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The effect of low-dose ketamine on postoperative quality of recovery in patients undergoing breast cancer surgery: A randomised, placebo-controlled trial

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Abstract

Background: Low-dose ketamine has been proved to reduce opioid consumption, prevent depressant action and improve postoperative analgesia. Women undergoing mastectomy experience may not only have persistent postoperative pain syndromes but also emotional problems. However, the effect of intraoperative infusion of low-dose ketamine on postoperative quality of recovery among these patients has not yet been fully studied.

Methods: In this prospective, randomised, single-centre trial, 100 patients planned for modified radical mastectomy were randomly assigned to one of two groups: control group (group C) or ketamine group (group K) at a ratio of 1:1. Group K received the bolus dose of 0.5 mg/kg ketamine and followed by 0.25 mg·kg\(^{-1}\)·h\(^{-1}\) after the completion of anaesthesia induction until the end of the surgery, whilst group C received an equivalent dose and regimen of normal saline was group K. The primary outcome was to assess the effects of low-dose ketamine on postoperative quality of recovery using the 40-Item Quality of Recovery (QoR-40) scale on a postoperative day 1 (POD1). The secondary outcome was to assess the numeric rating scale (NRS) at 4, 24 and 48 h after the operation, identity-consequence fatigue scale (ICFS) scores at 3 and 7 days after the operation, hospital anxiety and depression scale (HADS) scores at 2 days and 3 months, as well as chronic pain at 3 months. In a post hoc analysis, the 5 subsections of the QoR-40 scores were also analysed.

Results: A total of 100 subjects were randomised. The primary outcome of QoR-40 scores on POD1 was available in 97 patients (49 in group C and 48 in group K). Global QoR-40 scores were not significantly different between group C and group K (169.8 ± 10.7 vs. 172.7 ± 7.5, 95% CI −1.35 (−5.50, 2.80), \(p = .519\)). In a post hoc analysis, pain scores were significantly higher in group K than in group C (29.8 ± 3.8 vs. 31.7 ± 2.1, 95% CI −1.81 (−3.00, −0.62), \(p = .003\)). The secondary outcomes, including NRS, ICFS scores, HADS scores and chronic pain had no difference between groups (\(p\) value for each >.15).

Conclusion: Intraoperative low-dose ketamine infusion did not improve the overall quality of recovery on POD 1 in patients undergoing breast cancer surgery.
Breast cancer is one of the most common cancers that occur among the female population. Whilst advances in diagnosis and treatment have significantly improved the survival rates, the patients suffer persistent pain syndromes and emotional problems, such as depression and anxiety. It is crucial for finding a potential method to accelerate these patients’ recovery from the surgery.

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, is increasingly taken not only for an adjunct of pain control but also for rapid mood improvement. First, a randomised, blinded trial reported that intraoperative ketamine significantly reduced morphine consumption after lumbar fusion surgery in opioid-dependent patients. Secondly, ketamine may contribute to emotion and mood regulation via suppressing the nitric oxide synthase activity, protein expression by endotoxins, and inflammatory effects.

Increased female susceptibility to depression-like phenotypes is associated with higher dopamine system sensitivity, which can be suppressed by ketamine. Interestingly, studies have shown that women are more likely to be affected under pressure and stress, resulting in depression-like emotions. Therefore, we believe that low-dose ketamine can improve the total quality of postoperative recovery of breast cancer patients.

Although the effects of low-dose ketamine on the quality of recovery after laparoscopic cholecystectomy have been investigated, few studies have assessed how low-dose ketamine affects the quality of recovery after modified radical mastectomy. The 40-item quality of recovery questionnaire (QoR-40) is sensitive to changes in health status and provides an overall health status measure after surgery and anaesthesia. It is considered the best instrument for evaluating the complex and multidimensional process of postoperative recovery in the general surgical population.

We hypothesised that low-dose ketamine could enhance patients’ quality of recovery following modified radical mastectomy under general anaesthesia. This study’s primary objective was to assess the effects of intraoperative infusion of low-dose ketamine on the quality of recovery in patients undergoing modified radical mastectomy under remifentanil-propofol-based anaesthesia using the QoR-40 questionnaire.

2 | MATERIALS AND METHODS

2.1 | Subjects

We performed a prospective, randomised, single-centre clinical trial, which was approved by the Clinical Research Ethics Committee of the Affiliated Hospital of Xuzhou Medical University, Jiangsu, China (Certification No.XYFY2018-KL058-01, approved date, August 27, 2018) and was registered before patient enrolment at https://clinicaltrials.gov (number: NCT03676114; principal investigator: J.L.C.; date of Registration, September 18, 2018). Written informed consents were obtained from all patients participating in the trial. This manuscript adheres to all applicable CONSORT guidelines.

Female patients aged 20–65 years old. American Society of Anesthesiologists physical status (ASA) I or II, scheduled to have modified radical mastectomy under general anaesthesia were screened between September 2018 and February 2019. Exclusion criteria included: unstable hypertension, history of heart disease, hepatic or renal dysfunction, undergoing chemotherapy before surgery, history of chronic pain or chronic use of analgesics, mental illness or inability to cooperate with investigators and/or history of ketamine allergy.

2.2 | Intervention

Patients were randomly assigned to one of two groups based on computer-generated codes that were maintained in sequentially numbered opaque envelopes: control group (group C) or ketamine group (group K) at a ratio of 1:1. On the day of surgery, a responsible anaesthesiologist who was not involved in patient evaluation opened the envelope and prepared either 0.5% ketamine or normal saline in 20 ml syringes, then labelled them as ‘study drug’ for double-blind purposes.

After induction of anaesthesia and before surgical incision, a bolus dose of 0.5 mg/kg ketamine or an equivalent volume of normal saline was infused via a reliable intravenous catheter, followed by 0.25 mg-kg⁻¹·h⁻¹ ketamine or normal saline infusions until the end of surgery.

The ketamine diluents were mixed to concentrations of 5 mg/ml to ensure that all drugs were infused at a bolus of 0.1 ml/kg followed by 0.05 ml-kg⁻¹·h⁻¹ thereafter. None of the investigators involved in patient management or data collection were aware of the group assignments.

2.3 | Anaesthetic Management

All patients fasted for at least 6–8 hours before the surgery. After entering the operating room, venous access was opened. Heart rate (HR),
blood pressure (BP), pulse oxygen saturation (SpO₂) and electrocardiogram (ECG) were routinely monitored. Anaesthesia was induced with etomidate (0.3 mg/kg), sufentanil (0.5 μg/kg) and rocuronium (0.6–1 mg/kg). The tracheal intubation was performed under the video laryngoscope, and the ventilator was connected with a tidal volume of 6–8 ml/kg. The respiratory rate was adjusted to maintain the end-expiratory CO₂ partial pressure at 35–45 mm Hg. Propofol (4–6 mg·kg⁻¹·h⁻¹) and remifentanil (0.3 μg·kg⁻¹·min⁻¹) were used for anaesthesia maintenance. As it is well known that the Bispectral Index (BIS) is not suitable for monitoring the anaesthesia depth regarding ketamine, the anaesthetic depth was titrated by an experienced attending anaesthesiologist who is independent of the whole study, by adjusting the dosage of propofol and remifentanil based on the systolic blood pressure no greater or less than 20% compared with basal blood pressure. Also, the precise assumption of intraoperative propofol and also remifentanil in both groups were recorded and analysed. According to the surgical situation, the muscle relaxant is added, and no volatile anaesthetic is used for induction and maintenance. All anaesthetics were discontinued at the end of the suture. The tracheal tube can be removed when the patient regained consciousness and the desired tidal volume was achieved. The patients were then transferred to the postanaesthetic care unit (PACU). For postoperative pain management, the patient-controlled analgesia (PCA) pump was not routinely placed after the operation, and the doctor in the ward gave an appropriate amount of flurbiprofen axetil or dezocine according to the patient's pain complaint.

2.4 Primary outcome

The primary endpoint of the study was the global QoR-40 score on POD 1.

2.5 Secondary outcomes

The secondary endpoints were the numeric rating scale (NRS) at 4, 24 and 48 h after operation, Identity-consequence fatigue scale (ICFS) scores at 3 and 7 days after operation, Hospital anxiety and depression scale (HADS) scores at 2 days and 3 months after the operation and chronic pain at 3 months, as well as vital signs during the anaesthetic period, including heart rate, peripheral oxygen saturation and mean arterial pressure at three-time points (10 min after ketamine infusion [T1]; the moment of extubation [T2]; 10 min after extubation [T3]). We also analysed the 5 subsections of the global QoR-40 score, other perioperative data such as adverse reactions to ketamine, postoperative remedial analgesia were also recorded.

2.6 Outcome assessment

A researcher who was unaware of the group assignments visited each patient to administer the QoR-40 survey the day before surgery and POD1.

QoR-40 is a self-scoring questionnaire that examines the conditions associated with patients’ recovery, including 5 subsections: physical comfort, emotional state, physical independence, psychological support and pain, for a total of 40 items. The scores of each item are added together as the final total score. The lowest score is 40 points and the highest score is 200 points, the higher the score, the better the patients recover. The pain score in QoR-40 is in opposition to other pain scores as we knew before, and high pain scores in QoR-40 mean that patients improve their pain. The QoR-40 survey has been widely used and validated for patients undergoing a variety of surgical procedures.

2.7 Statistical analysis

All continuous variables data were assessed for normality using the Kolmogorov-Smirnov tests, and the Levene test was used to assess equality of variances. Group comparisons were made using two independent sample t tests for continuous variables with a normal distribution, the Mann-Whitney U test for continuous variables with a non-normal distribution, or the chi-square test or Fisher’s exact test for dichotomous and ranked data. A linear mixed-effect model with random effect was conducted in QoR-40 measurement with SAS, version 9.3. A value of p < .05 was used for all comparisons. Statistical analyses, except QoR-40 scores, were completed using SPSS, version 22.0 (IBM).

According to previous studies, a QoR-40 score of 10 or more differences was considered to be a clinically significant improvement or worsening of recovery quality. Based on our preliminary data, the variability (SD) of QoR-40 scores on the first day after breast cancer surgery was 15. The estimated sample size was 37 patients per group with a power of 80% at an α level of 0.05. We enrolled a final total of 50 patients per group, allowing for about a 30% drop-out rate.

3 RESULTS

Among 205 patients were screened between September 2018 and February 2019. 73 patients did not meet inclusion criteria. 10 patients satisfied the exclusion criteria, and 12 patients declined to participate. As 7 patients cancelled the operation and 3 patients withdrew consent, a total of 100 patients were finally randomly assigned to two groups. Primary outcome analysis is consisted of 49 patients in group C and 48 patients in group K, as 1 patient changed operation in group C, 1 patient changed surgery plan and 1 patient dropped out in group K (Figure 1). Demographic and baseline characteristics were generally comparable between the two groups (Table 1).

3.1 Primary outcome

The global QoR-40 scores and subsections for the two groups are shown in Table 2. There were no differences in global QoR-40 scores
on POD1 between the patients in group C and group K (169.8 ± 10.7 vs. 172.7 ± 7.5, 95% CI -1.35 (-5.50, 2.80), p = .519). In a post hoc analysis, among the subsection of QoR-40, pain scores were significantly higher in group K than in group C (29.8 ± 3.8 vs. 31.7 ± 2.1, 95% CI -1.81 (-3.00, -0.62), p = .003), which indicates patients may have better performance in pain in group K. Scores for the 4 other subsections on POD 1 were not significantly different between group C and group K (p value for each >.10) (Table 2).

### 3.2 Secondary outcomes

Postoperative recovery elements, such as NRS at rest and when moving at 4, 24, 48 h postoperatively, were not significantly different between groups (p value for each >.40). ICFS scores at 3 and 7 days after operation were similar between groups (p = .159 and 0.911, respectively). HADS scores at 2 days and 3 months after operation were also similar between groups (p = .764 and 0.727, respectively). Chronic pain at 3 months postoperatively was comparable between groups (p = .359) (Table 3).

### 3.3 Other parameters

Other surgery-related data and safety outcomes related to the usage of ketamine are presented in Tables 4 and 5. The vital signs, propofol and remifentanil consumption, the emergence time and duration of PACU stay, the analgesics required frequency, and safety outcomes had no difference between groups. No hallucinations or chills were observed in any of the participants.

### 4 DISCUSSION

In this study, we did not observe any significant difference in patients who received continuous intraoperative low-dose ketamine and control patients who did not receive ketamine, in terms of the global core of QoR following mastectomy. We did not find any improvements in NRS scores, ICFS scores, HADS scores and chronic pain regarding the ketamine intervention, either. However, among the 5 subsections of QoR-40, the pain score was significantly higher in the group that received ketamine. To our knowledge, the present study is the first to report the effects of continuous intraoperatively administered low-dose ketamine on quality of recovery using the QoR-40 survey among women undergoing modified radical mastectomy.

When defining the quality of postoperative recovery, not only pain control, but also patients’ emotional and psychological state, physical comfort and physical independence should be considered. The global QoR-40 is the first established and verified clinical tool for measuring functional recovery in the immediate postoperative period. Its scoring system contains five different subsections and assesses pain as well as the aforementioned aspects. Whilst it is
suggested that a minimum 10-point difference represents a clinically relevant improvement in quality of recovery,\textsuperscript{11} a recent study reported that a change of 6.3 can be the minimum clinically important difference.\textsuperscript{12} In the present study, even median QoR-40 scores in group K were \~3 higher than those in group C at POD1, this difference was not statistically significant. Further statistical analysis of each QoR-40 dimension may offer additional valuable information. Thus, we conducted post hoc statistical analysis of each subsection of QoR-40 between groups. This revealed that the ketamine group has higher pain scores than those in the control group. These data indicate that ketamine may help to improve patients’ analgesia but may not be beneficial for other aspects of the recovery.

By activating NMDA receptors, persistent nociceptive input can lead to pain sensitisation. The mechanism of ketamine-induced antihyperalgesia is predominantly by noncompetitive antagonism of the NMDA receptor. This promotes structural synaptic connectivity thereby leading to prolonged antidepressant effects.\textsuperscript{13} Opioid-induced hyperalgesia (OIH) refers to the long-term application of opioid analgesics, and the damage caused by peripheral tissue damage or inflammation has a strong nociceptive response to noxious stimuli, and NMDA receptors play a key role in OIH. As an NMDA receptor antagonist, ketamine is thought to prevent or reduce OIH through antagonising the NMDA receptor. Ketamine was also shown

\begin{table}
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\caption{Patients’ characteristics} \label{tab:1}
\begin{tabular}{|l|c|c|}
\hline
& Group C (n = 50) & Group K (n = 50) \\
\hline
Age (y) & 50.7 (8.3) & 50.4 (8.5) \\
Height (cm) & 159.6 (4.6) & 159.3 (4.3) \\
Weight (kg) & 60.0 (8.0) & 62.1 (8.5) \\
BMI (kg/m\textsuperscript{2}) & 23.6 (2.9) & 24.4 (3.0) \\
ASA physical status & \\
I & 39 (78%) & 37 (74%) \\
II & 11 (22%) & 13 (26%) \\
Operation time (min) & 101.9 (44.0) & 104.8 (40.3) \\
Anesthesia time (min) & 129.5 (45.5) & 136.6 (39.7) \\
Preoperative pain scores & \\
NRS at rest & 0 (0, 0) & 0 (0, 1.25) \\
NRS when moving & 0 (0, 2) & 0 (0, 2) \\
Preoperative ICFS scores & 36.9 (5.7) & 39.0 (9.2) \\
Preoperative HADS & 6.0 (4.0, 10.0) & 5.0 (4.0, 8.0) \\
\hline
\end{tabular}
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Note: Data are presented as mean (SD, standard deviation), median (IQR, interquartile range) or numbers (proportion, %).
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Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; Group C, control group; Group K, ketamine group; HADS, Hospital anxiety and depression scale; ICFS, Identity-consequence fatigue scale; NRS, numeric rating scale.
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\end{table}

\begin{table}
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\caption{The Global QoR-40 scores between groups} \label{tab:2}
\begin{tabular}{|l|c|c|c|c|}
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Subsections & group & Mean difference & p-value \\
& Group C & Group K & \(
\Delta \) (95%CI) & \\
\hline
Physical comfort & \\
Preoperative & 56.5 (3.6) & 57.0 (1.9) & Ref \hspace{1cm} – \\
POD 1 & 51.7 (5.1) & 52.5 (4.4) & -0.31 (-2.37, 1.73) & .760 \hspace{1cm} – \\
Emotional state & \\
Preoperative & 41.5 (4.9) & 42.3 (2.7) & Ref \hspace{1cm} – \\
POD 1 & 40.2 (3.4) & 41.7 (2.3) & -0.62 (-2.25, 1.01) & .452 \hspace{1cm} – \\
Physical independence & \\
Preoperative & 24.8 (1.0) & 24.9 (0.7) & Ref \hspace{1cm} – \\
POD 1 & 13.2 (4.0) & 12.2 (2.9) & -0.71 (-0.27, 2.55) & .114 \hspace{1cm} – \\
Psychological support & \\
Preoperative & 34.3 (1.5) & 34.6 (0.7) & Ref \hspace{1cm} – \\
POD 1 & 34.8 (0.8) & 34.6 (0.9) & -0.16 (-0.29, 0.62) & .478 \hspace{1cm} – \\
Pain & \\
Preoperative & 33.9 (1.4) & 33.9 (1.4) & Ref \hspace{1cm} – \\
POD 1 & 29.8 (3.8) & 31.7 (2.1) & -1.81 (-3.00, -0.62) & .003\textsuperscript{a} \hspace{1cm} – \\
QoR40 & \\
Preoperative & 190.8 (9.8) & 192.3 (5.2) & Ref \hspace{1cm} – \\
POD 1 & 169.8 (10.7) & 172.7 (7.5) & -1.35 (-5.50, 2.80) & .519 \hspace{1cm} – \\
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Note: Data are presented as mean (SD, standard deviation).
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Abbreviations: Group C, control group; Group K, ketamine group; POD1, postoperation day 1; QoR-40, quality of recovery 40.
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\textsuperscript{a}p < .05, linear mixed effect model.
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to reduce hyperalgesia, prevent opioid tolerance in animals, reduce morphine resistance in humans and decrease morphine consumption after transthoracic lung and heart surgery. A systematic review reported that perioperative use of ketamine could reduce opioid consumption and time to the first analgesic request.

There are several reasons for ketamine treatment for not improving the patients’ recovery. First, the timing, dose, and type of infusion of ketamine administration are critical factors modulating its effects. Subanesthetic doses of ketamine have sufficient analgesic efficacy by inhibiting NMDA receptor-mediated pain facilitation following noxious stimuli. Whilst high doses of ketamine may lead to severe side effects, such as the emergence of hallucinations and nightmares, thereby limiting its use. Since the clinical analgesia block provided by a bolus injection of ketamine would last for less than 5 min, continuous intravenous infusion of ketamine throughout the operation and even into the recovery period would be needed for greater effectiveness. Besides, subanaesthetic ketamine administered intraoperatively is unlikely to cause major psychomimetic adverse effects, whilst the postoperative long-term infusion is associated with limited and reversible psychomimetic adverse effects. So in the present study, considering the potential side effects caused by higher and long-term administration of ketamine, we administered subanesthetic ketamine during the surgery. Although the dosage we selected in this article mainly referred to the study in rectal adenocarcinoma surgery. We did not observe similar positive effects related to ketamine partially because of the difference in surgery types. In future study, the dose of ketamine or the length of infusion may have to be increased or prolonged to achieve better outcomes. Second, other analgesics, such as nonsteroidal anti-inflammatory drugs and glucocorticoids, were not restricted between groups in our study, which may also have the ability to block NMDA receptors and thus reduce the differences in recovery quality and analgesic effects between groups.

There are several limitations of our study. First, we excluded subjects with a history of chronic pain or those taking analgesics before surgery as this population would introduce a bias in the assessment of

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**TABLE 3** Postoperative recovery profiles

|                  | Group C (n = 49) | Group K (n = 48) | p value |
|------------------|------------------|------------------|---------|
| **NRS at rest**  |                  |                  |         |
| 4 h              | 2.0 (0.0, 4.0)   | 2.0 (0.0, 4.0)   | .751    |
| 24 h             | 2.0 (2.0, 4.0)   | 2.0 (1.3, 3.0)   | .810    |
| 48 h             | 2.0 (1.0, 3.0)   | 2.0 (0.0, 2.0)   | .701    |
| **NRS when moving** |                |                  |         |
| 4 h              | 3.0 (1.0, 5.0)   | 3.0 (1.3, 4.0)   | .491    |
| 24 h             | 3.0 (2.0, 5.0)   | 3.0 (2.3, 4.8)   | .895    |
| 48 h             | 2.0 (1.0, 3.5)   | 2.0 (2.0, 3.0)   | .795    |
| **ICFS scores**  |                  |                  |         |
| 3 days           | 68.3 (10.8)      | 65.5 (7.9)       | .159    |
| 7 days           | 55.5 (10.1)      | 55.3 (6.6)       | .911    |
| **HADS scores**  |                  |                  |         |
| 2 days           | 3.0 (1.0, 6.0)   | 2.5 (1.0, 5.0)   | .764    |
| 3 months         | 2.0 (0.0, 3.0)   | 2.0 (0.0, 4.0)   | .727    |
| Chronic pain     | 23 (46.9%)       | 27 (56.3%)       | .359    |

Note: Data are presented as mean (SD, standard deviation), median (IQR, interquartile range), or numbers (proportion, %). Abbreviations: HADS, Hospital anxiety and depression scale; ICFS, Identity-consequence fatigue scale; NRS, numeric rating scale.

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**TABLE 4** Perioperative parameters

|                  | Group C (n = 49) | Group K (n = 48) | p value |
|------------------|------------------|------------------|---------|
| **SpO₂ (%)**     |                  |                  |         |
| T1               | 99.0 (1.3)       | 99.2 (1.1)       | .436    |
| T2               | 99.6 (0.6)       | 99.3 (0.9)       | .139    |
| T3               | 97.9 (1.4)       | 97.8 (1.6)       | .888    |
| **HR (beats/min)** |                |                  |         |
| T1               | 62.6 (7.1)       | 62.5 (7.1)       | .939    |
| T2               | 61.0 (6.3)       | 60.7 (4.1)       | .774    |
| T3               | 66.3 (6.7)       | 62.8 (12.7)      | .092    |
| **MAP (mm Hg)**  |                  |                  |         |
| T1               | 87.1 (7.7)       | 87.6 (8.2)       | .727    |
| T2               | 86.8 (7.9)       | 86.6 (6.8)       | .897    |
| T3               | 88.8 (8.6)       | 86.3 (6.0)       | .100    |
| **Propofol consumption (ml·kg⁻¹·min⁻¹)** | 0.069 (0.011) | 0.069 (0.015) | .952    |
| **Remifentanil consumption (ug·kg⁻¹·min⁻¹)** | 0.244 (0.068) | 0.2240 (0.075) | .176 |
| **Emergence time (min)** | 16.3 (5.9) | 16.6 (8.7) | .865 |
| **Duration of PACU stay (min)** | 18.3 (5.0) | 18.2 (4.6) | .848 |

Note: Data are presented as mean (SD, standard deviation). Abbreviations: Emergence time, from discontinuation of anaesthetics to extubation; Group C, control group; Group K, ketamine group; HR, heart rate; MAP, mean arterial blood pressure; PACU, postanaesthetic care unit; SpO₂, peripheral oxygen saturation; T1, 10 min after ketamine infusion; T2, the moment of extubation; T3, 10 min after extubation.

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**TABLE 5** Postoperative safety outcomes

|                  | Group C (n = 49) | Group K (n = 48) | p value |
|------------------|------------------|------------------|---------|
| **Analgesics requirement** | 3 (6.1%) | 2 (4.2%) | 1.000 |
| **Nightmares**   | 1 (2.0%)         | 1 (2.1%)         | 1.000   |
| **Delirium**     | 0 (0%)           | 1 (2.1%)         | 1.000   |
| **Nausea**       | 26 (53.1%)       | 25 (52.1%)       | .838    |
| **Vomiting**     | 14 (28.6%)       | 15 (31.3%)       | .824    |
| **Drowsiness**   | 7 (14.3%)        | 9 (18.8%)        | .584    |

Note: Data are presented as median (IQR, interquartile range) or numbers (proportion, %). Hallucinations and chill are not found in this study. Analgesics refer to flurbiprofen axetil or dezocine. Abbreviations: Group C, control group; Group K, ketamine group.
postoperative recovery quality. A recent study has highlighted a possible role for ketamine in opioid-dependent chronic pain patients. Patients in the ketamine group had significantly reduced postoperative morphine consumption and better outcomes at 6 months, so the effect of ketamine in opioid-dependent patients is worth exploring. Second, we did not perform regional nerve block in both groups. On the one hand, the main purpose of the trial was to observe the effect of ketamine on the total score of QoR40, which involved acute pain as an important component. On the other hand, NAISIDS and other drugs for analgesic remediation were allowed to be used as the rescue of insufficient analgesia effect postoperatively. Third, nevertheless, as the median difference in QoR-40 between the two groups was only 3 and the minimum clinically important difference is at least 6.3, expanding the sample size to observe a greater effect may be worthwhile and should be considered in the future studies. Further studies should evaluate higher doses or extend the administration of ketamine into the recovery period in both male and female patients.

5 | CONCLUSION

In conclusion, based on this study, intravenous low-dose ketamine did not benefit female patients’ overall quality of recovery on POD 1 undergoing breast cancer surgery.

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DISCLOSURES

The authors have declared no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available because of privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher’s website.

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