The effects of S-ketamine on postoperative sleep quality in patients undergoing thoracoscopic surgery: a randomized study

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Abstract

Background: Postoperative sleep disturbance (PSD) is a common and uncomfortable experience for patients, which induces various negative clinical outcomes and increases the perioperative mortality. Thus, it is necessary to seek efficient methods to improve PSD. This study was designed to explore whether perioperative intravenous S-ketamine could improve sleep quality.

Methods: Patients undergoing elective thoracoscopic surgery were recruited and assigned into two groups randomly. 0.5 mg/kg of S-ketamine was given to the individuals in the experimental group during the period of anesthesia induction followed by 0.1mg/kg/h intravenous infusion until 15 minutes before the completion of the procedure, while normal saline in the same protocol was performed in the control group. The primary outcomes included the salivary melatonin (MT) concentration on the first day after surgery, and the Richard Campbell Sleep Questionnaire (RSCQ) scores on the first three days postoperatively. The secondary outcomes were the rest and movement Visual Analogue Scale (VAS) score at 6, 12, 24, and 48 hours postoperatively, the level of serum IL-6 and IL-10 on the first day postoperatively, and the incidence of postoperative negative complications.

Results: In the experimental group, the RSCQ scores on the first three days postoperatively and the level of MT on the first day after the procedure were significantly higher, and the rest and movement pain intensity at postoperative 6, 12 and 24 hours were statistically lower when compared with the control group, while the results at 48 hours postoperatively were comparable in both groups. In addition, the higher level of IL-6 and lower level of IL-10 postoperatively were noticed in the experimental group. In both groups, the incidence of negative outcomes was similar.

Conclusion: S-ketamine can effectively improve postoperative sleep quality, and reduce pain intensity and inflammation in patients undergoing thoracoscopic surgery.

1. Introduction

Postoperative sleep disturbance, characterized by shorter sleep duration, more times arousal or awakening, nightmares as well as fragmented sleep, is a common and uncomfortable experience for patients\textsuperscript{1}. It was reported that over 40% of patients suffered from decreased sleep quality on the night preoperatively which could persist for several days after surgery\textsuperscript{2}. The occurrence of PSD can be induced by various risk factors, including preoperative anxiety or depression, intraoperative general anesthetics, as well as postoperative pain\textsuperscript{3}. PSD can increase the risk of postoperative pain, neurocognitive disorders, mental diseases, cardiovascular adverse events, and even death\textsuperscript{4}. Considering the negative clinical outcomes of PSD, it is imperative to investigate efficient methods for the prevention and treatment of PSD.

Thoracoscopic surgery is a more acceptable treatment for patients with lung cancers than traditional thoracotomy, which reduces postoperative pain and improves the quality of life\textsuperscript{5}. Even though, many
patients after thoracoscopic procedures still complain about PSD and postoperative pain for a long time\textsuperscript{6,7}. To some extent, PSD and pain can interact with each other and ultimately create a vicious circle, which leads to persisting undesirable complications and additional burdens on patients\textsuperscript{8}. On one hand, PSD might induce hyperalgesia and facilitate the occurrence of pain, increase pain intensity, as well as extend pain durations\textsuperscript{9}. On the other hand, postoperative pain could shorter total sleep time, along with increased sleep arousal times\textsuperscript{10}. However, adequate sleep is beneficial to reducing pain intensity and analgesics requirement, promoting early motion and rehabilitation postoperatively\textsuperscript{11}. Although many studies have proposed that pharmacological and non-pharmacological treatments could enhance postoperative sleep quality\textsuperscript{3}, the specific mechanisms remain uncertain.

Ketamine possesses full anesthesia and profound analgesia efficacy without significant respiratory depression\textsuperscript{12}, which have been extensively studied. And a recent review proposed a novel use of ketamine in improving PSD probably through analgesia, anti-inflammatory, antidepression, as well as the interaction with the circadian system\textsuperscript{13}. However, the administration of ketamine is still limited owing to the dissociative efficacy and potential risk of abuse\textsuperscript{14}. S-ketamine, the S (+) enantiomer of ketamine, possesses a better anesthetic effect and a higher clearance rate, so it is considered more efficient and safer\textsuperscript{15}. Recently, plenty of studies demonstrated that S-ketamine also had the property of anti-inflammatory, analgesic and potent antidepressant effect\textsuperscript{16,17}, which might implicate the effects of S-ketamine on improving sleep quality. Interestingly, a recent RCT demonstrated that S-ketamine could decrease the incidence of PSD for patients undergoing gynecological laparoscopic surgery\textsuperscript{18}. To investigate whether perioperative administration of S-ketamine could enhance postoperative sleep quality, we designed the current study.

2. Materials and methods

2.1 Participants

The present prospective, randomized, double-blinded, placebo-controlled trial was conducted from June 1, 2022, to December 31, 2022. The study procedure was approved by the ethics committee of Hebei General Hospital (Ethics No. 2022 – 445), and was enrolled in the Chinese Clinical Trial Registry (Registration number: ChiCTR2200066742). Individuals were considered eligible when satisfying the inclusion criteria: patients undergoing elective thoracoscopic surgery with ASA grade II-III, aged 18 or older, and BMI of 18 \~ 32 kg/m\textsuperscript{2}. And the exclusion standards included: serious cardiovascular and cerebrovascular diseases, severe hepatic and renal dysfunction, a known history of mental illness, depression or sleep disorders (PSQI scores > 7)\textsuperscript{19}, contraindication and/or allergic to S-ketamine, patients who refused, and the surgical duration \(\geq\) 3 hours.

2.2 Randomization and blindness
Participants were randomly divided into the S-ketamine group or the control group by the ratio of 1:1. Randomization sequences were generated by a computer, and the sequences were hidden in opaque sealed envelopes. A non-blinded researcher diluted the study drugs or loaded normal saline into a 50 ml syringe according to sealed envelopes, and this researcher did not participate in the follow-up, data collection or analysis. Surgeons, patients themselves, and other investigators were all blind to the allocation.

2.3 Sample size estimation

According to the Pre-Experiment, the scores of the RSCQ were used to calculate the sample size. The RSCQ scores on the first night postoperatively were 62.5 ± 3.6 in the placebo group and 65.1 ± 3.6 in the S-ketamine group. A two-tailed alpha threshold of 0.05 and a power (1-beta) of 90% at a significance were assumed, then we calculated that each group required 42 patients. Considering a 10% data loss, 110 participants were recruited finally.

2.4 Intervention

A bolus of 0.5mg/kg S-ketamine was given to individuals in the S-ketamine group during the period of anesthesia induction followed by 0.1mg/kg/h intravenous infusion until 15 minutes before the completion of the operation. While participants in the placebo group received normal saline in the same protocol, based on their weight.

2.5 Anesthesia procedure

Patients were monitored for SpO₂, blood pressure, and electrocardiogram after entering the operating room. Midazolam (0.05 ~ 0.2 mg/kg), sufentanil (0.5 ~ 2µg/kg), propofol (2 ~ 3 mg/kg), and rocuronium (0.6–1.2 mg/kg) were administered intravenously for anesthesia induction. The patients were intubated with a bronchial blocker or double-lumen tracheal tube to establish one-lung ventilation, and inhaled 1% sevoflurane, intravenously pump propofol (4 ~ 8mg/kg/h) and remifentanil (0.1 ~ 0.25µg/kg/h) were used to maintain the appropriate depth of anesthesia. And intermittent injections of 5 mg of cisatracurium were used for the maintenance of muscle relaxation. When systolic blood pressure was reduced by 20% from baseline, patients would be treated with a bolus of 6 mg of ephedrine, and when bradyarrhythmia occurred, a bolus of 0.5 mg of atropine would be given. All patients received 30 mg of Homolac tromethamine and 10 mg of Metoclopramide at the end of surgery for postoperative analgesia and antiemetic prevention. When satisfied with the criteria of extubation, patients would be extubated and sent to the post-anesthesia care unit (PACU). 15 mg Butorphanol Tartrate and 30 mg Metoclopramide were diluted into 100 ml with 0.9% saline and administered through an intravenous PCA device for 48 h postoperatively.

2.6 Outcomes

The patient baseline characteristics and perioperative details were collected. The primary outcomes included the melatonin concentration of salivary on the first day postoperatively, and RSCQ scores on 1, 2, and 3 days postoperatively, containing six items, with higher scores indicating better sleep quality.
The secondary outcomes were the rest and movement VAS scores at 6, 12, 24, and 48 hours after the procedure, the level of IL-6 and IL-10 in serum on the first postoperative day, incidence of the pulmonary complications, central nervous system complications, and postoperative nausea and vomiting (PONV). The saliva tube was given to the patients the night before surgery, and a researcher instructed the procedures of self-collect 5 ml of saliva samples before 10 PM preoperatively and postoperatively. We extracted 5 ml of venous blood after anesthesia induction and on the morning of the first postoperative day. All specimens were centrifuged at 1500 RPM for 10 min, and the supernatant was transferred to a -80°C refrigerator (Qingdao Haier, China). Melatonin (EH3344), IL-6 (EH0201), and IL-10 (EH0173) were tested by enzyme-linked immunosorbent assay (Elisa) kits provided by Wuhan Fine Biotech Co., Ltd. All data collectors and specimen collectors were blinded.

2.7 Statistical Analyses

Continuous variables were shown as mean ± standard deviation, or median (interquartile range), while categorical variables were presented as numbers (%). The independent *t*-test or Mann–Whitney *U* test was used to analyze age, BMI, anesthetic and surgical duration, extubation time, PACU stay, intraoperative anesthetics consumption, intraoperative intake and output volume, perioperative MAP and HR, preoperative Pittsburgh Sleep Quality Index (PSQI) scores, postoperative RSCQ scores, PCA press times, and VAS scores, while the chi-squared or Fisher’s exact test were performed to compare gender, ASA classification, smoking status, working status, comorbidities, surgery types, numbers of rescue analgesia requirement and incidence of postoperative complications in the two groups. Social Sciences (SPSS) software version 22.0 was selected to perform statistical analysis, and *P* < 0.05 represented statistically significant.

3. Results

3.1 The patient baseline characteristics and perioperative details

In our research, a total of 110 patients were recruited. The CONSORT diagram was presented in Fig. 1. 9 were excluded for the reasons: 7 did not satisfy inclusion criteria, and 2 declined to participate. Thus, 101 patients were assigned to either the S-ketamine group or the control group randomly. In the S-ketamine group, 4 patients were excluded due to 3 patients converted to open thoracotomy and 1 patient lost to follow-up. And in the control group, 3 patients were lost to follow-up. Finally, the data from 94 participants were collected and analyzed. Baseline characteristics and perioperative details of the two groups were similar except for PCA press times during the first 24 hours postoperatively (*P* = 0.029). Detailed data were presented in Table 1 and Table 2. Besides, Table 3 showed that the HR at one minute after intubation was significantly increased in the S-ketamine group (*P* = 0.019).
Table 1
Patient baseline characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control group</th>
<th>S-ketamine group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>47</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Age (year)</td>
<td>54.66 ± 1.44</td>
<td>57.53 ± 1.14</td>
<td>0.122</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>25.15 ± 0.45</td>
<td>24.95 ± 0.35</td>
<td>0.732</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td>0.668</td>
</tr>
<tr>
<td>Male</td>
<td>18(38.3)</td>
<td>16(34.0)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>29(61.7)</td>
<td>31(66.0)</td>
<td></td>
</tr>
<tr>
<td>ASA classification n (%)</td>
<td></td>
<td></td>
<td>0.100</td>
</tr>
<tr>
<td>II</td>
<td>42(89.4)</td>
<td>36(76.6)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>5(10.6)</td>
<td>11(23.4)</td>
<td></td>
</tr>
<tr>
<td>Smoking status n (%)</td>
<td></td>
<td></td>
<td>0.515</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>30(63.8)</td>
<td>35(74.5)</td>
<td></td>
</tr>
<tr>
<td>Former smoker</td>
<td>9(19.1)</td>
<td>7(14.9)</td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>8(17.0)</td>
<td>5(10.6)</td>
<td></td>
</tr>
<tr>
<td>Labor situation, n (%)</td>
<td></td>
<td></td>
<td>0.837</td>
</tr>
<tr>
<td>Working</td>
<td>23(48.9)</td>
<td>23(48.9)</td>
<td></td>
</tr>
<tr>
<td>Retired</td>
<td>24(51.1)</td>
<td>24(51.1)</td>
<td></td>
</tr>
<tr>
<td>Comorbidities, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>12 (25.5)</td>
<td>13 (27.7)</td>
<td>0.815</td>
</tr>
<tr>
<td>CHD</td>
<td>1 (2.1)</td>
<td>3 (6.4)</td>
<td>0.308</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>0 (0)</td>
<td>3(6.4)</td>
<td>0.242</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5 (10.6)</td>
<td>7 (14.9)</td>
<td>0.536</td>
</tr>
</tbody>
</table>

Notes:
ASA: American Society of Anesthesiologists, BMI: body mass index, CHD: Coronary heart disease.
Table 2
Perioperative characteristics

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control group</th>
<th>S-ketamine group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery type, n (%)</td>
<td></td>
<td></td>
<td>0.153</td>
</tr>
<tr>
<td>wedge resection</td>
<td>30(63.8)</td>
<td>37(78.7)</td>
<td></td>
</tr>
<tr>
<td>Segmentectomy</td>
<td>15(31.9)</td>
<td>7(14.9)</td>
<td></td>
</tr>
<tr>
<td>mediastinal tumor resection</td>
<td>2(4.3)</td>
<td>3(6.4)</td>
<td></td>
</tr>
<tr>
<td>Anesthetic duration (min)</td>
<td>128.40 ± 5.46</td>
<td>127.49 ± 4.46</td>
<td>0.897</td>
</tr>
<tr>
<td>Surgical duration (min)</td>
<td>80.00</td>
<td>85.00</td>
<td>0.925</td>
</tr>
<tr>
<td>(60.00,120.00)</td>
<td>(70.00,110.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extubation time (min)</td>
<td>5.00</td>
<td>5.00</td>
<td>0.557</td>
</tr>
<tr>
<td>(5.00,5.00)</td>
<td>(5.00,5.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PACU stay (min)</td>
<td>60.00</td>
<td>55.00</td>
<td>0.921</td>
</tr>
<tr>
<td>(50.00,65.00)</td>
<td>(50.00,60.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remifentanil dosage (µg)</td>
<td>1169.70</td>
<td>936.70</td>
<td>0.237</td>
</tr>
<tr>
<td>(813.70,1396.30)</td>
<td>(743.70,1267.80)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol dosage (mg)</td>
<td>643.00</td>
<td>731.00</td>
<td>0.698</td>
</tr>
<tr>
<td>(448.00,840.00)</td>
<td>(480.00,832.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion volume (mL)</td>
<td>1000</td>
<td>1200.00</td>
<td>0.521</td>
</tr>
<tr>
<td>(800.00,1600.00)</td>
<td>(1000.00,1500.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding (mL)</td>
<td>10.00</td>
<td>10.00</td>
<td>0.684</td>
</tr>
<tr>
<td>(5.00,20.00)</td>
<td>(5.00,20.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine output (mL)</td>
<td>200.00</td>
<td>200.00</td>
<td>0.828</td>
</tr>
<tr>
<td>(100.00,300.00)</td>
<td>(100.00,300.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCA press times</td>
<td>3.00</td>
<td>3.00</td>
<td>0.029*</td>
</tr>
<tr>
<td>(3.00,4.00)</td>
<td>(3.00,4.00)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes:
PCA: Patient Controlled Analgesia, PONV: Postoperative nausea and vomiting, PR: Preoperative, PO: Postoperative. WBC: White Blood Cells, NEU: neutrophil cells. *: P value < 0.05.
### Table 3
Perioperative MAP and HR

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control group</th>
<th>S-ketamine group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>102.26 ± 1.45</td>
<td>98.55 ± 1.47</td>
<td>0.077</td>
</tr>
<tr>
<td>T2</td>
<td>97.04 ± 1.65</td>
<td>95.72 ± 1.43</td>
<td>0.547</td>
</tr>
<tr>
<td>T3</td>
<td>92.02 ± 1.43</td>
<td>92.89 ± 1.32</td>
<td>0.645</td>
</tr>
<tr>
<td>T4</td>
<td>96.77 ± 1.35</td>
<td>97.30 ± 1.38</td>
<td>0.783</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>76.06 ± 1.34</td>
<td>76.23 ± 1.49</td>
<td>0.933</td>
</tr>
<tr>
<td>T2</td>
<td>76.40 ± 1.33</td>
<td>80.30 ± 0.94</td>
<td>0.019*</td>
</tr>
<tr>
<td>T3</td>
<td>71.62 ± 1.31</td>
<td>70.23 ± 1.42</td>
<td>0.475</td>
</tr>
<tr>
<td>T4</td>
<td>80.66 ± 1.67</td>
<td>80.32 ± 1.13</td>
<td>0.866</td>
</tr>
</tbody>
</table>

**Notes:**
- MAP: Mean arterial pressure, HR: Heart rate; T1: the movement after entering the operating room, T2: one minute after intubation, T3: immediately after skin incision, T4: the movement before transfer to PACU. *: P value < 0.05.

### 3.2 Sleep Quality

Preoperative PSQI scores and concentration of MT were similar between the two groups, but the RSCQ scores on the first three days after surgery (P = 0.002, P = 0.028, and P = 0.027 respectively) and the melatonin concentration of salivary on the first day after the procedure (P = 0.02) were statistically higher in the S-ketamine group, presented in Table 4 and Fig. 2.
### 3.3 Pain intensity

In Table 5, the obvious differences in pain intensity both at rest and movement appraised by VAS scores at 6, 12, and 24 hours after the procedure were observed in the two groups (postoperative 6 hours: $P = 0.022$ and $P = 0.041$; postoperative 12 hours: $P = 0.032$ and $P = 0.038$; postoperative 24 hours: $P = 0.033$ and $P = 0.042$), while the rest and movement pain intensity at 48 hours postoperatively were comparable between the two groups.

---

### Table 4
Sleep Quality

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control group</th>
<th>S-ketamine group</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSQI scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR 1d</td>
<td>5.00(4.00,6.00)</td>
<td>5.00(4.00,6.00)</td>
<td>0.320</td>
</tr>
<tr>
<td>RSCQ scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PO 1d</td>
<td>64.00(62.00,66.00)</td>
<td>66.00(64.00,68.00)</td>
<td>0.002*</td>
</tr>
<tr>
<td>PO 2d</td>
<td>68.00(66.00,70.00)</td>
<td>70.00(68.00,70.00)</td>
<td>0.028*</td>
</tr>
<tr>
<td>PO 3d</td>
<td>70.00(64.00,72.00)</td>
<td>70.00(68.00,72.00)</td>
<td>0.027*</td>
</tr>
</tbody>
</table>

**Notes:**
PSQI: Pittsburgh Sleep Quality Index, RSCQ: Richard Campbell Sleep Questionnaire, PR: Preoperative, PO: Postoperative. *: $P$ value < 0.05.

---

### Table 5
Pain intensity at rest and movement

<table>
<thead>
<tr>
<th>VAS score</th>
<th>Control group</th>
<th>S-ketamine group</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO 6h (rest)</td>
<td>3.00(3.00,3.00)</td>
<td>3.00(2.00,3.00)</td>
<td>0.022*</td>
</tr>
<tr>
<td>PO 6h (movement)</td>
<td>4.00(3.00,4.00)</td>
<td>4.00(3.00,4.00)</td>
<td>0.041*</td>
</tr>
<tr>
<td>PO 12h (rest)</td>
<td>3.00(2.00,3.00)</td>
<td>2.00(2.00,3.00)</td>
<td>0.032*</td>
</tr>
<tr>
<td>PO 12h (movement)</td>
<td>4.00(3.00,4.00)</td>
<td>3.00(3.00,4.00)</td>
<td>0.038*</td>
</tr>
<tr>
<td>PO 24h (rest)</td>
<td>2.00(2.00,3.00)</td>
<td>2.00(2.00,2.00)</td>
<td>0.033*</td>
</tr>
<tr>
<td>PO 24h (movement)</td>
<td>3.00(2.00,4.00)</td>
<td>3.00(2.00,3.00)</td>
<td>0.042*</td>
</tr>
<tr>
<td>PO 48h (rest)</td>
<td>2.00(1.00,2.00)</td>
<td>1.00(1.00,2.00)</td>
<td>0.367</td>
</tr>
<tr>
<td>PO 48h (movement)</td>
<td>2.00(1.00,2.00)</td>
<td>2.00(1.00,2.00)</td>
<td>0.305</td>
</tr>
</tbody>
</table>

**Notes:**
PO: Postoperative, VAS: Visual Analogue Scale. *: $P$ value < 0.05.
3.4 The level of inflammation

Figure 3 and Fig. 4 showed that the level of preoperative IL-6 and IL-10 were comparable in the two groups, and the level of IL-6 and IL-10 postoperatively was statistically increased in both groups. Decreased level of IL-6 and increased level of IL-10 postoperatively were observed in the S-ketamine group ($P = 0.038$ and $P = 0.034$).

3.5 Postoperative recovery and complications

In Table 6, the length of hospital stay of patients in the S-ketamine group ($P = 0.023$). While the incidence of pulmonary and central nervous system complications, as well as PONV were comparable ($P = 0.370$, $P = 0.261$, and $P = 0.552$, respectively).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control group</th>
<th>S-ketamine group</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of Hospital stay (days)</td>
<td>6.00 (5.00,7.00)</td>
<td>5.00 (4.00,6.00)</td>
<td>0.023*</td>
</tr>
<tr>
<td>Pulmonary complications, n (%)</td>
<td>4(8.5)</td>
<td>6(12.8)</td>
<td>0.740</td>
</tr>
<tr>
<td>POD, n (%)</td>
<td>4(8.5)</td>
<td>7(14.9)</td>
<td>0.523</td>
</tr>
<tr>
<td>PONV, n (%)</td>
<td>5(10.6)</td>
<td>8(17.0)</td>
<td>0.552</td>
</tr>
</tbody>
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Notes: POD: Postoperative delirium, PONV: Postoperative nausea and vomiting.

4. Discussion

This research found that perioperative intravenous S-ketamine could improve sleep quality in patients undergoing thoracoscopic surgery. Moreover, decreased pain intensity, decreased level of serum IL-6, and increased level of serum IL-10 were noticed in patients given S-ketamine. And the S-ketamine use did not increase the incidence of postoperative complications.

Although thoracoscopic surgery is less invasive than traditional thoracotomy, there are still many patients reporting postoperative poor sleep quality and pain, seriously affecting postoperative recovery. PSD and pain can interact with each other. Postoperative pain could induce sleep disturbances including a reduction of total sleep time and higher sleep arousal times. In turn, sleep can mediate pain through opioid, monoaminergic, immune, and other systems. Besides, inflammation is also one of the risk factors triggering the incidence of PSD. Improved sleep quality can enhance immunity, facilitate early motion, accelerate recovery, and improve the quality of life. A multimodal strategy is recommended to
improve transient sleep quality in surgical patients\textsuperscript{3}, but the incidence of perioperative sleep disturbance is still over 40\%\textsuperscript{2}. Fortunately, a recent review shed light on a possible application of ketamine for improving sleep quality\textsuperscript{24}. S-ketamine is more efficient and safer than ketamine, so it is speculated that S-ketamine might improve PSD.

Our research suggested that S-ketamine could significantly increase sleep quality in patients after thoracoscopic surgery. The same conclusion was drawn by a recent RCT, in which 0.3 mg/kg/h was used for patients after gynecological laparoscopy surgery\textsuperscript{18}. In addition, another study revealed that ketamine played an important role in achieving better sleep for patients admitted in the intensive care unit\textsuperscript{25}. All these studies demonstrated the efficacy of S-ketamine in improving sleep quality.

A previous study showed that both 0.5 mg/kg and 0.25 mg/kg dosages of S-ketamine provided pain relief effects in cervical carcinoma surgery, and the analgesic effects were dose-dependent\textsuperscript{26}. Therefore, we chose the higher dose of 0.5 mg/kg in our study. On the contrary, another research revealed that S-ketamine's analgesic effects in patients undergoing major lumbar fusion surgery were inapparent\textsuperscript{27}, which could be explained by dramatic surgical trauma covering the analgesic effects. And we also found that S-ketamine reduced the rest and movement pain intensity at postoperative 6, 12, and 24 hours, which was the same conclusion as a meta-analysis published by Wang et al\textsuperscript{28}.

Additionally, researchers established that the high level of pro-inflammatory cytokines was associated with poor sleep quality\textsuperscript{29,30}, while the increased level of anti-inflammation factor IL-10 contributed to the longer sleep duration\textsuperscript{30}. Sleep loss could induce higher levels of TNF-\(\alpha\), IL-6, and C-reactive protein (CRP)\textsuperscript{31}. Furthermore, numerous studies confirmed that surgical trauma and anesthesia could induce the occurrence of PSD by triggering a variety of inflammatory factors and stress responses\textsuperscript{32,33}. S-ketamine could decrease the level of IL-6 and increase the level of IL-10 postoperatively, which was similar to previous studies\textsuperscript{34,35}. By contrast, the anti-inflammatory effects of S-ketamine in patients undergoing colorectal cancer surgery were not obvious, which could be explained by the lower dosage\textsuperscript{36}.

Notably, our results showed that S-ketamine improved sleep quality and reduced pain intensity, which implicated the underlying relationship between sleep and pain. And other mechanisms need to be explored further, including improvement of mood behavioral\textsuperscript{10}. Furthermore, more ways to manage sleep disturbances and postoperative pain should be explored, and it is necessary to consider the interaction effect of sleep and pain in future research.

In our study, the limitations were as followed. Firstly, only a single administration dose of S-ketamine was performed in the thoracoscopic surgery. Additional research should be conducted to find out the optimal administration scheme. Furthermore, the measure of sleep quality in our study was relatively subjective, so more objective measurements such as actigraphy and polysomnography are needed to provide strong evidence. Besides, we only investigated the short-time effect of S-ketamine on sleep quality, future studies should pay attention to the long-term efficacy.
5. Conclusion

Intravenous administration of S-ketamine can improve the sleep quality on the first 3 days postoperatively, reduce the pain intensity at rest and movement, as well as the level of inflammation. Our results may provide a new method to improve the postoperative sleep quality and facilitate recovery.

Abbreviations

PSD: Postoperative sleep disturbance; MT: melatonin; RSCQ: Richard Campbell Sleep Questionnaire; VAS: Visual Analogue Scale; PACU: Post-anesthesia care unit; PONV: Postoperative nausea and vomiting; PSQI: Pittsburgh Sleep Quality Index; ASA: American Society of Anesthesiologists; BMI: body mass index; CHD: Coronary heart disease; PCA: Patient Controlled Analgesia; PR: Preoperative; PO: Postoperative; WBC: White Blood Cells; NEU: neutrophil cells; MAP: Mean arterial pressure; HR: Heart rate; PR: Preoperative; PO: Postoperative; POD: Postoperative delirium; CRP: C-reactive protein.

Declarations

Ethics Approval and Consent to Participate

Informed consent was obtained from all subjects involved in the study.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Clinical trial registration:

The study procedure was approved by the ethics committee of Hebei General Hospital (Ethics No. 2022-445), and was enrolled in the Chinese Clinical Trial Registry (Registration number: ChiCTR2200066742).

Author Contributions:
YYL and JFR conceptualized the study; JLL and YZ contributed to methodology; YYL, JFR, and JLL validated the study; YZ was responsible for the randomization; MNL collected the relevant data; YYL and JFR wrote the manuscript; JLL, YZ, SH, and MNL reviewed and edited the manuscript; SH visualized the study; JLL and SH supervised the study. All authors have read and agreed to the published version of the manuscript.

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None

References


Figures
Figure 1

CONSORT 2010 flow diagram
Figure 2

The level of salivary melatonin on a day preoperatively and postoperatively in both groups. MT: melatonin, PR: Preoperatively, PO: Postoperatively. *: $P<0.05$ vs preoperative values, #: $P<0.05$ vs control group values.
Figure 3

The levels of serum IL-6 on a day preoperatively and postoperatively in both groups. PR: Preoperatively, PO: Postoperatively. *: $P<0.05$ vs preoperative values, #: $P<0.05$ vs control group values.

![Graph showing IL-6 levels](image)

Figure 4

The levels of serum IL-10 on a day preoperatively and postoperatively in both groups. PR: Preoperatively, PO: Postoperatively. *: $P<0.05$ vs preoperative values, #: $P<0.05$ vs control group values.