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ORIGINAL RESEARCH

Effects of S-ketamine on Postoperative Recovery Quality and Inflammatory Response in Patients Undergoing Modified Radical Mastectomy

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ABSTRACT

Introduction: S-ketamine plays an important role in reducing postoperative pain, but its impact on the quality of recovery in breast cancer has not been clarified. We designed this trial to explore the effects of s-ketamine on the quality of postoperative recovery and inflammatory response in modified radical mastectomy.

Methods: A total of 138 patients were randomly assigned to group C (group control), group K1 (group of s-ketamine dose 1) and group K2 (group of s-ketamine dose 2). Groups K1 and K2 were given 0.1 mg/kg, 0.2 mg/kg s-ketamine intravenous (IV) after induction, followed by 0.1 mg/kg/h or 0.2 mg/kg/h continuous intravenous infusion, respectively. Group C received the same volume of saline. A 40-item Quality of Recovery Questionnaire (QoR-40) was used to assess the quality of recovery at 24 h postoperatively. Changes in inflammatory markers, nociceptive thresholds, and the occurrence of adverse events were recorded at 24 h postoperatively.

Results: The QoR-40 scores at 24 h postoperatively were higher in group K2 [182.00 (179.00–185.00)] compared to group K1 [174.00 (169.50–180.50)] and group C [169.00 (163.75–174.25)] (group K2 vs. group K1, $P < 0.001$; group K2 vs. group C, $P < 0.001$). At 24 h postoperatively, the neutrophil count, NLR (neutrophil–lymphocyte ratio), and CRP (C-creative protein) were all significantly lower in group K2 than group C($P < 0.05$), no differences were observed between group K1 and C($P > 0.05$), group K1 and K2($P > 0.05$), respectively. There was no significant difference

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in the incidence of adverse effects among the three groups ($P > 0.05$).
Conclusions: A high dose of s-ketamine improved the quality of recovery at 24 h after surgery, as well as alleviated the inflammatory response without increasing the incidence of adverse effects.

Keywords: Modified radical mastectomy; NLR; QoR-40; S-ketamine

Key Summary Points

The use of anesthetic drugs is related to the quality of postoperative recovery in breast cancer patients.

The objective of this trial was to explore the effect of s-ketamine on the quality of recovery in breast cancer patients.

Intravenous of 0.2 mg/kg after induction of anesthesia, followed by a continuous intraoperative infusion of 0.2 mg/kg/h of s-ketamine, improved the quality of recovery at 24 h after surgery, as well as alleviated the inflammatory response of patients without increasing the incidence of adverse effects.

The effect of s-ketamine in promoting postoperative recovery of breast cancer patients is obvious, which provides a new idea for future clinical work.

INTRODUCTION

In women, breast cancer is one of the most commonly diagnosed cancers and modified radical mastectomy (MRM) is the common surgical procedure used to treat it [1]. However, surgical trauma and postoperative pain can cause large stress and inflammatory response to patients, which can affect their postoperative recovery [2]. Recent studies have reported that the use of anesthetic drugs is also closely related to the quality of postoperative recovery in breast cancer patients [3].

Opioids and nerve blocks are widely used for perioperative pain management in breast surgeries. However, the side effects, such as respiratory depression, opioid tolerance, and opioid-induced hyperalgesia (OIH), can lead to increased consumption of opioids and poor pain control [4]. Activation of the *N*-methyl-D-aspartate (NMDA) receptor system by opioids has been identified as a major cause of OIH [5]. Ketamine has become part of multimodal analgesia by inhibiting NMDA receptors in injurious neurons, activating downstream inhibitory monoaminergic pain pathways, preventing central sensitization, diminishing OIH, and improving postoperative pain in various types of surgery [6–8]. As the right isomer of ketamine, s-ketamine has four times the affinity for NMDA receptors and twice the analgesic effect of ketamine, reducing the incidence of adverse effects [9]. When given as a single bolus or continuous infusion, s-ketamine reduces perioperative opioid consumption, alleviates hyperalgesia, and improves postoperative pain [5, 10, 11]. The analgesic efficacy of s-ketamine is enhanced when the two administrations are combined [12, 13]. Surgical trauma, stress and pain can stimulate the inflammatory system and inflammatory factors also promote hyperalgesia and aggravate the intensity of pain [14]. S-ketamine can alleviate organismal stress, inhibit the release of inflammatory factors, and promote postoperative recovery [15]. In the analysis of Wang et al., the intravenous (IV) dose of s-ketamine ranged from 0.075 to 0.5 mg/kg with an infusion rate of 0.075–0.6 mg/kg/h [16]. In this study, we propose to IV 0.1 mg/kg and 0.2 mg/kg after induction of anesthesia and continuous infusion of 0.1 mg/kg/h and 0.2 mg/kg/h of s-ketamine to explore its function in MRM.

Patient-centered assessment of health status or quality of recovery has gradually become a major endpoint in clinical research [17]. The QoR-40 comprehensively assesses the quality of recovery from five dimensions: physical comfort (12 items), emotional state (nine items), physical independence (five items), psychological support (seven items), and pain (seven

items), and the QoR-40 scale has been proposed as an appropriate measurement of the quality of recovery in a range of clinical and research situations [18]. The neutrophil–lymphocyte ratio (NLR) is a sensitive indicator of the systemic inflammatory response and useful to assess the relationship between inflammatory response and postoperative pain [19].

The effect of s-ketamine on the quality of recovery in breast cancer patients is not clear yet. In this study, the QoR-40 score was used as the primary endpoint and NLR as the secondary endpoint to explore the effects of s-ketamine on the quality of early postoperative recovery and inflammatory response in patients with MRM, providing a reference and new idea for clinical work.

METHODS

The prospective, randomized, double-blinded, placebo-controlled clinical trial was conducted from September 28, 2021 to September 27, 2022. This manuscript adheres to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Compliance with Ethics Guidelines

This study (B2020-244-01) was provided by the Ethical Committee Sun Yat-sen University Cancer Centre, Guangzhou, China. This trial was registered before patient enrollment at the Chinese Clinical Trial Registry (ChiCTR2000034930). Written informed consent was obtained from each subject. This manuscript was conducted in compliance with the Declaration of Helsinki.

Study Population

Inclusion criteria were as follows: patients aged from 18 to 75 years old, classified as American Society of Anesthesiologists (ASA) physical status I or II, female, and scheduled for MRM under general anesthesia. The exclusion criteria were as follows: allergy to drugs in the protocol; co-existing high blood pressure, increased eye pressure, diabetes, cardiovascular disease, psychiatric disease, other malignancies or abnormal liver or kidney function; taking drugs that affect immune function; inflammatory breast cancer; history of breast cancer surgery; radiation or chemotherapy before surgery; BMI $> 30\ kg/m^2$; pregnant or breast-feeding women; usage of pain medications.

Randomization and Preoperative Management

The patients were randomly assigned in a 1:1:1 ratio into one of the three groups according to the computer-generated random sequence with a sealed envelope. A third person not involved in this study opened the envelope and prepared the drug according to the grouping information. The drug was placed in syringes of identical appearance and volume, and marked with the study drug and patient number. The anesthesiologist was required to be independent of the evaluation of efficacy and safety. All subjects and investigators were blinded. The day before the surgery, one of the investigators blinded to the random assignment conducted preoperative visits, including informing the patients of the study protocol, demonstrating how to use the QoR-40 scale and assessing the baseline mechanical pain thresholds.

Anesthesia Protocol

General anesthesia was standardized. Electrocardiogram (ECG), non-invasive blood pressure (NBP), heart rate (HR), pulse oximetry, and Narcotrend (NCT) index were routinely monitored throughout the surgery. Without any premedication, anesthesia was induced with propofol 2 mg/kg, fentanyl 3 μg/kg, and cisatracurium 0.2 mg/kg, followed by continuous infusion of propofol at a dose to maintain a NCT index 35–55 and remifentanil infusion rate is adjusted to maintain NBP and HR within 15% of baseline values. Palonosetron 0.25 mg was administered at induction to prevent postoperative nausea and vomiting (PONV).

- Group C received a bolus of IV 0.9% saline 0.1 ml/kg, followed by 0.9% saline infusion of 0.1 ml/kg/h.
- Group K1 received a bolus of IV s-ketamine 0.1 mg/kg, followed by s-ketamine infusion of 0.1 mg/kg/h.
- Group K2 received a bolus of IV s-ketamine 0.2 mg/kg, followed by s-ketamine infusion of 0.2 mg/kg/h.

When the systolic pressure (SBP) < 80 mmHg or mean arterial pressure (MAP) < 60 mmHg, additional fluid and metaraminol bitartrate (Aramine, 100 ug) were administered. Atropine (0.2 mg) was given in cases of severe bradycardia (HR < 45 bpm). Additional cisatracurium was stopped 45 min before the end of surgery; Approximately 30 min before the anticipated end of surgery, all the patients received a bolus of intravenous flurbiprofen 1 mg/kg and fentanyl 1 ug/kg slowly. The administration of anesthetics was discontinued 5 min before the end of the procedure. All patients were admitted to the postanesthesia care unit (PACU) for observation of resuscitation without antagonists. Patients with numeric rating scales (NRS) $\geq$ 4 were given fentanyl 1.0 ug/kg for additional analgesia. When the Aldrete score reached 9, the patients were discharged to the ward.

Primary End Point

The primary end point was the QoR-40 score at 24 h after surgery (see the Supplementary Table 1).

Second End Points

1. Inflammatory indicators: the neutrophils, lymphocytes, NLR, C-creative protein (CRP) were recorded before the surgery and at 24 h postoperatively.
2. Mechanical pain threshold: one trained investigator used the Electronic von Frey device (IITC Life Science, Woodland Hills, CA) to measure the pain threshold before the surgery and at 24 h postoperatively. On the nonoperative inner forearm, the average of three results at 3, 6, and 9 cm distal to the middle of the antecubital crease was calculated.
3. Perioperative hemodynamic data, amount of propofol, remifentanil, and the administration of rescue analgesics.
4. Postoperative side effects.

Statistical Analysis

SPSS version 25.0 (IBM Corporation, Armonk, NY) was used for statistical analysis. Quantitative variables were presented as the mean ± standard deviation (SD) or median (interquartile range [IQR]), categorical variables were expressed as number (proportion). The Shapiro–Wilk test was applied to assess the normality of the data. To verify the homogeneity of variance, a Levene's test was performed. The data of patients was analyzed by one-way analysis of variance (ANOVA). Pearson's χ^2 test or Fisher's exact test, Kruskal–Wallis test were used to analyze the data of surgery and anesthesia among groups. The scores of QoR-40 were analyzed by Kruskal–Wallis test. Wilcoxon signed-ranks test and Kruskal–Wallis test were used to analyze the inflammatory indicators, pain threshold, and hemodynamic data among or within groups. Incidence of hyperalgesia, rescue analgesics requirement, and postoperative side effects were compared among groups with Pearson's χ^2 test or Fisher's exact test. For pairwise comparisons, Bonferroni-adjusted P value was presented. A statistically significant difference was determined at a P value < 0.05.

In previous research and our pilot study, the global QoR-40 score was 173.9 ± 8.4 on postoperative day (POD) 1 in patients treated with saline after breast cancer surgery [20]. Based on the mean and range of previously reported QoR-40 score for patients after anesthesia and surgery, a 10-point difference represents a clinically relevant improvement in the quality of recovery [21]. The minimal clinically important difference (MCID) for the QoR-40 score was 6.3-point [22]. We assumed a ten-point increase in the global QoR-40 score in group K2 and 6.3-point increase in group K1 at 24 h after surgery, respectively. To detect a significant difference

($\alpha = 0.05$), a sample size of 41 subjects per group with a power of 80% was required. Assuming a dropout rate of 10%, 46 subjects per group were considered for our study.

RESULTS

One hundred and thirty-eight patients were included in this trial, and 46 were randomized into each group. One patient in group K1 was withdrawn due to the change of surgical plan. There were no outcome data, so the patient could not be analyzed. Thus, the data from 137 patients were analyzed (Fig. 1). Table 1 shows the characteristics of the patients, surgery, and anesthesia.

Primary Endpoint

The total QoR-40 scores and the sub-scores of QoR-40 dimensions on POD 1 are presented in Table 2 and Fig. 2.

Compared with group C, the total scores in both group K1 and K2 were significantly improved on POD 1 (group C vs. group K1, $P = 0.003$; group C vs. group K2, $P < 0.001$). The total score was significantly higher in group K2 than group K1 ($P < 0.001$). In the dimension of physical comfort, the scores of group K2 and K1 both were higher than group C ($P < 0.001$), but there was no difference between group K1 and K2 ($P = 0.552$). In terms of emotional status, the score of group K2 was higher than group K1 and group C ($P < 0.001$), no significant difference was observed between group K1 and group C ($P = 0.349$). Regarding physical independence, the score of group K2 was statistically higher than group C ($P = 0.004$), no difference was observed between group K2 and K1 ($P = 0.870$), group K1 and group C ($P = 0.093$). In the dimension of psychological support, both group K2 and K1 scored higher than group C ($P < 0.001$), and group K2 scored higher than group K1 ($P < 0.001$); In terms of pain, scores were significantly higher in group K2 compared to group C and K1 ($P < 0.001$), while there was no significant difference between group C and K1 ($P = 0.108$).

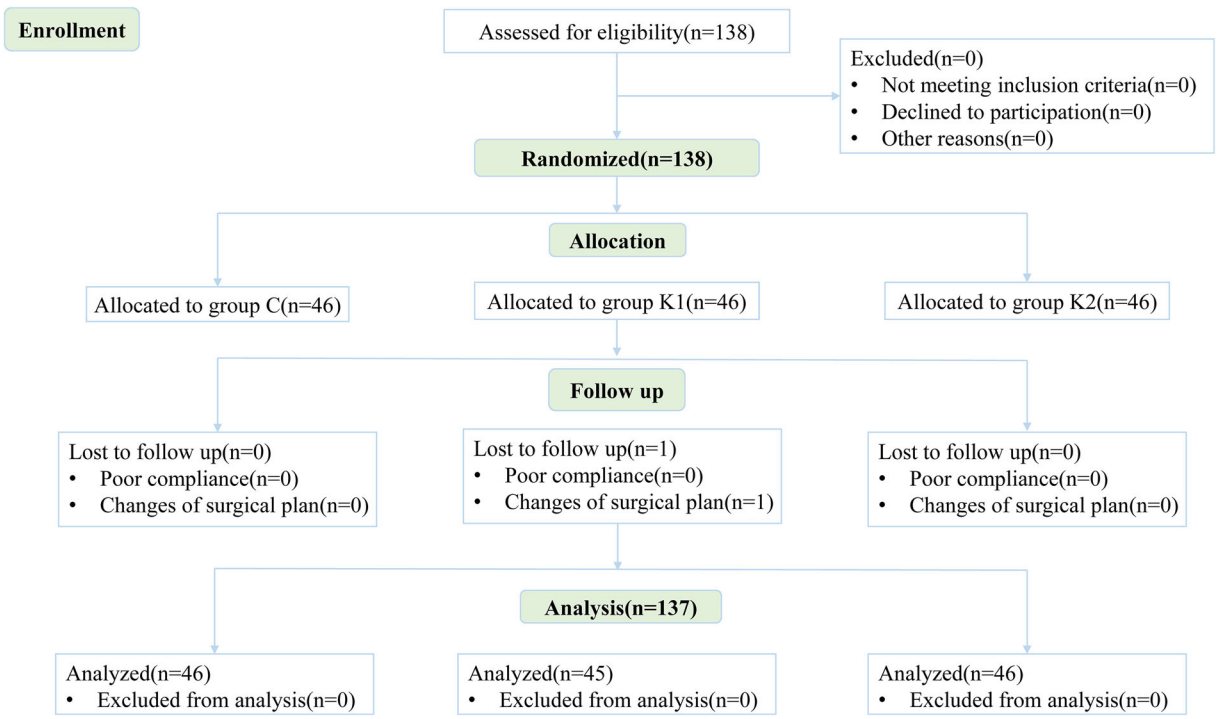

Fig. 1 CONSORT flow diagram

Table 1 Characteristics of patients, surgery, and anesthesia

Variable	Group			*P* value
	C ***n* = 46**	***K*1** ***n* = 45**	***K*2** ***n* = 46**	
Age; years	49.48 ± 6.13	47.27 ± 7.54	47.43 ± 7.30	0.247[a]
Weight; kg	56.87 ± 6.62	57.48 ± 8.17	54.39 ± 7.94	0.124[a]
Height; cm	157.48 ± 5.80	157.40 ± 4.75	156.11 ± 4.36	0.342[a]
BMI; kg/m^2	22.93 ± 2.41	23.20 ± 3.25	22.31 ± 3.11	0.336[a]
Operation side (left/right)	23/23	18/27	20/26	0.621[c]
Patient receiving Aramine; *n*	4 (9%)	1 (2%)	0 (0%)	0.087[d]
Patient receiving Atropine; *n*	2 (4%)	0 (0%)	0 (0%)	0.328[d]
Duration of surgery; min	64 (50–79)	65 (49–76)	59 (47–78)	0.899[b]
Duration of anesthesia; min	87 (70–109)	88 (71–110)	85 (69–104)	0.744[b]
Amount of s-ketamine; mg	0	11.95(10.14–15.52)	23.61(19.17–27.53)	
Amount of fentanyl; mg	0.23 ± 0.03	0.23 ± 0.03	0.22 ± 0.03	0.124[a]
Amount of propofol				
mg	451.36 ± 123.99	498.32 ± 145.65	484.69 ± 172.97	0.304[a]
mg/kg/h	5.28 (4.51–6.10)	5.68 (5.24–6.09)	6.13 (4.95–7.25)*	0.010[b]
Amount of remifentanil				
mg	0.51 ± 0.21	0.59 ± 0.21	0.56 ± 0.26	0.171[a]
ug/kg/min	0.10 (0.08–0.12)	0.11 (0.10–0.12)	0.12 (0.08–0.15)*	0.017[b]
Bleeding; ml	50 (50–50)	50(50–50)	50(50–50)	0.315[b]
Total volume of fluid; ml	1000 (1000–1000)	1000 (750–1000)	1000 (500–1000)	0.205[b]
Extubation time; min	20 (10–27)	17 (11–30)	15 (10–25)	0.719[b]
PACU stay duration; min	37 (30–45)	40 (30–50)	33 (25–53)	0.099[b]
Hospital stay duration; day	5 (3–6)	6 (3–7)	5 (3–7)	0.641[b]

Values are mean ± SD, numbers of patients, number (proportion), or median (IQR)
BMI body mass index, *PACU* post-anesthesia care unit, *SD* standard deviation, *IQR* interquartile range, *ANOVA* analysis of variance
*$P < 0.05$ versus group C
[a]One-way ANOVA
[b]Kruskal–Wallis test
[c]Pearson's χ^2 test
[d]Fisher's exact test

Table 2 The total QoR-40 scores and the sub-scores of QoR-40 on POD 1

Variable	Group			*P* value
	C *n* = 46	*K*1 *n* = 45	*K*2 *n* = 46	
Total	169.00 (163.75–174.25)	174.00 (169.50–180.50)*	182.00 (179.00–185.00)*†	< 0.001[a]
Physical comfort	51.00 (48.00–52.25)	53.00 (51.00–56.50)*	54.00 (53.00–55.25)*	< 0.001[a]
Emotional status	40.00 (38.00–40.25)	39.00 (38.50–40.00)	41.00 (40.00–42.00)*†	< 0.001[a]
Physical independence	20.00 (16.00–22.00)	21.00 (19.00–22.00)	22.00 (20.00–22.00)*	0.004[a]
Psychological support	31.00 (31.00–31.00)	32.00 (32.00–32.00)*	34.00 (34.00–34.00)*†	< 0.001[a]
Pain	29.00 (28.00–30.00)	30.00 (28.50–0.00)	32.00 (31.00–33.00)*†	< 0.001[a]

Values are median (IQR)
POD post-operative day, *IQR* interquartile range
*$P < 0.05$ vs. group C
†$P < 0.05$ vs. group K1
[a]Kruskal–Wallis test

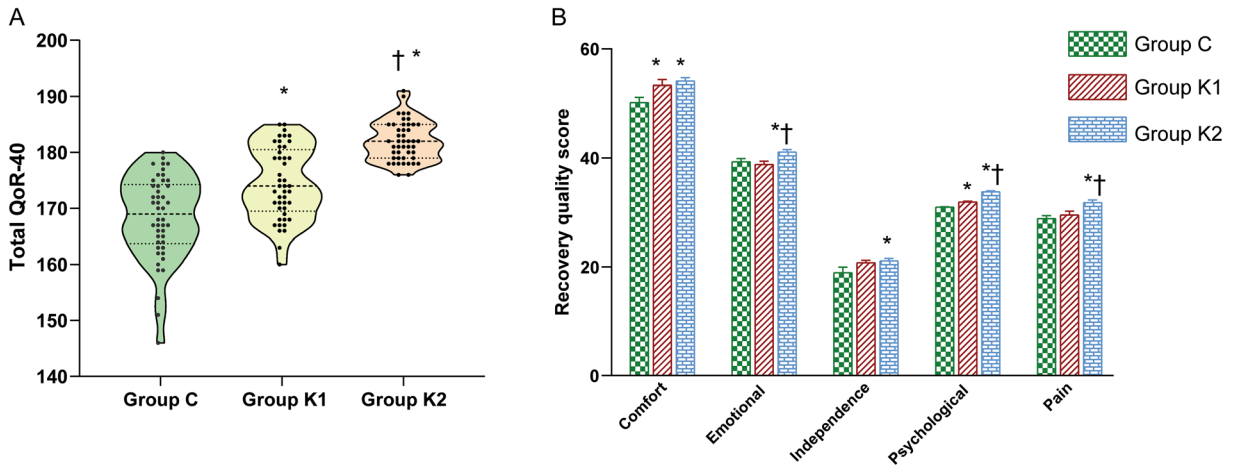

Fig. 2 The total QoR-40 scores (**A**) and sub-scores (**B**) on the POD 1. The scores are shown as median (IQR), and were analyzed with Kruskal–Wallis tests followed by Bonferroni post hoc comparison. *$P < 0.05$ vs. group C; †$P < 0.05$ vs. group K1. *IQR* interquartile range, *POD* post-operative day

Secondary Endpoint

Inflammatory Indicators

The inflammatory indexes of the three groups are presented in Table 3. Neutrophils, NLR, and CRP were significantly higher ($P < 0.001$) and lymphocyte counts were lower ($P < 0.001$) in all three groups on POD1 compared to preoperatively. The neutrophil count was significantly lower in group K2 than group C postoperatively ($P = 0.003$), however, there was no statistical difference between group C and K1, group K1 and K2 ($P > 0.05$). NLR on POD1 was significantly lower in group K2 than in group C ($P = 0.022$), but no difference was observed between group K2 and K1 ($P = 0.316$), group K1 and group C ($P = 0.896$). Compared with group C, CRP was significantly lower in group K2 at 24 h postoperatively ($P = 0.042$), however, there was no statistical difference in CRP between

Table 3 Inflammatory indicators

Variable/time points	Group			*P* value
	C *n* = 46	*K*1 *n* = 45	*K*2 *n* = 46	
Neutrophils (10E9/l)				
Before surgery	3.11 (2.79–4.51)	3.56 (3.05–4.43)	3.71 (2.98–4.48)	0.392[a]
POD1	10.72 (8.32–12.94)[†]	10.12 (7.87–12.24)[†]	8.65 (7.93–9.74)*[†]	0.004[a]
Lymphocytes (10E9/l)				
Before surgery	1.62 (1.41–1.91)	1.67 (1.29–2.22)	1.60 (1.36–1.94)	0.692[a]
POD1	1.20 (0.98–1.46)[†]	1.25 (0.96–1.75)[†]	1.30 (1.00–1.68)[†]	0.747[a]
NLR				
Before surgery	2.72 (1.62–2.90)	2.10 (1.54–2.71)	2.35 (1.68–3.27)	0.644[a]
POD1	8.75 (6.47–12.10)[†]	7.71 (5.01–12.39)[†]	6.64 (4.91–8.23)*[†]	0.026[a]
CRP (mg/l)				
Before surgery	1.03 (0.36–2.27)	1.19 (0.44–2.18)	1.18 (0.48–2.52)	0.732[a]
POD1	13.58 (8.15–29.81)[†]	11.40 (5.27–28.85)[†]	10.40 (5.04–15.03)*[†]	0.047[a]

Values are median (IQR)

NLR neutrophil–lymphocyte ratio, *CRP* C-creative protein, *POD* post-operative day, *IQR* interquartile range

*$P < 0.05$ vs. group C

†$P < 0.05$ vs. pre-operative

[a]Kruskal–Wallis test

group K2 and K1 ($P = 0.432$), group K1 and C ($P = 0.981$), respectively.

Mechanical Pain Threshold

The mechanical pain thresholds of the three groups are presented in Table 4. Compared with group C, mechanical pain thresholds were significantly higher in groups K1 and K2 respectively ($P < 0.05$), but no difference was found between group K1 and K2 on POD1 ($P > 0.999$). Only patients in group C ($P = 0.003$) had a significant decrease in mechanical pain threshold at 24 h postoperatively compared with preoperatively, and there was no statistical difference in group K1 ($P = 0.243$) and K2 ($P = 0.638$) compared with preoperatively. The incidence of hyperalgesia was significantly lower in group K2 compared with group C ($P = 0.032$), whereas there was no difference between group K1 and group C, as well as between group K1 and group K2 ($P > 0.05$).

Hemodynamic Data

There were no significant differences in MAP, HR among the three groups at baseline (T0), 20 min after the beginning of surgery (T1), skin closure (T2), extubation (T3), and leaving the PACU (T4); detailed in Fig. 3.

Postoperative Side Effects

No significant difference among the groups was found in postoperative side effects, as shown in Table 5.

DISCUSSION

In this randomized, double-blind, and placebo-controlled study, a single IV of 0.2 mg/kg after

Table 4 Mechanical pain threshold of the nonoperative forearm

Variable/time points	Group			*P* value
	C *n* = 46	*K*1 *n* = 45	*K*2 *n* = 46	
Mechanical pain threshold				
Before surgery	90.02 (82.40–115.33)	103.43 (79.77–127.78)	96.82 (81.45–119.82)	0.498[a]
POD1	86.78 (72.74–99.65)[†]	94.13 (87.85–112.30)*	99.82 (84.04–108.68)*	0.015[a]
Incidence of hyperalgesia	35 (76%)	26 (58%)	23 (50%)*	0.031[b]

Values are median (IQR) or number (proportion)
POD post-operative day, *IQR* interquartile range
*$P < 0.05$ versus group C
†$P < 0.05$ versus pre-operative (Wilcoxon signed-ranks test)
[a]Kruskal–Wallis test
[b]Pearson's χ^2 test

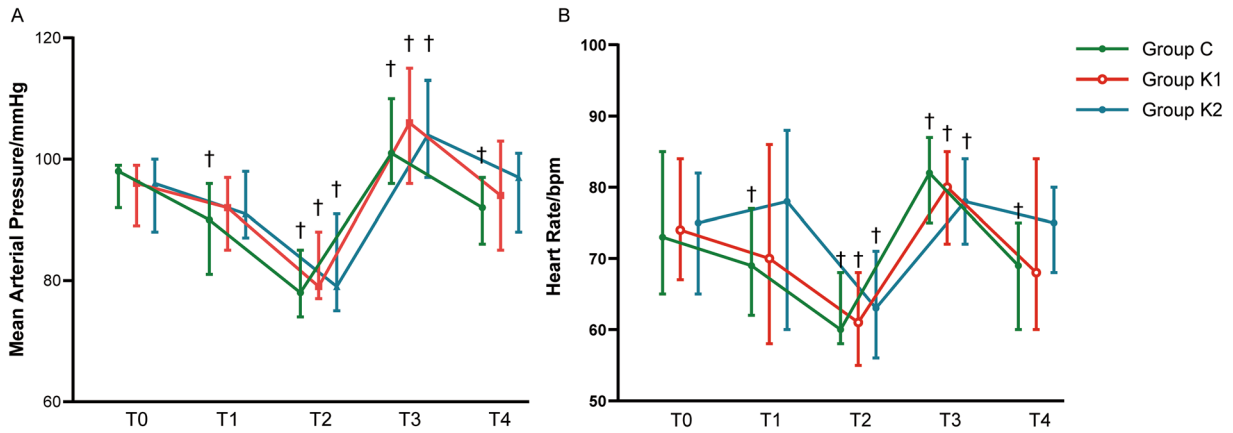

Fig. 3 The MAP for the three groups in the perioperative period is detailed in **A** and the HR is detailed in **B**. T0, baseline; T1, 20 min after the beginning of surgery; T2, skin closure; T3, extubation; T4, leaving the PACU; †$P < 0.05$ vs. T0 (Wilcoxon signed-rank test)

induction of anesthesia, followed by a continuous intraoperative infusion of 0.2 mg/kg/h of s-ketamine improved the quality of recovery at 24 h after surgery, as well as alleviated the inflammatory response of patients without increasing the incidence of adverse effects.

In this study, the mechanical pain threshold of the non-operative forearm was significantly lower in group C at 24 h postoperatively compared to the preoperative period, which could be considered as hyperalgesia; While the threshold of mechanical pain was not changed in group K1 and K2 compared to the preoperative period, and both were higher than group C. Meanwhile, the incidence of hyperalgesia was significantly lower in group K2 than group C, which are related to the attenuated central sensitization and anti-hyperalgesic effects of s-ketamine [23, 24]. Previous studies found that IV 0.5 mg/kg after induction of anesthesia followed by continuous infusion of 0.12, 0.3, and 0.5 mg/kg/h of s-ketamine alleviated hyperalgesia and improved postoperative pain in patients [8, 12, 25]. In this study, a single IV after induction followed by continuous intraoperative infusion of s-ketamine was

Table 5 Postoperative side effects

Variable	Group			*P* value
	C *n* = 46	*K*1 *n* = 45	*K*2 *n* = 46	
Dizziness	5 (11%)	2 (4%)	2 (4%)	0.507[a]
Drowsiness	3 (6%)	1 (2%)	1 (2%)	0.619[a]
PONV	7 (15%)	3 (7%)	3 (6%)	0.298[a]
Shivering	2 (4%)	2 (4%)	4 (9%)	0.730[a]
Pruritus	1 (2%)	2 (4%)	3 (6%)	0.699[a]
Respiratory depression	0 (0%)	0 (0%)	0 (0%)	> 0.999[a]
Delirium	0 (0%)	0 (0%)	0 (0%)	> 0.999[a]
Patients receiving rescue analgesics	5 (11%)	3 (7%)	2 (4%)	0.515[a]

Values are number (proportion)
PONV postoperative nausea and vomiting
[a]Fisher's exact test

taken, and the QoR-40 score in group K2 reached 182.0 on POD1, 174.0 in group K1 and 169.0 in group C. Simultaneously, in the dimension of pain, the group K2 scored higher than group K1 and group C. This indicates that s-ketamine may improve the quality of recovery by relieving hyperalgesia and alleviating postoperative pain. Not only is the quality of postoperative recovery related to pain control, but physical comfort and emotional state can also affect postoperative recovery. Women with cervical cancer, breast cancer and other malignancies are at higher risk of depression, about 20–45% of breast cancer patients experience post-operative depression [26]. Postoperative depression can lead to additional emotions and cognitive deficits, change pain thresholds, and impair patients' recovering and quality of life after surgery [10, 27]. A meta-analysis showed that ketamine exerts antidepressant effects within a few hours and the effects last up to 7 days [28]. The antidepressant effect of s-ketamine is superior to ketamine, and the clearance rate is higher and better tolerated [29]. A single IV 0.25 mg/kg of s-ketamine with antidepressant effect can last 3 days after surgery [10]. In our study, patients in group K2 had higher scores on the emotional state, physical comfort, and psychological support than group C on POD1, suggesting that s-ketamine may also improve patients' postoperative emotions and enhance the quality of recovery due to its antidepressant effect.

Inflammatory factors can indirectly modulate pain, leading to peripheral and central hyperesthesia and affecting the quality of the recovery [15]. Some studies have shown that intraoperative intravenous lidocaine and dexamethasone can attenuate the postoperative inflammatory response of patients, thus improving the quality of recovery [30, 31]. Administration of ketamine at 0.25 mg/kg and 0.5 mg/kg diminishes the release of inflammatory factors and decreased CRP in patients on POD1 [32]. Welters et al. found that a single IV after induction combined with intraoperative infusion of s-ketamine attenuated inflammatory level after surgery [33]. Compared with the preoperative period, the three groups in this study showed obvious inflammatory reactions after the operation. Among them, patients in group K2 had apparently reduced inflammatory response and their recovery quality was improved compared with group C, suggesting that the improvement of recovery quality may

be related to the anti-inflammatory effect of s-ketamine.

In this study, the average speed of propofol and remifentanil were higher in group K2 than group C, but the total amount consumed was not statistically distinct. First, we considered this may be the result of the effect of s-ketamine on the EEG (electroencephalogram). Ketamine decreases alpha wave amplitude and increases theta wave amplitude, causing an incompatible increase in BIS (bispectral index) values with depth of anesthesia [34, 35]. Hirota et al. found that ketamine at 0.4 mg/kg elevated the BIS value, while Faraoni et al. showed no effect of ketamine at 0.2 mg/kg on the BIS value [36, 37]. Narcotrend was used to monitor the depth of anesthesia in this study because of adequate correlation and comparability between NCT index and BIS [38]. EEG index can influence the administration of anesthetic drugs under EEG monitoring by elevated EEG index [35]. So the infusion speed of propofol was adjusted timely to maintain NCT at 35–55. Considering that s-ketamine is twice as effective as ketamine, it is consistent with the findings of Hirota and Faraoni in our study. Secondly, it may be related to the sympathomimetic effect of s-ketamine [29, 39]. It was demonstrated that IV 0.5–1.0 mg/kg ketamine can cause temporary tachycardia and higher blood pressure [40]. Naturally, the remifentanil infusion rate is adjusted promptly to maintain NBP and HR within 15% of baseline values. In our study, there was no statistical difference in MAP and HR within the normal range among the three groups. Thus, these factures may result in a high average speed, but no difference in total consumption. Previous studies have indicated that propofol combined with remifentanil may attenuate stress and alleviate the inflammatory response [14]. In our study, the total amount of propofol and remifentanil was not statistically distinct. It makes the results of this study more convincing and further suggests that s-ketamine play important roles in relieving pain, alleviating inflammation, and promoting recovery.

In a multicenter clinical study by Avidan et al., the incidence of postoperative hallucinations and nightmares increased with increasing doses of ketamine; and the incidence of postoperative delirium and PONV was not decreased [41]. There was no obvious difference in the occurrence of postoperative delirium, PONV, hallucinations, and nightmares among the three groups in this study. This may be attributed to the fact that the subjects in this study were comparatively young, and different anesthetic combinations and types of surgery could have produced different results.

There are still limitations in this study. First, this study is a single-center clinical study, and the results need to be confirmed by a larger sample of multicenter studies. Secondly, assessment can be performed within 24 h, or more than POD1. Finally, interleukin or tumor cell necrosis factor may be preferable to assess the inflammatory response.

CONCLUSIONS

Intravenous of 0.2 mg/kg after induction of anesthesia followed by intraoperative continuous infusion of 0.2 mg/kg/h of s-ketamine was effective in improving the quality of recovery and alleviating the inflammatory response in patients undergoing modified radical mastectomy for 24 h after surgery without increasing the incidence of adverse effects.

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Compliance with Ethics Guidelines. This study (B2020-244-01) was provided by the Ethical Committee Sun Yat-sen University Cancer Centre, Guangzhou, China. This trial was registered before patient enrollment at the Chinese Clinical Trial Registry (ChiCTR2000034930). Written informed consent was obtained from each subject. This manuscript was conducted in compliance with the Declaration of Helsinki.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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