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ORIGINAL RESEARCH

Effects of the Different Doses of Esketamine on Postoperative Quality of Recovery in Patients Undergoing Modified Radical Mastectomy: A Randomized, Double-Blind, Controlled Trial

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Purpose: This study aims to investigate the effects of the different doses of esketamine on postoperative quality of recovery in patients undergoing modified radical mastectomy.

Methods: Ninety-nine female patients were randomly allocated to three groups: the low-dose esketamine group (group E_1) (0.5 mg/kg loading, 2 μg/kg/h infusion), the high-dose esketamine group (group E_2) (0.5 mg/kg loading, 4 μg/kg/h infusion), the control group (group C) (received normal saline). The primary outcome was the quality of recovery-15 (QoR-15) scores on postoperative day 1 (POD1) and days 3 (POD3). The secondary outcomes were the sleep quality scores on POD1, bispectral index (BIS) value at 10, 30, and 60 min after operation, numeric rating scale (NRS) pain scores within 24 h after surgery, nausea, vomiting, drowsiness, nightmare, and intraoperative awareness.

Results: The total QoR-15 scores were higher in group E_1 and group E_2 than in group C on POD1 and POD3 ($P<0.05$). The sleep quality scores on POD1 and BIS value at 10, 30, and 60 min after operation were higher in group E_1 and group E_2 than in group C ($P<0.05$). The NRS pain scores at 2, 4 and 6 h after surgery in group E_1 and at 2, 4, 6, 12 and 24 h after surgery in group E_2 were lower than in group C ($P<0.05$). The NRS pain scores at 6, 12 and 24 h after surgery in group E_2 were lower than in group E_1 ($P<0.05$). The incidence of drowsiness was higher in group E_1 and group E_2 than in group C ($P<0.05$).

Conclusion: Esketamine infusion improved to some extent the quality of recovery on POD1 and POD3 in patients undergoing modified radical mastectomy, especially 4 μg/kg/h esketamine was better, but the BIS value and incidence of drowsiness were significantly increased.

Keywords: esketamine, postoperative quality of recovery, radical mastectomy

Introduction

Breast cancer is one of the most common malignant tumors in women with a high mortality rate. Modified radical mastectomy is recommended as most effective clinical treatment options for breast cancer. Due to the large extent of surgical resection, nerve injury and inflammatory stimulation, most of the patients undergoing modified radical mastectomy were experienced postoperative pain after surgery, the inadequate pain management affects quality of life and causes reduced physical function,[1,2] so adequate pain control is necessary for improving the quality of recovery after surgery.

Opioids have been widely used for the postoperative analgesia due to their powerful analgesic effect. However, opioids also inevitably produce some adverse effects, such as respiratory depression, nausea, vomiting, and postoperative hyperalgesia.[3] With the development of the concept of opioid-free anesthesia (OFA), multimodal analgesia is considered the optimal strategy for postoperative pain management through nerve blockade[4,5] and non-opioid medications.[6–8]

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Ketamine is an antagonist of the N-methyl-D-aspartate (NMDA) receptor, which has a powerful sedative and analgesic effects for clinical anesthesia for many years. Esketamine, the right-handed split, has a faster metabolism, stronger potency, and fewer side effects.[9,10] Some evidence states that ketamine or esketamine administration has an analgesic effect.[11–13] Currently, existing evidence has shown that esketamine via intranasal way is more effective and safe than via intravenous way for major resistant depression disorder because the pharmacokinetics of nasal spray and intravenous administration were similar, but the former had a greater antidepressant effect and less overall adverse reactions.[14–16] In addition, several studies showed that esketamine promoted postoperative recovery by reducing postoperative pain, and there was no significant difference in the incidence of postoperative nausea and vomiting.[17–19] Therefore, we hypothesized that the esketamine infusion provides better the quality of recovery in patients undergoing modified radical mastectomy.

Materials and Methods

The current study was approved by the Ethics Committee of Anqing Municipal Hospital and prospectively registered at www.clinicaltrials.gov (NCT05289440, date of registration: March 19, 2022). All methods were performed in accordance with the relevant guidelines and regulations in our present study. We enrolled 99 female patients who received elective modified radical mastectomy under general anaesthesia from March 2022 to September 2022. Written informed consent was obtained from all patients. The inclusion criteria included the American Society of Anesthesiologists (ASA) physical status I (A normal healthy patient) and II (A patient with mild systemic disease), and aged 32–72 years. The exclusion criteria were as follows: severe pulmonary hypertension, arrhythmia, liver and kidney dysfunction, uncontrolled hypertension, take analgesics and sedatives recently, history of chronic pain, psychosocial abnormalities, history of alcohol abuse, pregnant, and lactating.

Patients were randomly divided into 3 groups using computer-generated random numbers. The low-dose esketamine group (group E_1) received 0.5 mg/kg esketamine diluted with normal saline to 20 mL by intravenous injection over 1 minute before surgical incision, followed by at a rate of 2 μg/kg esketamine diluted with normal saline to 20 mL every hour until closure of surgical incisions; the high-dose esketamine group (group E_2) received 0.5 mg/kg esketamine diluted with normal saline to 20 mL by intravenous injection over 1 minute before surgical incision, followed by at a rate of 4 μg/kg esketamine diluted with normal saline to 20 mL every hour until closure of surgical incisions; the control group (group C) received equal volume of normal saline. All participants including enrolled patients, anesthesiologists, surgeons, and the follow-up personnel were kept blind to the drug and the group assignments.

All patients were abstained from food and water 6 hours before surgery. After entering the operation room, the non-operative peripheral vein was opened and the sodium lactate Ringer injection was infused. Routine monitoring, including systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), peripheral pulse oximeter (SpO_2), electrocardiogram (ECG), temperature, and end-tidal CO_2 pressure ($PetCO_2$), bispectral index (BIS) were performed after the patients entered the operation room.

Patients in the three groups received inhalation of pure oxygen (100%) 3 minutes before induction of anesthesia, followed by intravenous administration of dexamethasone 10 mg and penehyclidine 0.5 mg. The induction of anesthesia was as follows: midazolam 0.05 mg/kg, sufentanil 0.4 μg/kg, etomidate 0.3 mg/kg, and cisatracurium 0.15 mg/kg. Flurbiprofen 0.1 mg/kg was injected before skin incision. After loss of corneal and palpebral reflexes, BIS<60 and muscle relaxation was perfect enough to achieve intubation conditions, endotracheal intubation was performed with video laryngoscope (endotracheal intubation diameter was 6.5–7.0 mm, distance from incisor 21–23 cm). After successful intubation, respiratory parameters such as tidal volume and respiratory rate were set at 6–8 mL/kg and 12–14 beat/min (bpm) to maintain the $PetCO_2$ between 35 and 45 mmHg during the intraoperative period, respectively. Remifentanil and propofol were continuously infused at a rate of 0.15 μg/kg/min and 4–6 mg/kg/h during the anesthesia period, respectively. BIS values were kept between 45 and 75 by adjusting the infusion dose of propofol during the anesthesia period. Atropine (0.5 mg) was intravenously given when the HR<50 beats/min. Ephedrine (6 mg) was intravenously given when the mean blood pressure (MBP)<60 mmHg. During the operation period, 1–2 mg cis-atracurium was injected intermittently, and sufentanil was injected intermittently 5–10 μg according to the hemodynamic parameters to maintain the blood pressure and HR at 20% of the basal value. At the end of the operation, the infusion of propofol and remifentanil was stopped. And the endotracheal tube was removed and

transferred to the post-anesthesia care unit (PACU) after the patient was naturally awake. If the postoperative numeric rating scale (NRS) pain score>3, non-steroidal anti-inflammatory drugs could be given for remedial analgesia.

Primary and Secondary Outcomes

Anesthesiologist who was not participated in this study evaluated the total postoperative recovery quality scores based on the QoR-15 scale on POD1 and POD3. The QoR-15 questionnaire is composed of 15 questions, including physical comfort (5 items), emotional state (4 items), physical independence (2 items), psychological support (2 items), and pain (2 items). The higher of the QoR-15 scores, the better of the quality of recovery after surgery (range is 0 to 150 points).[20]

NRS pain scores were assessed for all patients at 2, 4, 6, 12 and 24 h after surgery (0 points: painless; 1–3 points: mild pain; 4–6 points: moderate pain; 7–10 points: severe pain). The quality of sleep was evaluated using a 10-point rating scale (0 = terrible sleep, 10 = excellent sleep).[21] If severe nausea requiring antiemetics and retching or vomiting (greater than or equal 2 times) occurred, ondansetron 0.1 mg/kg was given intravenously or metoclopramide 10 mg was injected intramuscularly. BIS values were recorded at 10, 30 and 60 min after the surgical incision. The adverse effects, including nausea, vomiting, drowsiness, nightmares, and intraoperative awareness were also recorded.

Statistical Analysis

Based on our pilot study, the results indicated that the mean values of total QoR-15 scores were 106.2, 110.5, and 116.2 in the three groups on POD1; the standard deviations (SD) were 6.8, 8.2, and 10.5, respectively. The sample size was calculated by PASS 11.0. Eventually, we selected 33 patients in each group with a power of 0.9 and an α of 0.05, allowing for a 10% drop-out rate.

We completed statistical analyses based on SPSS v.20 (IBM Corp., Armonk, NY, USA) in the present study. Categorical data analysis were adopted $\chi 2$ or Fisher's exact test as appropriate and were presented as numbers. Continuous data were evaluated normality and homogeneity using Kolmogorov–Smirnov test and Levene's test, respectively. Normally distributed data were expressed as the mean (SD) and were analyzed by one-way analysis of variance (ANOVA). When a significant difference was found among the three groups, Dunnett's T_3 analysis was performed. Nonparametric distribution of data were expressed as median (interquartile range [IQR]) and analyzed by the Kruskal–Wallis tests. The P value <0.05 was viewed as statistical significance.

Results

A total of 105 patients were enrolled in this study. Five patients did not conform to inclusion criteria. One patient did not consent to participate research. Eventually, 33 patients were included in each group. Three patients had an intraoperative HR<50 beats/min and were given atropine 0.5 mg intravenously. Thirteen patients had MBP<60 mmHg and were given ephedrine 6 mg intravenously. All patients did not injected sufentanil during the perioperative period. No awareness occurred in all patients during the intraoperative period (Figure 1).

There were no significant differences in all three groups with regard to age, height, weight, body mass index (BMI), and ASA grade (Table 1).

The QoR-15 Scores on POD1 and POD3 and Sleep Quality Scores Between Groups

Compared with group C, The total QoR-15 scores were significantly higher on POD1 and POD3 in group E_1 and group E_2 (P<0.001, P<0.001, P = 0.016, P<0.001, respectively). The total QoR-15 scores were the highest in group E_2 on POD1 and POD3. There were no significant differences with regard to total QoR-15 scores at POD1 and POD3 in group E_1 and group E_2 (P = 0.263 and P = 0.221). The sleep quality scores were higher on POD1 in group E_1 and group E_2 compared to group C (P = 0.001 and P<0.001). The sleep quality scores were no significant differences between group E_1 and group E_2 (P = 0.230) (Table 2).

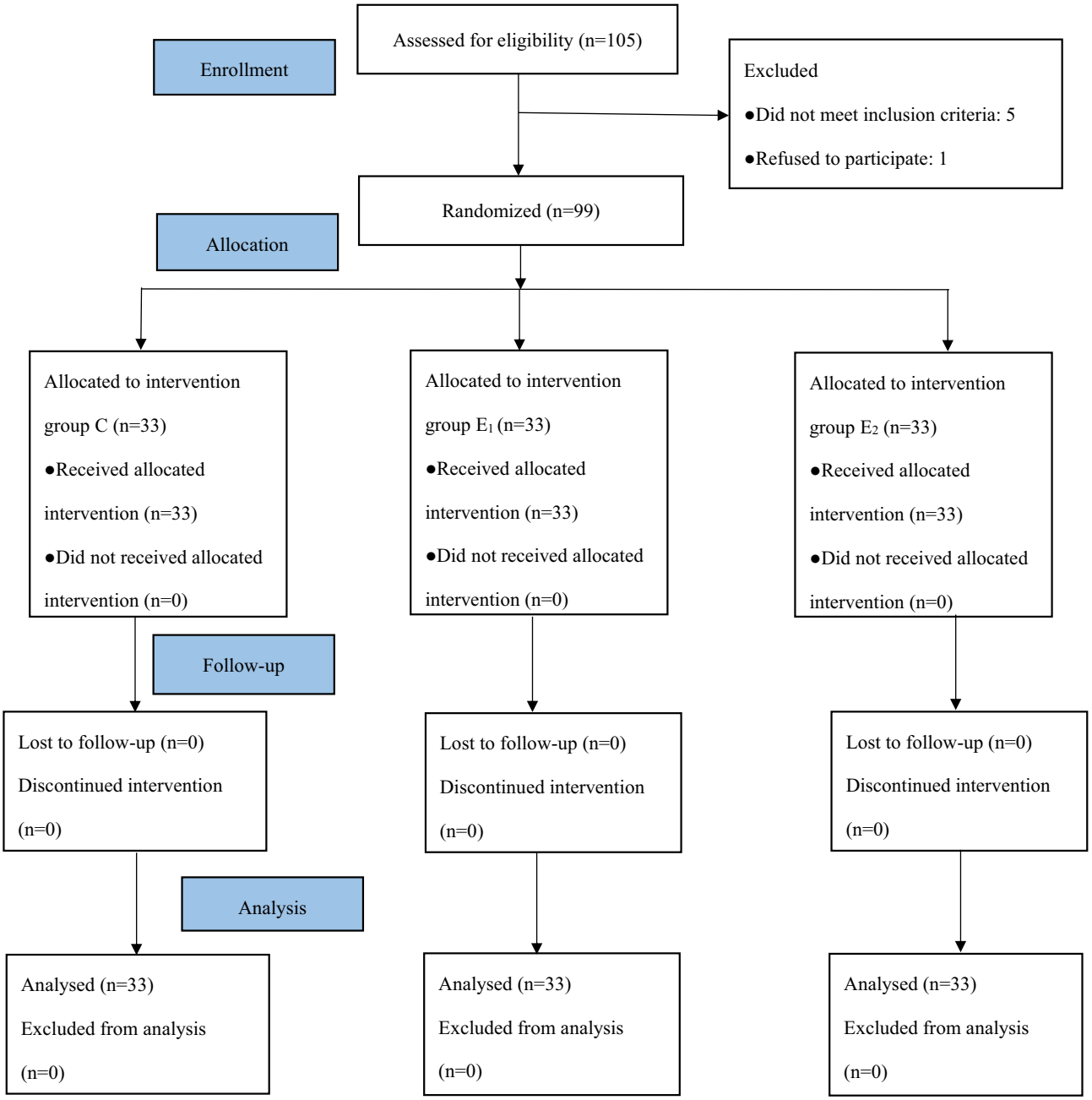

Figure 1 Consolidated Standards of Reporting Trials (CONSORT) flow diagram. Adapted from Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c332. Open Access.[40]

The BIS Values at Any Time Points After Surgical Incision

The BIS values were higher in group E_1 and group E_2 than in group C at 10, 30, and 60 min after surgical incision ($P<0.001$, $P<0.001$, $P<0.001$, $P<0.001$, $P<0.001$, $P<0.001$, respectively). The BIS values were no significant differences in group E_1 and group E_2 10, 30, and 60 min after surgical incision ($P = 0.890$, $P = 0.993$, $P = 0.398$) (Table 3).

The NRS Pain Scores During the First 24 h After Surgery

The NRS scores were lower at 2, 4 and 6 hours after surgery in group E_1 than in group C ($P<0.001$, $P = 0.003$, $P = 0.027$, respectively), the NRS pain scores were lower at 2, 4, 6, 12 and 24 hours after surgery in group E_2 than in group C ($P<0.001$, $P<0.001$, $P<0.001$, $P<0.001$, $P = 0.001$, respectively); the NRS pain scores were lower at 6, 12 and 24 hours after surgery in

Table 1 Clinical Characteristics of All Patients

Index	Group C (n = 33)	Group E_1 (n = 33)	Group E_2 (n = 33)	*P*
Age (years)	51.6±6.1	53.9±9.1	54.1±9.5	0.411
Height (cm)	156.0±3.8	157.6±4.4	157.5±4.3	0.220
Weight (kg)	56.6±5.8	59.2±6.4	58.3±7.8	0.288
BMI	23.3±2.3	23.8±1.9	23.5±2.7	0.694
ASA (I/II)	23/10	20/13	22/11	0.731

Note: Data are present as mean±standard deviation or number.
Abbreviations: Group C, control group; Group E_1, low-dose esketamine group; Group E_2, high-dose esketamine group; BMI, body mass index; ASA, American Society of Anesthesiologists.

Table 2 The Comparison of QoR-15 Scores and Sleep Quality Scores Between Groups

Index	Group C (n = 33)	Group E_1 (n = 33)	Group E_2 (n = 33)	*P*
Total QoR-15 scores on POD1	108(103.0–112.0)	118(114.0–121.0)[a]	121(117.0–126.0)[a]	<0.001
Total QoR-15 scores on POD3	124(120.0–128.0)	129(125.0–131.5)[a]	130(127.5–135.5)[a]	<0.001
Total sleep quality scores	2(2.0–3.0)	3.0(2.5–3.5)[a]	3.0(3.0–4.0)[a]	<0.001

Notes: [a]*P* versus Group C, *P*<0.05. Data are present as median (IQR).
Abbreviations: Group C, control group; Group E_1, low-dose esketamine group; Group E_2, high-dose esketamine group; QoR-15, quality of recovery-15; POD, Postoperative day; POD1, Postoperative day 1; POD3, Postoperative day 3.

Table 3 The BIS Values at Any Time Points After Surgical Incision

BIS value	Group C (n = 33)	Group E_1 (n = 33)	Group E_2 (n = 33)	*P*
10 min after surgical incision	51.5±4.3	68.6±3.0[a]	69.0±2.7[a]	<0.001
30 min after surgical incision	53.3±4.0	69.8±2.6[a]	70.1±2.5[a]	<0.001
60 min after surgical incision	53.0±4.0	68.6±3.8[a]	69.8±2.9[a]	<0.001

Notes: [a]*P* versus Group C, *P*<0.05. Data are present as mean±standard deviation.
Abbreviations: Group C, control group; Group E_1, low-dose esketamine group; Group E_2, high-dose esketamine group; BIS, bispectral index.

group E_2 than in group E_1 ($P = 0.027$, $P = 0.003$, $P = 0.042$). The NRS scores were no significant differences at 2 and 4 hours after operation in group E_1 and group E_2 ($P = 0.317$ and $P = 0.103$). The NRS scores were also no significant differences at 12 and 24 hours after surgery in group C and group E_1 ($P = 0.181$ and $P = 0.727$) (Table 4).

The Incidence of Adverse Effects at 24 h After Surgery and Remedial Treatment

The incidence of drowsiness was higher in group E_1 and group E_2 than in group C (P<0.001 and P<0.001). There were no significant differences with respect to drowsiness between the group E_1 and group E_2 ($P = 0.378$). Compared with group C, postoperative nausea, vomiting, nightmares, intraoperative awareness, rescue analgesia, and anti-emetics required were not statistically significant in groups E_1 and E_2 (all P>0.05) (Table 5).

Table 4 The NRS Pain Scores During the First 24 h After Surgery

NRS Pain Scores	Group C (n = 33)	Group E_1 (n = 33)	Group E_2 (n = 33)	*P*
Postoperative 2 h	2(2.0–3.0)	2(1.0–2.0)[a]	1(1.0–2.0)[a]	<0.001
Postoperative 4 h	3(3.0–3.0)	2(2.0–3.0)[a]	2(1.0–2.5)[a]	<0.001
Postoperative 6 h	3(3.0–3.0)	3(2.0–3.0)[a]	2(1.0–3.0)[ab]	<0.001
Postoperative 12 h	3(3.0–3.0)	3(2.0–3.0)	2(2.0–3.0)[ab]	<0.001
Postoperative 24 h	3(2.0–3.0)	2(2.0–3.0)	2(2.0–2.0)[ab]	0.001

Notes: [a]*P* versus Group C, *P*<0.05; [b]*P* versus Group E_1, *P*<0.05. Data are present as median (IQR).
Abbreviations: Group C, control group; Group E_1, low-dose esketamine group; Group E_2, high-dose esketamine group; NRS, numeric rating scale.

Table 5 The Incidence of Adverse Effects at 24 h After Surgery and Remedial Treatment

Index	Group C (n = 33)	Group E_1 (n = 33)	-Group E_2 (n = 33)	*P*
Nausea, n (%)	5(15.2%)	4(12.1%)	4(12.1%)	0.915
Vomiting, n (%)	2(6.1%)	2(6.1%)	1(3.0%)	0.810
Nightmares, n (%)	0	1(3.0%)	2(6.1%)	0.357
Drowsiness, n (%)	2(6.1%)	24(72.7%)[a]	27(81.8%)[a]	<0.001
Intraoperative awareness, n (%)	0	0	0	
Remedial analgesia, n (%)	9(27.3%)	5(15.2%)	3(9.1%)	0.317
Anti-emetics required, n (%)	2(6.1%)	1(3.0%)	1(3.0%)	0.771

Notes: [a]*P* versus Group C, *P*<0.05. Data are present as number (%).
Abbreviations: Group C, control group; Group E_1, low-dose esketamine group; Group E_2, high-dose esketamine group.

Discussion

The results of our study indicated that esketamine infusion especially 4 μg/kg/h esketamine provided better quality of recovery 1 and 3 days after surgery in patients undergoing modified radical mastectomy. In addition, our results also found that 4 μg/kg/h esketamine administration significantly alleviated postoperative 24 h intensity of pain, but esketamine infusion could increase BIS values and the incidence of drowsiness.

Modified radical mastectomy is one of the method for treatment of breast cancer, most of patients usually experience postoperative acute pain, which may be affect endocrine function, immune function, and lead to some adverse events such as atelectasis and pneumonia.[22,23] Acute pain after surgery affects quality of recovery, moreover, if it is not adequately controlled, it may be develop into chronic pain, which affects quality of life of patients.[24] Miziara et al reported that S(+)-ketamine infusion alleviated postoperative pain and reduced morphine requirement undergoing laparoscopic cholecystectomy.[25] Su et al found that esketamine administration significantly decreased the dosage of remifentanil and reduced the incidence of severe pain with liver tumor ablation.[26] However, Brinck et al revealed that intraoperative S(+)-ketamine administration did not alleviate postoperative pain and oxycodone consumption undergoing major lumbar fusion surgery.[27] In the present study, our results indicated that low-dose esketamine infusion relieved NRS pain scores during the first postoperative 6 h period and high-dose esketamine alleviated NRS pain scores during the first postoperative 24 h period. It might be related to the analgesia property of esketamine infusion in a dose-dependent manner. In addition, the results of our study also showed that high-dose esketamine further decreased postoperative pain intensity at 6, 12, and 24 h after surgery. It might be associated with high-dose esketamine infusion prolong the analgesic time and inhibit opioid-induced hyperpathia.

BIS value is usually used for monitoring the depth of anesthesia in clinical practice. Some studies found that ketamine administration could increase BIS value by affecting the relative power of slow wave (θ) and fast wave (γ). Therefore, BIS value can no longer objectively reflect the depth of anesthesia during the ketamine administration period.[28,29] A study has proved that esketamine injection increase BIS value at 1 and 5 min after intubation, but it was not affect the intraoperative BIS value.[10] In present study, we found that esketamine continuous infusion increased BIS value during the intraoperative period. The results of our study were inconsistent with the results of above-mentioned study, it might attribute to the various method of esketamine administration.

The QoR-15 questionnaire is sensitive and reliable tool, which is usually used for assessing the quality of recovery after surgery and easily complete in clinical practice.[30,31] Zhao et al revealed that low-dose ketamine did not enhanced the overall quality of postoperative recovery undergoing breast cancer surgery, but it provided better emotional state and pain scores.[32] Cheng et al indicated that S-ketamine administration improved quality of postoperative recovery, postoperative analgesia, and depression after operation in patients undergoing video-assisted thoracic surgery.[19] In our study, we found that low-dose esketamine infusion was higher total QoR-15 scores on POD1 and POD3. Moreover, our results also demonstrated that high-dose esketamine infusion had the highest overall QoR-15 scores on POD1 and POD3. This suggested that esketamine infusion enhanced quality of recovery on POD1 and POD3 in patients undergoing modified radical mastectomy in a dose-dependent manner, which was associated with lower postoperative NRS pain scores and better the quality of sleep. On the contrary, Moro et al proved that ketamine administration did not enhanced the quality

of postoperative recovery undergoing laparoscopic cholecystectomy.[33] These inconsistent results might be associated with the dose of ketamine or esketamine, the type of surgery, and the duration of ketamine or esketamine.

Nausea and vomiting is the most common complication after surgery with general anesthesia. The higher incidence of postoperative nausea and vomiting affects the quality of recovery, which may be prolong the length of stay and decrease the patients' satisfaction. Some studies showed that esketamine or S-ketamine did not the occurrence of postoperative nausea and vomiting.[34–36] However, Brinck et al revealed that ketamine reduced the nausea and vomiting after operation.[11] In the present study, our results showed that the different dose of esketamine did not decrease the incidence of postoperative nausea and vomiting. It might be attributed to the same rate of remifentanil during the perioperative period and non-steroidal anti-inflammatory drugs could be given for remedial analgesia. Racemic ketamine with an loading followed by continuous infusion (0.04–0.25 mg/kg/h) was used in most studies.[37–39] Brinck et al indicated that intraoperative high-dose S-ketamine (0.5 mg/kg loading, 0.6 mg/kg/h infusion) administration had higher rate of sedation than low-dose S-ketamine (0.5 mg/kg loading, 0.12 mg/kg/h infusion).[27] We selected esketamine with an loading (0.5 mg/kg) followed by continuous infusion (2 μg/kg/h and 4 μg/kg/h) was used in the present study. We also observed that esketamine administration significantly increased the incidence of drowsiness. It could be related to sedation effect of esketamine.

There are some limitations in our study. Firstly, remifentanil was continuous infusion at a rate of 0.15 μg/kg/min in the three groups during the anesthesia period, which did not reflect opioid-sparing effect of esketamine, therefore, we should adjust the rate of remifentanil based on changes of hemodynamic parameters. Secondly, esketamine may be cause hypertension and tachycardia, however, in the present study, we did not observe changes of hemodynamic parameters during the esketamine administration period. Thirdly, esketamine can produce dissociative symptoms and worsening of psychiatric symptoms (like anxiety or agitation), but we did not observe the incidence of anxiety or agitation. Fourthly, in the present study, we did not perform multivariate analysis for quality of the recovery, level of pain, and quality of sleep. Our results could be more forceful if we would have used multivariate analysis for quality of the recovery, level of pain, and quality of sleep. Hence we will perform multivariate analysis in the future study. Finally, we selected 33 cases in each group based on Power analysis of our preliminary results, but we thought that the sample size was small for clinical study. Therefore, we need large sample, multi-center, randomized, double-blinded controlled study to further explore effect of esketamine infusion on the quality of postoperative recovery in the future clinical research.

Conclusions

The different doses of esketamine infusion especially 4 μg/kg/h esketamine improved to some extent the quality of recovery 1 and 3 days after surgery, decreased the intensity of postoperative pain in patients undergoing modified radical mastectomy. However, esketamine administration could increase BIS values and the incidence of drowsiness.

Data Sharing Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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