Randomized Controlled Trial

Intraoperative Intravenous Infusion of Esmketamine Has Opioid-Sparing Effect and Improves the Quality of Recovery in Patients Undergoing Thoracic Surgery: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial

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Background: Postoperative thoracic surgery is often accompanied by severe pain, and opioids are a cornerstone of postoperative pain management, but their use may be limited by many adverse events. Several studies have shown that the perioperative application of esketamine adjuvant therapy can reduce postoperative opioid consumption. However, whether esketamine has an opioid-sparing effect after thoracic surgery is unclear.

Objectives: To explore the opioid-sparing effect of different doses of esketamine infusion during thoracic surgery and its impact on patient recovery.

Study Design: Randomized controlled study.

Setting: A single-center study with a total of 120 patients.

Methods: Patients were randomly allocated to 1 or 3 groups receiving intraoperative intravenous infusions of esketamine 0.15 mg · kg^{-1}· h^{-1} (group K1), esketamine 0.25 mg · kg^{-1}· h^{-1}(group K2), or placebo (group C). Postoperative opioid consumption, and postoperative indicators like extubation time, PACU stay time, and adverse events were recorded for each group.

Results: The consumption of hydromorphone during the first 24 and 48 postoperative hours was significantly reduced in patients of group K2 compared to those of group C and group K1. The time to extubation and post anesthesia care unit (PACU) stay were significantly shorter in group K2 than in group K1 and group C. The time to first feed and off the bed time after surgery were shorter in groups K1 and K2 than in group C. Patients in group K2 were significantly satisfied with patient controlled intravenous analgesia (PCIA) than in groups K1 and C.

Limitations: The sample size calculation was based mainly on the index of hydromorphone consumption.

Conclusions: Intraoperative intravenous esketamine at 0.25 mg · kg^{-1} · h^{-1} reduced postoperative opioids consumption by 34% in postoperative 24 hours and 30% in postoperative 48 hours in patients undergoing thoracic surgery. It also improved the quality of perioperative recovery.

Key words: Anesthetics, thoracic surgery, esketamine, opioid savings

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Postoperative pain is a major clinical problem that needs to be addressed (1), especially for thoracic surgery (2). Visual-assisted thoracic surgery (VATS) is a minimally invasive thoracic procedure that reduces surgical stress and postoperative pain (3). However, a prospective observational study showed that patients undergoing thoracoscopic surgery did not experience less acute postoperative pain compared with thoracotomy surgery, and there was no difference in the incidence and severity of chronic pain 6 months after thoracotomy and thoracoscopy (4). Traditional opioids remain the standard of care for the management of acute postoperative pain (5). Opioid analgesics may cause many side effects such as respiratory depression, nausea, vomiting, urinary retention, sleep disturbance, and pain hypersensitivity (6). In order to reduce some of these side effects, non-opioid analgesics can be administered as an adjunct to analgesia to improve postoperative analgesia. Ketamine, an antagonist of N-methyl-d-aspartate (NMDA) receptors, has the potential to prevent the effects of nociceptive hyperalgesia and is considered to be an effective adjunct to opioid analgesics (7). However, the psychedelic side effects limit its use (8). Esketamine, the S (+)-isomer of ketamine, possesses the advantages of a lower incidence of side effects like hallucinations, faster recovery, and the maintenance hypoxic pulmonary vasoconstriction during one-lung ventilation (9).

Several studies have investigated the opioid-sparing effects of perioperative use of esketamine (10-13). A study of opioid-dependent patients showed that subjects received esketamine infusion consumed 35% less morphine over 24 hours than the placebo group (10). Brinck et al (14) revealed that the analgesic and side effects of esketamine are dose-dependent. However, different dosages of esketamine were not superior to placebo in lowering post-opioid dosage in patients receiving spinal fusion surgery and were not dose-related, according to Elina CV et al (15). Based on this ambiguous clinical evidence, it remains unclear how the analgesic esketamine affects postoperative pain in thoracic surgery and whether this effect is dose-related. Therefore, we conducted this prospective, randomized clinical trial to investigate the analgesic effect for patients undoing thoracic surgery.

The primary outcome was the consumption of analgesic medication at 24 and 48 hours postoperatively. As secondary outcomes, postoperative indicators such as extubation time, post anesthesia care unit (PACU) stay time, time to first feeding, and time to first getting out of bed were recorded. Adverse events such as hallucinations, drowsiness, and itching were recorded in the first 48 hours after surgery.

Methods

Patients

Patients included were: aged 18-70 years, with American Society of Anesthesiologists (ASA) grade I or II; body mass index (BMI) 18.5-30.0 kg/m^2; intended to undergo thoracoscopic lung surgery (thoracoscopic radical lung cancer, thoracoscopic lobectomy, or segmental lung resection) under general anesthesia; receiving postoperative patient-controlled intravenous analgesia (PCIA); have a full understanding of the purpose and significance of this trial, voluntarily participate in this clinical trial, and sign the informed consent form. Exclusion criteria were: preoperative history of chronic pain or a medical history of opioid abuse; allergy to medications required for this study; psychiatric illness that prevents cooperation; preoperative inability to communicate due to cognitive dysfunction or language impairment; dysfunction of the cardiac, liver, or kidney; blood pressure ≥ 180/100 mmHg (1 mmHg = 0.133 kPa) or hypertension grade III; untreated or poorly controlled hypertension; glaucoma, increased intracranial pressure, hyperthyroidism, or alcohol abuse; other conditions that, rely on the judgment of the investigator, considering the patient unsuitable for participation in this clinical trial.

Study Design

Patients were assigned to one of 3 groups using a random number table: low-dose esketamine group (group K1), sub anesthesia-dose esketamine group

(group K2), and control group (group C). The low-dose ketamine group was a continuous intravenous infusion of esketamine at a rate of 0.15 mg · kg^{-1}· h^{-1} during surgery; the sub anesthesia-dose ketamine group was a continuous intravenous infusion of esketamine at a rate of 0.25 mg · kg^{-1} · h^{-1} during surgery; the control group was continuous intravenous infusion of normal saline at the same rate during surgery. The independent trial investigator randomized the patients into groups and equipped them with the corresponding drugs. The dose of esketamine is based on the recommendations in the literature (11,13,16) and clinical experience in our hospital.

Anesthesia was induced with midazolam 0.05 mg/kg, propofol 1~2 mg/kg, sufentanil 0.6 μg/kg, and rocuronium 0.6 mg/kg. The patients' tracheas were intubated with a double-lumen endotracheal tube, and the patients were mechanically ventilated. Different doses of esketamine or normal saline were intravenously infused to the patients by the anesthesiologist after tracheal intubation, depending on the grouping scheme. All 3 groups were maintained intraoperatively with total intravenous anesthesia, i.e., intravenous infusion of propofol 4~8 mg· kg^{-1}· h^{-1}, remifentanil 0.1~0.4 μg· kg^{-1}· min^{-1}, and intermittent additional rocuronium 0.2~0.4 mg/kg. The rate of intraoperative anesthetic drug infusion was adjusted by the anesthesiologist according to the change in the patients' vital sign parameters, surgical progress, and stimulation intensity. The patient' bispectral index (BIS) values were maintained from 40~60; heart rate and blood pressure fluctuation range were maintained within 20% of the basal value. Patients received hydromorphone 0.5 mg, flurbiprofen 50 mg, and palonosetron 0.25 mg intravenously at the beginning of chest closure. Rocuronium was discontinued approximately 30 minutes before the end of surgery. Propofol and remifentanil were discontinued at the end of surgery. Then all the patients were transferred to the PACU with a double lumen endotracheal tube. Sugammadex sodium of 200 mg was injected intravenously to the patient in the PACU.

Patients were closely monitored by a nurse, and the tracheal tube was removed after the criteria for extubation were met. The criteria for extubation were as follows: the patient was completely awake and could respond to calls; tidal volume > 6 mL/kg; respiratory rate > 12 breaths/min; breathing air SpO2 > 90%: swallowing and coughing reflexes recovered completely. Patients were assessed for pain by nurses and treated with hydromorphone 0.2 mg if the patient developed pain, with the goal of reducing the pain scores to less than 4 on a numeric scale (NRS, from 0 to 10, 0, no pain; 10, worst pain imaginable). Patients were transitioned to a hydromorphone PCIA device when adequate pain control (numeric rating scale, NRS < 4 points) was achieved. PCIA pump composition: hydromorphone 14 mg, flurbiprofen 200 mg, palonosetron 0.25 mg, titrated to 200 mL with saline. The background infusion rate of the PCIA pump was 2 mL/h, and the bolus dose was 4 mL with an 8 minute lockout interval. If the subject had inadequate analgesia during PCIA (NRS ≥ 4 points after 3 consecutive single injections), remedial analgesia was administered intravenously with hydromorphone 0.2 mg and counted toward the total hydromorphone consumption. Injection of palonosetron 0.25 mg if moderate to severe postoperative nausea or vomiting occurred. Pain was controlled with a hydromorphone PCIA device for the first 2 days postoperatively to keep the NRS ≤ 4.

Patients' sleep was assessed using a numerical scale from 0 to 10. At the end of the PCIA, an 11-point numeric rating scale was used to measure overall patient satisfaction with the analgesic therapy. Patients were also followed up postoperatively for the development of chronic pain. Patients were followed up at 3 and 6 months to assess whether there was pain or abnormal sensation at the surgical incision site.

Statistical Analysis

Data for the primary outcome variable (milligrams of intravenous hydromorphone administered at 24 and 48 hours postoperatively) were presented at the median (quartiles) for groups C, K1, and K2. The Kruskal-Wallis test was used to compare these data between groups and to estimate the median difference. The criterion for rejecting the null hypothesis was a 2-tailed $P < 0.05$.

All other data, including secondary outcome data, are reported as mean ± SD, median (interquartile range), or number (percentage) of patients. Check whether the continuous data meet the normality test, and for the data that meet the normality test, check whether the variances are equal. Those data that did not satisfy the normality test or the assumption of equal variances were transformed into ordinal data and reported as median (quartiles). Data reported as mean ± SD were compared with one-way ANOVA, data reported as median (quartiles) were compared with the Kruskal-Wallis test, and data reported as number of patients (%) were compared using the chi-square test unless at least 20% of the expected counts were

less than 5, in which case the Fisher exact test was used. For the pairwise comparisons among 3 groups, the continuous data satisfy the normal distribution, and the homogeneity of variance test uses LSD, and the nonparametric test for the pairwise comparisons uses the Kruskal-Wallis H test.

The 2 primary outcomes measure of this study were hydromorphone consumption at 24 and 48 hours postoperatively. In this study, group C was expected to have 10 mg of hydromorphone consumption at 48 hours postoperatively, and it was assumed that hydromorphone consumption would be reduced by 30% in the K1 and K2 groups. In this study, group C had 10 mg of hydromorphone consumption and assumed a mean ± SD hydromorphone volume of 7 ± 4 mg in the K1 and K2 groups at 48 hours postoperatively. Set $\alpha = 0.05$ (bilateral), $\beta = 0.10$, and the number of groups k = 3, the minimum sample size of 34 cases per group was calculated. One hundred twenty patients were recruited to ensure complete data collection, considering the trial's drop-out rate, exclusion rate, and compliance. All statistical analyses were performed using SPSS version 24.0 (IBM Corporation, Armonk, NY).

Results

One hundred twenty patients were enrolled in the study, of which 13 patients did not meet the inclusion criteria, and 16 patients refused to participate and were excluded. Thus, 91 patients were randomized and allocated to the 3 groups. Three patients in Group C did not receive allocated intervention, and 4 were lost to follow-up and excluded. Two patients in the K2 group were excluded because one patient underwent a second surgery within 48 hours after surgery, and another was admitted to the intensive care unit because of pulmonary edema. Therefore, data from a total of 82 subjects (23 patients in group C, 30 patients in group K1, and 29 patients in group K2) were collected and analyzed. The flow diagram is presented in Fig. 1.

The preoperative characteristics of the patients in the 3 groups were similar (Table 1). Perioperative data are shown in Table 1, and there were no differences in propofol usage and remifentanil usage in the 3 study groups.

Primary Outcome

The use of hydromorphone during the first 24 and

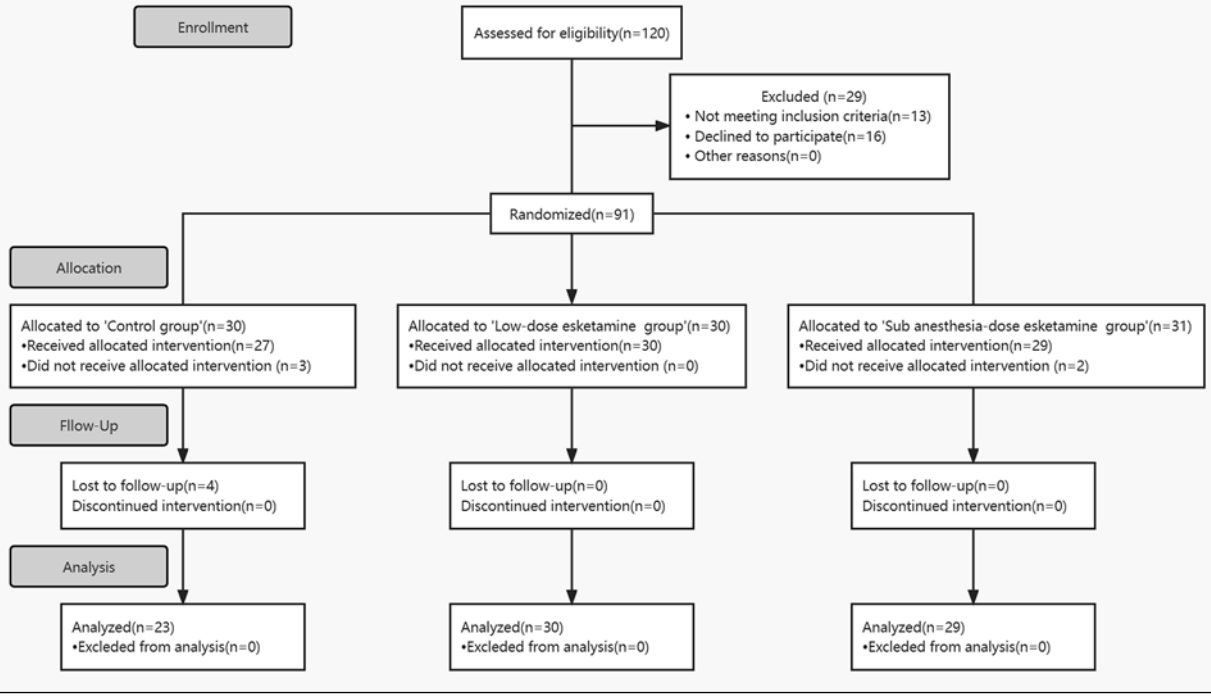

Fig. 1. *Consolidate Standards of Reporting Trials (CONSORT) flow diagram for the randomized, placebo-controlled, double-blind trial of placebo (control group), esketamine (low-dose esketamine group/ sub anesthesia-dose esketamine group) in patients undergoing thoracic surgery.*

48 postoperative hours (Table 2) was significantly different in the 3 groups ($P < 0.001$).

In the first 24 hours after surgery, the mean difference in hydromorphone consumption between groups C and K1 was 0.8 mg, which was a reduction in hydromorphone use of approximately 14% ($P = 0.168$); the mean difference in hydromorphone consumption between groups C and K2 was 2 mg, which was a reduction in hydromorphone use of approximately 34% ($P < 0.001$); the mean difference in hydromorphone consumption between groups K1 and K2 was 1.2 mg, resulting in a relative reduction in hydromorphone consumption of approximately 24% ($P = 0.008$).

Similarly, during the first 48 postoperative hours, the mean difference in hydromorphone consumption between groups C and K1 was 1.7 mg, which was a reduction in hydromorphone use of approximately 16% ($P = 0.204$); the mean difference in hydromorphone consumption between groups C and K2 was 3.2 mg, which was a reduction in hydromorphone use of approximately 30% ($P < 0.001$); the mean difference in hydromorphone consumption between groups K1 and K2 was 1.5 mg, resulted in a decrease of approximately 17% ($P = 0.002$).

Secondary Outcome Parameters

Table 3 reports the indicators related to the quality of postoperative recovery. Time to extubation and

Table 1. *Patient characteristics*.

Group	Control group (n = 23)	Low-dose esketamine group (n = 30)	Sub anesthesia-dose esketamine group (n = 29)	Overall significance (*P*-value)
Age, yr	53 ± 12	55 ± 11	56 ± 12	0.773
Gender, female	16 (70%)	21 (70%)	23 (79%)	0.650
Height, cm	165 (160 to 170)	160 (157 to 170)	161 (158 to 167)	0.129
Weight, kg	66 (55 to 70)	60 (56 to 66)	63 (58 to 66)	0.700
Body mass index (BMI), kg · m^{-2}	24 (21 to 25)	23 (22 to 25)	24 (22 to 26)	0.779
ASA physical status				0.718
ASA I	13 (57%)	20 (67%)	19 (66%)	
ASA II	10 (43%)	10 (33%)	10 (34%)	
History				
Smoking	4 (17%)	5 (17%)	6 (21%)	0.915
Drinking	7 (30%)	6 (20%)	6 (21%)	0.685
Postoperative nausea and vomiting (PONV)/Motion sickness	11 (48%)	12 (40%)	11 (38%)	0.756
Operation time, min	111 (90 to 210)	115 (92 to 153)	140 (100 to 180)	0.662
Propofol dose, mg	840 (600 to 1100)	500 (653 to 913)	800 (700 to 900)	0.226
Remifentanil dose, μg	1600 (1300 to 2800)	1550 (1122 to 2125)	1500 (1400 to 2000)	0.587

The data are means ± SD, median (interquartile range), or number of patients (%). Data reported as mean ± SD were compared with one-way ANOVA, data reported as median (interquartile range) using Krustal-Wallis test, and data reported as number of patients (%) were compared using R×C chi-square test or, when more than 1/5 of the cells in the contingency table had an expected n < 5, Fisher's exact probability test was used for comparison. $P < 0.05$ was considered as statistically significant.

Table 2. *Primary outcome: hydromorphone requirements in the first 24 h and 48 h postoperatively.*

Group	Control group (n = 23)	Low-dose esketamine group (n = 30)	Sub anesthesia-dose esketamine group (n = 29)	Overall significance (*P* value)
Total hydromorphone consumption in 24 hours, mg	5.9(5.2 to 6.2)	5.1(3.7 to 6.0)	3.9(3.6 to 4.3) a, b	0.000
Total hydromorphone consumption in 48 hours, mg	10.5(9.2 to 11.5)	8.8(7.4 to 12)	7.3(6.8 to 7.9) a, b	0.000

The data are reported as median (interquartile range) and were compared between groups using the Krustal-Wallis test.
a $P < 0.05$ when comparing with the control group; b $P < 0.05$ when comparing with the low-dose esketamine group.

PACU stay were significantly shorter in group K2 than in groups C (P = 0.024) and K1 (P = 0.012), while there was no difference between groups C and K1 (P = 1.0). For time to the first feeding, both the K1 (P = 0.030) and K2 (P = 0.001) groups were significantly shorter compared with the C group, and there was no significant difference between the K1 and K2 groups (P = 0.728). For time to the first getting out of bed after surgery, both the K1 (P = 0.030) and K2 (P = 0.001) groups were significantly shorter compared with the C group, and there was no significant difference between the K1 and K2 groups (P = 0.144). We also evaluated numeric scores of sleep satisfaction for the first 24 and 48 hours postoperatively. For 24 hours postoperatively, the results showed that the K1 group (P = 0.002) and K2 group (P = 0.008) were significantly higher compared with the C group, with no significant difference between the K1 and K2 groups (P = 1.0). Also, for 48 h postoperatively, the K1 group (P = 0.003) and K2 group (P < 0.001) were significantly higher compared with the C group, with no significant difference between the K1 and K2 groups (P = 1.0).

At 48 hours after surgery, the PCIA device was removed and patients were assessed for satisfaction with analgesic treatment; we found significantly higher satisfaction in group K2 compared to group C (P < 0.001) and group K1 (P < 0.001), with no significant difference between the K1 and C groups (P = 0.423). The number of remedial analgesia at 48 hours postoperatively was significantly less in the K2 group than in the C group (P = 0.001), while there was no significant difference between the other groups (P > 0.05).

Table 4 reports the adverse events during awakening in the PACU. There was no difference in the incidence of catheter-related bladder irritation signs (P = 0.309) and delirium (P = 0.510) among the 3 groups. The incidence of extubation agitation was significantly lower in group K2 than in group C (P = 0.002). The incidence of hallucinations (P = 0.198), drowsiness (P = 0.209), and itching (P = 0.264) did not differ between the 3 groups, with only 2 patients in the K2 group experiencing hallucinations on the first postoperative day. The incidence of chronic pain in group C was 39.1% at 3 months and 30.4% at 6 months after surgery; in group K1 the incidence of chronic pain was 23.3% at 3 months and 16.7% at 6 months after surgery; in group K2 the incidence of chronic pain was 17.2% at 3 months and 13.8% at 6 months after surgery. There was no significant difference in the incidence of postoperative pain between the 3 groups at 3 (P = 0.187) and 6 months (P = 0.286) after surgery.

Discussion

This was a randomized, double-blind, placebo-controlled study to evaluate the effect of intraoperative intravenous infusion of esketamine on postoperative analgesia, the quality of recovery from general anesthesia, and chronic pain in patients undergoing thoracic surgery.

Table 3. *Post-operative indicators*.

Group	Control group (n = 23)	Low-dose esketamine group (n = 30)	Sub anesthesia-dose esketamine group (n = 29)	Overall significance (P value)
Extubation time, min	24 (15 to 45)	23 (19 to 29)	12 (10 to 24)[a, b]	0.005
Post anesthesia care unit (PACU) stay time, min	78 (60 to 100)	65 (60 to 83)	60 (45 to 68)[a, b]	0.002
Time of first feeding after surgery, h	19 (14 to 21)	15 (12 to 18)[a]	13 (12 to 16)[a]	0.001
Time of first getting off to bed after surgery, h	20 ± 4	18 ± 5[a]	16 ± 4[a]	0.003
Numeric rating scale (NRS) of sleep satisfaction for the first 24 h postoperatively	5 (4 to 6)	7 (5 to 8)[a]	6 (5 to 8)[a]	0.001
NRS of sleep satisfaction for the first 48 h postoperatively	5 (5 to 6)	7 (6 to 8)[a]	7 (6 to 8)[a]	0.000
Satisfaction with the patient controlled intravenous analgesia (PCIA) therapy	5 (4 to 6)	5 (5 to 7)	8 (8 to 9)[a, b]	0.000
Rescue analgesia	17 (74%)	14 (47%)	8 (28%)[a]	0.004

The data are means ± SD, median (interquartile range), or number of patients (%). Data reported as mean ± SD were compared with one-way ANOVA, data reported as median (interquartile range) using the Krustal-Wallis test, and data reported as number of patients (%) were compared using R×C chi-square test. Overall satisfaction with sleep satisfaction and pain management on a 0 to 10 scale: 0 = worst possible to 10 = best possible.

[a] P < 0.05 when comparing with the control group; [b] P < 0.05 when comparing with the low-dose esketamine group.

Table 4. *Adverse events*.

Group	Control group (n = 23)	Low-dose esketamine group (n = 30)	Sub anesthesia-dose esketamine group (n = 29)	Overall significance (*P* value)
Post anesthesia care unit (PACU) adverse events				
extubation agitation	11 (47.8%)	8 (26.7%)	3 (10.3%)[a]	0.010
catheter-related bladder irritation signs	5 (21.7%)	4 (13.3%)	2 (6.9%)	0.309
delirium	4 (17.4%)	3 (10%)	2 (6.9%)	0.510
Adverse events in the first 24 h postoperatively				
Hallucination	0 (0%)	0 (0%)	2 (6.9%)	0.198
Drowsiness	9 (39.1%)	9 (30%)	5 (17.2%)	0.209
Itching	4 (17.4%)	4 (13.3%)	1 (3.4%)	0.264
Adverse events in the first 48 h postoperatively				
Hallucination	0 (0%)	0 (0%)	0 (0%)	
Drowsiness	6 (26.1%)	6 (20%)	2 (6.9%)	0.172
Incidence of postoperative chronic pain				
3 months	9 (39.1%)	7 (23.3%)	5 (17.2%)	0.187
6 months	7 (30.4%)	5 (16.7%)	4 (13.8%)	0.286

The data are the number of patients (%). They were compared using the R×C chi-square test or when more than 1/5 of the cells in the contingency table had an expected n < 5, Fisher's exact probability test was used for comparison.
[a] $P < 0.05$ when comparing with the control group.

Our study found that intraoperative intravenous esketamine at 0.25 mg· kg-1· h-1 reduced hydromorphone use by 34% in the first 24 hours postoperatively and by 30% in the first 48 hours postoperatively compared with the control group. Intravenous esketamine at 0.15 mg· kg-1· h-1 also reduced postoperative hydromorphone consumption, but this reduction was not statistically significant. In this study, the opioid-sparing effect of esketamine was found to be dose-dependent, with intraoperative intravenous esketamine at 0.25 mg· kg-1· h-1 reducing hydromorphone use by 24% in the first 24 hours postoperatively and by 17% in the first 48 hours postoperatively compared with esketamine at 0.15 mg· kg-1· h-1. These findings suggest that continuous intravenous infusion of esketamine at a rate of 0.25 mg · kg-1· h-1 can significantly reduce hydromorphone consumption during the first 24 and 48 postoperative hours.

In recent years, despite the increasing emphasis on postoperative analgesic treatment and multimodal analgesia, patients undergoing thoracic surgery continue to suffer from moderate to severe postoperative pain. NMDA receptor antagonists such as esketamine, which inhibit NMDA receptors, bind to μ-opioid receptors (17), increase 5-hydroxytryptamine and norepinephrine concentrations in the brain (18), are able to prevent opioid-associated activation of the injury nociceptive system and attenuate opioid tolerance and nociceptive hypersensitivity (19). Patient-controlled analgesia with esketamine was reported to reduce opioid dosage after lumbar spine fusion without increasing other adverse effects (12). A review of perioperative intravenous S-ketamine for acute postoperative pain showed that intravenous esketamine adjunct to general anesthesia is an effective adjunct to analgesia and reduces the intensity of pain in the short postoperative period (20). The above studies suggest that esketamine may be a good adjuvant for postoperative opioid-sparing. To our knowledge, it is unclear whether esketamine has better opioid-sparing effects or clinical value when used in patients undergoing thoracoscopic pulmonary surgery, so we conducted this trial to verify the value of esketamine for thoracic surgery. Unlike the above studies, our study demonstrated the opioid-sparing effect of esketamine as a pain adjuvant in thoracoscopic surgery, confirming its value in thoracic surgery patients.

In patients with inadequate analgesia for PCIA, we administered intravenous hydromorphone 0.2 mg per time for rescue analgesia. Only 28% of the sub anesthesia-dose esketamine group required rescue analgesia, which was significantly less than the control group (74%). Esketamine has a good analgesic effect and is converted to norethindrone in vivo, mainly by

hepatic microsomal enzymes. Norethindrone is pharmacologically active and has an anesthetic potency equivalent to 1/5 to 1/3 that of esketamine but with a longer elimination half-life. This can be used to explain the pain-relieving effect of esketamine even after the patient has awakened from anesthesia (21,22).

We unexpectedly found that intraoperative application of esketamine can help patients recover spontaneously after surgery and has a good effect on promoting postoperative outcomes of patients. We observed that patients who received a sub anesthesia-dose of intraoperative intravenous esketamine had a faster and better recovery of respiratory rate and tidal volume postoperatively, resulting in shorter extubation time and earlier transfer from the PACU to the inpatient ward, which may be a benefit to the patients due to esketamine. Jonkman et al found that esketamine was effective against remifentanil-induced respiratory depression, an effect attributed to the increased ventilatory CO_2 chemosensitivity reduced by remifentanil (23). This suggests that the perioperative application of esketamine not only reduces the use of opioids but also maintains better respiration, thus reducing complications, improving the quality of patient recovery, and enhancing patient regression. Another interesting finding was that patients who received continuous intraoperative esketamine infusion had significantly improved subjective sleep comfort within 24 and 48 hours after surgery. This finding may provide new ideas for future research on esketamine.

Post-thoracotomy pain is a common complication after thoracic surgery. Studies have shown esketamine may alleviate post-thoracotomy pain by preventing central sensitization (24). Our study showed that intraoperative intravenous infusion of esketamine did not reduce the incidence of chronic pain at 3 months and 6 months postoperatively. Although we observed a decrease in incidence, this decrease was slight and not statistically significant, which may be related to the small sample size or the insufficient follow-up time. We observed the occurrence of postoperative adverse reactions like hallucinations, drowsiness, and pruritus in the first 24 and 48 hours after surgery, and there was no difference in the incidence of adverse effects among the 3 groups. Most of the adverse events we observed were uncommon in the clinic and coupled with the relatively small sample size of our study, the incidence of adverse events we observed may have been inaccurate, resulting in the fact that we did not observe differences in the incidence of these adverse events.

Limitations

Our study has some limitations, the main objective of this study was to observe the effect of continuous intraoperative infusion of different doses of esketamine on postoperative opioid-sparing in patients undergoing thoracic surgery, and the sample size calculation was based mainly on the index of hydromorphone consumption. It is possible that our relatively small sample size led to imperfect observation of secondary indicators, such as the incidence of postoperative adverse events and chronic pain, so subsequent trials with larger sample sizes are still needed for observation.

Conclusion

In conclusion, our study shows that intraoperative intravenous infusion of 0.25 $mg \cdot kg^{-1} \cdot h^{-1}$ esketamine can conserve postoperative opioid use and contribute to the patient's postoperative recovery.

Author Contributions

Jingjing Yuan helped with conceptualization, methodology, analysis, preparation of the manuscript, and review and editing of the manuscript. Shuhan Chen helped with conceptualization, methodology, analysis, preparation of the manuscript, and review and editing of the manuscript. Yanle Xie helped with interpretation of data, methodology, resources, analysis, and project administration. Yize Li helped with research design, supervision, interpretation of data, preparation of the manuscript, and approval of the final manuscript. Zhongyu Wang helped with research supervision and review editing. Fei Xing helped with data collection and research supervision. Yuanyuan Mao helped with conceptualization, methodology and review and editing of the manuscript. Jingping Wang helped with interpretation of data, preparation of the manuscript, and review editing. Jianjun Yang helped with research design, supervision and review editing. Xiaochong Fan helped with research design, supervision, interpretation of data, preparation of the manuscript, and approval of the final manuscript.

Disclosure

Ethical approval for this study (2021-KY-0044-002) was provided by The Ethics Committee of the First Affiliated Hospital of Zhengzhou University, Zhengzhou City, Henan Province, China on 20 April 2021. Name of the person who approved the protocol: Li Tian. The trial was registered at Chinese Clinical Trial Registry (https://www.chictr.org.cn/hvshowproject.aspx?id=159614)

prior to patient enrollment (ChiCTR2000040885, Principal Investigator: Jingjing Yuan, registration date: 2020-12-13). All participants in this study have agreed to participate in this trial.

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