，5）
χ^2 **value**	14.434	18.225	15.311
P **value**	0.001	＜0.001	＜0.001

Tab.5 Comparison of awakening time, extubation time, and incidence of adverse reactions among three groups

Group	*n*	Awakening time（min,$\bar{x}\pm s$）	Extubation time（min,$\bar{x}\pm s$）	Adverse Reactions（case）				
				Delirium	Nausea and vomiting	Agitation	Delayed recovery	Total [case(%)]
EK1 group	29	8.55±0.95	9.97±1.12	0	1	1	1	3（10.34）
EK2 group	28	9.07±1.12	10.00±1.31	1	1	1	1	4（14.29）
C group	30	8.57±0.68	9.43±0.94	2	2	1	1	6（20.00）
***F*/χ^2 value**		2.891	2.348					1.096
***P* value**		0.061	0.102					0.578

3 Discussion

Although thoracic surgery has rapidly advanced towards minimally invasive techniques, postoperative pain remains significant. Severe postoperative pain can lead to complications such as pulmonary infections, atelectasis, hypoxemia, and postoperative delirium. Poor control of acute postoperative pain may even develop into chronic pain syndrome following thoracic surgery [1]. Therefore, effective and rational pain management after thoracoscopic surgery is crucial. Compared to ketamine, esketamine has a faster onset, quicker elimination, and stronger analgesic capabilities [2]. It also has milder psychoactive effects and fewer extrapyramidal reactions [3]. Previous studies have shown that administering esketamine before and during surgery can effectively alleviate acute postoperative pain [4]. However, there is limited clinical research on the use of esketamine in thoracic surgery, and the optimal drug dosage and administration methods are not yet clear.

According to widely accepted standards, the observation period for preventive analgesic effects should exceed 5.5 drug half-lives [5]. The half-life of low-dose intravenous esketamine is 186 minutes, and that of continuous intravenous infusion is 79 minutes. Therefore, appropriate evaluation times for postoperative analgesia with esketamine are 17 hours (for low-dose intravenous injection) and 7 hours (for continuous intravenous infusion) after discontinuation of the drug. Consequently, postoperative time points of 6, 12, 24, and 48 hours were selected for NRS scoring.

Studies found that intravenous administration of 0.125–0.500 mg/kg esketamine during surgery significantly relieved pain and reduced anxiety and depression in patients with breast and cervical cancers [6-7]. Liu *et al.* [8] found that low-dose intravenous infusion of esketamine (<0.15 $mg\cdot kg^{-1}\cdot h^{-1}$) did not increase the risk of hallucinations or cognitive impairment. Due to the dose-dependent nature of esketamine's side effects, this study chose sub-anesthetic doses of esketamine, divided into 0.25 mg/kg intravenous bolus and 0.125 mg•kg^-1•h^-1 continuous intravenous infusion.

The study found that the esketamine groups (EK1 and EK2) had lower postoperative NRS scores, fewer rescue analgesia requirements, and reduced doses of dezocine compared to the control group, indicating that intraoperative esketamine reduced acute postoperative pain in patients undergoing thoracoscopic lung surgery. However, the different administration methods of esketamine did not show a significant effect on these outcomes. The study also found that esketamine could prolong the time to the first use of the patient-controlled analgesia pump after surgery. This mechanism may be related to the failure time of intercostal nerve block, although whether esketamine extends the duration of intercostal nerve block was not addressed in this study. Future research with larger sample sizes could further investigate this.

The mechanism by which esketamine reduces acute postoperative pain may include: esketamine inhibits NMDA receptors while promoting the release of endogenous opioid peptides, activating μ, δ, and κ opioid receptors to inhibit monoaminergic neurons [9]; it obstructs pain ascending pathways, reduces Ca^{2+} release, and increases cyclic adenosine monophosphate levels [10]; it also influences leukocyte-related immune responses by inhibiting neutrophil chemotaxis and superoxide compound formation [10], reducing pro-inflammatory cytokines such as IL-6 and IL-1β, thereby exerting anti-inflammatory effects and reducing stress responses [11-12]; esketamine can also lower NMDA receptor activity [13], reduce central sensitization, increase pain thresholds, and diminish pain hypersensitivity caused by anesthetic drugs [14], thereby effectively suppressing postoperative stress responses. While opioids are widely used for postoperative pain management, their adverse effects warrant attention [15]. Esketamine, by non-competitively inhibiting NMDA receptors in both central and peripheral nervous systems, can reduce hypersensitivity and central sensitization, decrease opioid usage during and after surgery, and lower the incidence of pain sensitization [16].

Research has shown that esketamine has mild sympathomimetic effects, partially counteracting the vasodilatory effects of propofol, stabilizing hemodynamic trends [17-18]. It can also cause catecholamine release, inhibit norepinephrine reuptake, and activate the sympathetic nervous system, leading to cardiovascular stimulation, elevated blood pressure, and increased heart rate. Even at low doses, esketamine stimulates the cardiovascular system, increasing cardiac workload and myocardial oxygen consumption. In this study, no significant hemodynamic differences were observed among the three groups. Esketamine groups (EK1 and EK2) did not experience severe hypertension or tachycardia

requiring intervention, indicating that sub-anesthetic doses of esketamine administered either as a bolus or continuous infusion did not cause significant hemodynamic fluctuations, maintaining relatively stable vital signs. The blood gas analysis results showed no statistically significant differences in blood gas parameters among the three groups, possibly due to insufficient sample size. Future studies with larger samples could further investigate this.

Esketamine has a higher demethylation capacity and a 22% higher clearance rate compared to the left-handed enantiomer of ketamine, resulting in faster overall recovery times [19]. In this study, there were no differences in recovery or extubation times among the three groups, indicating that sub-anesthetic doses of esketamine do not prolong recovery or extubation times. Multiple studies have confirmed that esketamine does not increase the incidence of delirium, nausea, or vomiting [20]. This study also confirmed that sub-anesthetic doses of esketamine administered either as a bolus or continuous infusion did not increase postoperative adverse reactions.

In conclusion, administering sub-anesthetic doses of esketamine during thoracoscopic lung surgery, whether as a single intravenous bolus or continuous intravenous infusion, effectively reduces acute postoperative pain, prolongs the time to the first use of the patient-controlled analgesia pump, and decreases the need for rescue analgesia. Both administration method did not increase the incidence of postoperative adverse reactions and are relatively safe. A single preoperative intravenous injection of esketamine is more straightforward and avoids concerns about delayed recovery, making it more recommended for pain management in thoracoscopic lung surgeries.

The authors report no conflict of interest

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·论　著·

艾司氯胺酮不同给药方式对胸腔镜肺手术术后疼痛的影响

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摘要：目的　探究静脉推注和静脉泵注艾司氯胺酮对胸腔镜肺手术患者术后疼痛的影响。**方法**　选择青岛市市立医院 2023 年 1 月至 6 月择期行胸腔镜肺手术的患者 90 例，采用随机数字表法分为三组，艾司氯胺酮 1 组（EK1 组，气管插管后予以艾司氯胺酮 0.25 mg/kg 静脉推注）；艾司氯胺酮 2 组（EK2 组，气管插管后以 0.125 mg·kg^{-1}·h^{-1}的速度静脉泵注艾司氯胺酮 2 h）；对照组（C 组，不给予艾司氯胺酮），各 30 例。三组均采用静脉快速诱导，双腔气管插管后，超声引导下行手术切口肋间神经阻滞。术后疼痛数字分级评分法（NRS）评分≥4 分时，给予地佐辛静脉注射补救镇痛，单次剂量 5 mg。记录患者术后不同时间点的 NRS 评分、血流动力学指标、血气指标。比较三组补救镇痛情况及不良反应。**结果**　三组间 NRS 评分差异有统计学意义（P<0.05），艾司氯胺酮组（EK1 组、EK2 组）在各时间点的 NRS 评分低于 C 组（P<0.05）。EK1 组、EK2 组、C 组术后 48 h 内补救镇痛例数分别为 2、3、13 例。艾司氯胺酮组（EK1 组、EK2 组）的补救镇痛率、地佐辛用量均低于 C 组（P<0.05），首次按压镇痛泵时间晚于 C 组（P<0.05）。三组术后不良反应发生率比较差异无统计学意义（P>0.05）。**结论**　胸腔镜肺手术患者术中应用亚麻醉剂量艾司氯胺酮，单次静脉推注和持续静脉泵注均可达到减轻患者术后急性疼痛的目的，不增加术后不良反应。术前单次静脉注射较持续静脉泵注操作简便，且无苏醒延迟的顾虑，更推荐用于胸腔镜肺手术的镇痛。

关键词：艾司氯胺酮；胸腔镜；术后疼痛；血压；地佐辛；静脉推注；静脉泵注；亚麻醉剂量

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Effect of different administration methods of esketamine on postoperative pain after thoracoscopic lung surgery

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Abstract: Objective　To investigate the effect of itravenous injection or infuson of esketamine on postoperative pain in patients undergoing thoracoscopic lung surgery. **Methods**　A total of 90 patients who underwent elective thoracoscopic lung surgery in Qingdao Municipal Hospital from January to June 2023 were selected and randomly divided into three groups: esketamine group 1 (EK1 group, 0.25 mg/kg of esketamine was injected intravenously after endotracheal intubation), esketamine group 2 (EK2 group, intravenous infusion of esketamine at a rate of 0.125 mg·kg^{-1}·h^{-1} for 2 hours after endotracheal intubation), and control group (C group, no administration of esketamine). All three groups were treated with intravenous rapid induction, double lumen tracheal intubation, and ultrasound guided surgical incision intercostal nerve block. When the postoperative pain numerical rating scale (NRS) score≥4 points, dezocine was given intravenously for rescue analgesia, with a single dose of 5 mg. The NRS score, hemodynamic indexes and blood gas indexes at different time points after operation were recorded. The rescue analgesia and adverse reactions of the three groups were compared. **Results**　There was significant difference in NRS scores among the three groups (P<0.05), and NRS scores of esketamine group (EK1 group and EK2 group) at each time point were lower than those of C group (P<0.05). The number of cases of rescue analgesia within 48 h after operation in EK1 group, EK2 group and C group were

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2, 3 and 13 cases respectively. The rescue analgesic rate and dezocine dosage of esketamine group (EK1 group and EK2 group) were lower than those of C group (P <0.05), and the time of first pressing analgesic pump was later than that of C group (P<0.05). There was no significant difference in the incidence of postoperative adverse reactions among the three groups (P > 0.05). **Conclusion** Intraoperative use of subanesthetic dose of esketamine, single intravenous injection, and continuous intravenous infusion can achieve the goal of reducing postoperative acute pain in patients undergoing thoracoscopic lung surgery, without increasing postoperative adverse reactions. Pre-operative single intravenous injection is more convenient to operate than continuous intravenous infusion, and there is no concern of delayed recovery. It is more recommended for pain relief in thoracoscopic lung surgery.

Keywords: Esketamine; Thoracoscopy; Postoperative pain; Blood pressure; Dezocine; Intravenous injection; Intravenous infusion; Subanaesthetic dose

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胸腔镜辅助肺手术虽较传统开胸手术创伤小,但因手术部位肋间肌肉及神经的牵拉,患者术后疼痛明显,术后急性疼痛处理不当可能转为慢性疼痛,因此有效的围术期镇痛对促进患者术后康复非常重要。N-甲基-D-天冬氨酸(NMDA)受体拮抗剂氯胺酮已被证明具有预防性镇痛作用,新药艾司氯胺酮是其 *S*-对映体。目前有关艾司氯胺酮在胸外科手术中的应用报道有限。因此,本研究拟探究艾司氯胺酮不同给药方式对胸腔镜肺手术患者术后疼痛的影响,为胸腔镜手术疼痛管理提供参考。

1　资料和方法

1.1　*一般资料*　研究经医院医学伦理委员会批准(KTLL202306127),患者或家属签署知情同意书。纳入 2023 年 1 月至 6 月青岛市市立医院拟行择期胸腔镜肺手术的患者 90 例,纳入标准:年龄<65 岁;美国麻醉医师协会(ASA)分级为Ⅰ~Ⅲ级;身体质量指数(BMI)18~30 kg/m^2;手术时间预计≤3 h。剔除标准:手术时间>3 h;术中泵注艾司氯胺酮时间<2 h;术中转为开放手术;发生严重不良事件(大出血等)。

1.2　*研究分组*　采用随机数字表法将患者分为 3 组。艾司氯胺酮 1 组(EK1 组,n=30),气管插管后予以艾司氯胺酮 0.25 mg/kg 静脉推注。艾司氯胺酮 2 组(EK2 组,n=30),气管插管后以 0.125 mg/(kg·h)的速度静脉泵注艾司氯胺酮 2 h。对照组(C 组,n=30),不给予艾司氯胺酮。

1.3　*研究方法*　入室后开放外周静脉,常规监测血压、心率(HR)、脉搏,血氧饱和度(SpO_2),心电图(ECG),局麻下行桡动脉置管测量有创血压(IBP)。C 组、EK1 组和 EK2 组均采用静脉快速诱导,静脉注射舒芬太尼 0.4~0.5 μg/kg、丙泊酚 1.5~2.0 mg/kg、罗库溴铵 0.9 mg/kg 行麻醉诱导,经口明视插入双腔气管导管,纤维支气管镜确认导管位置正确。

导管位置确认后,连接麻醉机机械通气,EK1 组静脉推注 0.25 mg/kg 艾司氯胺酮后以 10 mL/h 的速度泵注生理盐水,EK2 组推注相同容量的生理盐水后以0.125 mg/(kg·h)的速度泵注艾司氯胺酮 2 h,C 组未予艾司氯胺酮。术中监测患者 IBP、HR、SpO_2、ECG、脑电双频指数(BIS),维持 BIS 值于 40~60,根据 BIS 值调整麻醉深度。患者改侧卧位后,超声引导下行手术切口肋间神经阻滞,于切口处肋间及相邻肋间注射0.375%罗哌卡因总量 25 mL。术中全凭静脉麻醉维持,静脉泵注丙泊酚 4~8 mg/(kg·h),瑞芬太尼0.1~0.2 μg/(kg·h)镇痛,间断静脉推注罗库溴铵 0.3 mg/kg。

术毕停止泵注丙泊酚和瑞芬太尼,给予酮咯酸氨丁三醇 30 mg 静脉滴注。连接术后静脉镇痛泵,3 组镇痛泵药物为:舒芬太尼 2 μg/kg+托烷司琼 5 mg,镇痛泵药物总容量为 100 mL,输注量为 2 mL/h。术后疼痛数字分级评定法(NRS)评分≥4 分时,给予地佐辛静脉注射补救镇痛,单次剂量 5 mg。

1.4　*观察指标*　(1) 记录患者术后 6、12、24、48 h 的 NRS 疼痛评分。(2) 血流动力学指标:记录切皮时(T_1),手术 30 min(T_2)、60 min(T_3)、90 min(T_5)的收缩压(SBP)、舒张压(DBP)、平均动脉压(MAP)、HR。(3) 血气指标:术前(T_0)、单肺 60 min(T_4)、术后 30 min(T_6)的氧分压(PaO_2)、二氧化碳分压($PaCO_2$)、乳酸值及血糖值。(4) 补救镇痛情况:记录每组患者第一次按压镇痛泵的时间,48 h 内补救镇痛的例数,及地佐辛总用量。(5) 苏醒时间及拔管时间。(6) 不良反应:记录各组术后 48 h 内出现谵妄、恶心呕吐、烦躁、苏醒延迟的例数。

1.5　*统计学方法*　采用 SPSS 27.0 软件分析数据。计量资料采用 S-W 检验分析正态性,正态分布的资料用 $\bar{x}\pm s$ 表示,组间比较采用单因素方差分析,多时点测量资料使用重复测量方差分析。非正态分布资

料采用 $M(Q_1, Q_3)$ 表示，组间比较采用秩和检验。计数资料以例(%)表示，组间比较采用 χ^2 检验。$P<0.05$ 为差异有统计学意义。

2 结　果

2.1　患者一般情况　EK1 组因手术时间>3 h 剔除 1 例，EK2 组因术中转为开放手术剔除 2 例。三组患者年龄、性别、身高、体重、BMI、麻醉时间、手术时间的差异无统计学意义($P>0.05$)。见表 1。

2.2　NRS 疼痛评分　术后 6、12、24、48 h 的 NRS 疼痛评分，EK1 组分别为 1.69±0.47、2.38±0.56、3.10±0.31、2.93±0.26；EK2 组为 1.57±0.63、2.43±0.63、3.04±0.43、2.93±0.26；C 组分别为 2.07±0.58、3.00±0.83、3.70±1.21、3.33±0.71。不同时间点 NRS 评分差异有统计学意义($F=105.774$, $P<0.05$)，三组患者的疼痛高峰均在术后 24 h。三组间 NRS 评分差异有统计学意义($F=20.490$, $P<0.05$)，艾司氯胺酮组(EK1 组、EK2 组)在各个时间点的 NRS 评分均较 C 组低($P<0.05$)，EK1 组与 EK2 组差异无统计学意义($P>0.05$)。

2.3　血流动力学指标　不同时间点(T_1、T_2、T_3、T_5)DBP、MAP 差异有统计学意义($P<0.05$)；但三组各项血流动力学指标比较差异无统计学意义($P>0.05$)。见表 2。

2.4　血气指标　不同时间点(T_0、T_4、T_6)PaO_2、$PaCO_2$、血糖值差异有统计学意义($P<0.05$)，但三组之间各项血气指标比较差异无统计学意义($P>0.05$)。见表 3。

2.5　补救镇痛情况　EK1 组、EK2 组、C 组术后 48 h 内补救镇痛例数分别为 2、3、13 例。EK1 组、EK2 组的补救镇痛率、地佐辛用量均低于 C 组($P<0.05$)，首次按压镇痛泵时间晚于 C 组($P<0.05$)，但 EK1 组与 EK2 组之间的差异无统计学意义($P>0.05$)。见表 4。

2.6　苏醒时间、拔管时间及不良反应发生率　三组苏醒时间、拔管时间、术后不良反应发生率差异无统计学意义($P>0.05$)。见表 5。

表 1　三组患者一般情况比较　($\bar{x}\pm s$)

Tab. 1　Comparison of general conditions among three groups　($\bar{x}\pm s$)

项目	EK1 组 ($n=29$)	EK2 组 ($n=28$)	C 组 ($n=30$)	F/χ^2 值	P 值
年龄(岁)	49.03±5.08	52.11±5.59	51.63±6.47	2.384	0.098
男/女(例)	16/13	14/14	14/16	0.432	0.806
身高(cm)	168.21±7.17	168.04±6.45	168.63±5.95	0.065	0.937
体重(kg)	66.48±8.69	66.82±7.55	65.60±9.52	0.155	0.856
BMI(kg/m^2)	23.38±1.84	23.61±2.28	22.93±2.52	0.687	0.506
麻醉时间(min)	181.10±10.16	185.04±6.10	183.80±9.09	1.482	0.233
手术时间(min)	132.55±8.99	136.50±6.76	134.57±10.16	1.330	0.270

表 2　三组患者血流动力学指标比较　($\bar{x}\pm s$)

Tab. 2　Comparison of hemodynamic indicators among three groups　($\bar{x}\pm s$)

组别	例数	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (次/min)
EK1 组	29				
T_1		112.48±4.70	74.07±1.96	86.87±2.50	70.52±4.76
T_2		112.31±4.48	70.07±4.17	84.15±3.97	69.55±3.79
T_3		111.93±4.56	69.28±3.05	83.49±2.67	68.07±4.26
T_5		110.76±3.97	68.21±2.85	82.38±2.89	70.31±3.88
EK2 组	28				
T_1		113.82±5.22	74.39±4.68	87.54±4.72	70.96±3.65
T_2		111.07±3.77	67.68±3.15	82.14±2.77	67.96±4.05
T_3		111.25±3.59	71.00±4.33	84.42±3.31	70.50±3.85
T_5		112.57±5.02	68.89±5.81	83.43±5.32	68.82±4.07
C 组	30				
T_1		109.93±2.12	71.93±2.61	84.60±1.64	68.17±3.23
T_2		112.10±5.17	68.70±5.66	83.17±5.22	68.13±4.07
T_3		111.87±4.52	68.80±5.62	83.16±3.97	68.70±3.63
T_5		112.20±4.44	70.63±4.26	84.40±4.12	68.13±4.20
$F_{时间}/P_{时间}$ 值		0.126/0.944	27.118/<0.001	15.075/<0.001	1.500/0.227
$F_{时间}/P_{组间}$ 值		0.595/0.554	0.282/0.755	0.464/0.631	1.606/0.207
$F_{时间}/P_{交互}$ 值		2.596/0.019	3.885/0.002	3.483/0.004	0.874/0.477

表 3　三组患者血气指标比较　($\bar{x}\pm s$)

Tab. 3　Comparison of blood gas indicators among three groups　($\bar{x}\pm s$)

组别	例数	PaO_2 (mmHg)	$PaCO_2$ (mmHg)	乳酸 (mmo/L)	血糖 (mmo/L)
EK1 组	29				
T_0		92.89±4.03	42.81±3.14	0.43±0.57	5.95±0.98
T_4		196.48±8.94	48.32±2.59	0.48±0.55	5.59±0.51
T_6		194.29±21.52	47.95±2.62	0.29±0.48	5.32±0.36
EK2 组	28				
T_0		92.88±4.13	41.95±3.42	0.21±0.46	5.78±0.92
T_4		196.18±7.66	48.29±1.63	0.25±0.49	5.82±0.48
T_6		200.71±8.66	46.68±2.87	0.32±0.51	5.38±0.28
C 组	30				
T_0		91.28±7.20	42.83±3.14	0.25±0.46	5.94±0.73
T_4		195.23±8.59	47.99±2.24	0.26±0.49	6.12±0.43
T_6		194.52±11.30	46.49±3.05	0.27±0.49	5.47±0.24
$F_{时间}/P_{时间}$ 值		3 192.759/<0.001	103.394/<0.001	0.164/0.849	20.696/<0.001
$F_{时间}/P_{组间}$ 值		1.556/0.217	1.524/0.224	2.054/0.135	2.898/0.061
$F_{时间}/P_{交互}$ 值		1.138/0.337	0.921/0.453	0.722/0.578	1.991/0.115

表 4　三组补救镇痛情况比较

Tab. 4　Comparison of remedial analgesia among three groups

组别	例数	补救镇痛[例(%)]	首次按压时间[min, $M(Q_1, Q_3)$]	地佐辛用量[mg, $M(Q_1, Q_3)$]
EK1 组	29	2(6.9)[a]	13(12,14)[a]	0(0,0)[a]
EK2 组	28	3(10.7)[a]	13(12,15)[a]	0(0,0)[a]
C 组	30	13(43.3)	10(9,12)	0(0,5)
χ^2/H 值		14.434	18.225	15.311
P 值		0.001	<0.001	<0.001

注：与 C 组比较，[a]$P<0.05$。

表 5　三组苏醒时间、拔管时间及不良反应发生率比较

Tab. 5　Comparison of awakening time, extubation time, and incidence of adverse reactions among three groups

组别	例数	苏醒时间（min，$\bar{x}\pm s$）	拔管时间（min，$\bar{x}\pm s$）	不良反应（例）				
				谵妄	恶心呕吐	术后烦躁	苏醒延迟	合计[例（%）]
EK1 组	29	8.55±0.95	9.97±1.12	0	1	1	1	3（10.34）
EK2 组	28	9.07±1.12	10.00±1.31	1	1	1	1	4（14.29）
C 组	30	8.57±0.68	9.43±0.94	2	2	1	1	6（20.00）
F/χ^2 值		2.891	2.348					1.096
P 值		0.061	0.102					0.578

3　讨　论

虽然胸科手术快速微创化发展，但肺部手术术后疼痛明显，剧烈的术后疼痛可导致肺部感染、肺不张、低氧血症、术后谵妄等并发症，术后急性疼痛控制不佳，甚至会发展为慢性疼痛综合征[1]。因此，胸腔镜术后合理有效的镇痛管理非常重要。艾司氯胺酮较氯胺酮具有起效快、消除快、镇痛能力更强等特点[2]，精神症状及拟交感作用轻微，少有锥体外系反应[3]。以往的研究表明，术前和术中应用艾司氯胺酮可以有效减轻术后急性疼痛[4]。但有关艾司氯胺酮用于胸科手术的临床研究较少，合理的药物剂量和给药方式尚不明确。

根据目前广泛接受的观察药物预防性镇痛作用的时间点要长于 5.5 个药物半衰期的标准[5]，低剂量静脉注射艾司氯胺酮的半衰期是 186 min，连续静脉泵注艾司氯胺酮的半衰期是 79 min，可得出适宜的艾司氯胺酮的术后镇痛评价时间是停药后 17 h（低剂量静脉注射）和 7 h（连续静脉泵注），因此将术后 6、12、24、48 h 作为进行 NRS 评分的时间点。

研究发现，术中静脉注射 0.125～0.500 mg/kg 艾司氯胺酮能显著缓解疼痛，降低乳腺癌及宫颈癌患者术后的焦虑抑郁情绪[6-7]；刘国凯等[8]研究发现小剂量艾司氯胺酮静脉泵注[<0.15 mg/（kg·h）]不增加幻觉或认知功能障碍的风险。由于艾司氯胺酮的副作用具有剂量依赖性，本研究选择亚麻醉剂量艾司氯胺酮，分为 0.25 mg/kg 静脉推注和 0.125 mg/（kg·h）持续静脉泵注两组。

研究发现，艾司氯胺酮组（EK1 组、EK2 组）较 C 组相比，术后 NRS 评分更低，补救镇痛率更低、地佐辛用量更少，显示胸腔镜肺手术患者术中应用艾司氯胺酮减轻了术后急性疼痛，但艾司氯胺酮不同给药方式对上述作用并无明显影响。本研究还发现应用艾司氯胺酮可延长术后首次按压镇痛泵时间，其机制可能与肋间神经阻滞失效时间有关，但艾司氯胺酮是否延长了肋间神经阻滞时间本研究尚未涉及，未来可进一步扩大样本量进行研究。

艾司氯胺酮减轻术后急性疼痛的机制可能为：艾司氯胺酮抑制 NMDA 受体，同时促进内源性阿片肽释放，激动 δ 和 κ 等阿片受体抑制单胺能神经元[9]；阻碍疼痛上行传导通路，减少 Ca^{2+} 释放，提高环磷酸腺苷水平[10]；还通过影响白细胞相关的免疫反应，抑制中性粒细胞趋化和超氧化合物形成[11]，减少 IL-6、IL-1β 等促炎因子的产生[12]，发挥抗炎作用来降低应激反应，从而发挥镇痛作用；艾司氯胺酮还可降低 NMDA 受体活性[13]，降低中枢敏感化，提高疼痛阈值，减少麻醉药物使用后导致的疼痛过敏现象[14]，进而有效抑制术后应激反应[15]。阿片类药物用于术后镇痛不良反应需要引起重视，艾司氯胺酮可通过非竞争性抑制阻断中枢和外周神经系统中的 NMDA 受体，减轻过敏性痛觉和中枢致敏，减少术中及术后对阿片类药物的使用量，降低痛觉敏化发生率[16]。

有研究表明艾司氯胺酮具有拟交感作用，可部分抵消丙泊酚的扩血管作用，使血流动力学变化趋势平稳[17-18]；还可引起儿茶酚胺释放，抑制去甲肾上腺素重摄取，激活交感神经系统而产生间接的心血管刺激作用，导致血压升高、HR 加快，小剂量使用即可刺激心血管系统，引起心脏做功和心肌氧耗增加。本研究中三组之间的血流动力学指标差异并无统计学意义，艾司氯胺酮组（EK1 组、EK2 组）未发生严重的高血压以及需要处理的心动过速，表明应用亚麻醉剂量艾司氯胺酮静脉推注或持续静脉泵注均未引起明显的血流动力学波动，使患者生命体征维持在相对稳定的状态。

艾司氯胺酮较氯胺酮去甲基化的能力更高，清除率较左旋单体高出 22%，整体苏醒时间快于氯胺酮[19]。本研究中，三组患者的苏醒时间和拔管时间无差异，应用亚麻醉剂量艾司氯胺酮并不会延长患者术后苏醒和拔管时间。多项研究均证实艾司氯胺酮未增加谵妄、恶心呕吐等不良反应发生率[8,20]。本研究也证实应用亚麻醉剂量艾司氯胺酮静脉推注或持续静脉泵注均未增加术后不良反应。

胸腔镜肺手术患者术中应用亚麻醉剂量艾司氯胺酮，单次静脉推注和持续静脉泵注均可达到减轻患者术后急性疼痛的目的，可延长首次按压镇痛泵时间，减少补救镇痛药物用量。两种给药方式并未增加患者术后不良反应的发生率，安全性高。术前单次静脉注射艾司氯胺酮较持续静脉泵注操作简便，且无苏醒延迟的顾虑，更推荐用于胸腔镜肺手术的镇痛。

利益冲突　无

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