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Effect of esketamine combined with serratus anterior plane block on postoperative analgesia after modified radical mastectomy for breast cancer

CONG Wenbo*, ZHU Wei, ZHONG Mingjie, SHEN Shuai, SUN Yue

**Department of Anesthesiology and Periorperative Medicine, Suqian First Hospital Affiliated to Nanjing Medical University, Suqian, Jiangsu 223800, China*

Corresponding author: ZHU Wei, E-mail: zhuweijsph@ 163.com

Abstract: Objective To explore the effects of esketamine combined with serratus anterior plane block (SAPB) on postoperative analgesia, anxiety and depression in patients with breast cancer undergoing modified radical mastectomy. depression in patients with breast cancer undergoing modified radical mastectomy. **Methods** From January 2023 to January 2024, 96 patients with breast cancer underwent modified radical mastectomy in Suqian First Hospital were selected and randomly divide into three groups (n=32): esketamine combined with SAPB group (KS group), SAPB group (S group), and blank control group (C group). The KS group underwent SABP on the affected side after induction of general anesthesia, 0.25 mg/kg of esketamine was slowly injected intravenously before skin incision, with a continuous flow of 0.25 mg/kg of esketamine. The KS group underwent SABP on the affected side after induction of general anesthesia, 0.25 mg/kg of esketamine was slowly injected intravenously before skin incision, with a continuous infusion dose of 0.12 mg· kg^{-1}·h^{-1} during surgery. The medication was stopped 30 minutes before the end of the surgery; S group SABP on the affected side after induction of general anesthesia; C group received general anesthesia. The S group and C group were given the same dose of physiological saline to the KS group after anesthesia induction and during surgery. The resting/exercise visual analogue scale (VAS) scores of patients at 2, 6, 12, 24 hours post-surgery and the Hospital Anxiety and Depression Scale (HADS) for patients 1 day before surgery, 3 days after surgery, and 1 week after surgery were recorded. The number of compressions of the analgesic pump and the occurrence of adverse reactions within 48 hours after surgery were compared. The number of compressions of the analgesic pump and the occurrence of adverse reactions within 48 hours after surgery were compared. **Results** Compared with C group, KS and S groups had lower resting/exercise VAS scores at 6 and 12 hours postoperatively, and fewer number of compressions of the analgesic pump within 48 hours postoperatively (P<0.05). Compared with group C and S, the KS group had lower VAS exercise scores at 12 hours post-surgery and HADS scores at 3 days and 1-week post- surgery (P<0.05), as well as a lower incidence of insomnia within 48 hours post-surgery (KS group 0, S group 19.4%, C group 22.6%, P<0.05). However, there was no statistically significant incidence of adverse reactions among three groups (P>0.05). **Conclusion** In the modified radical mastectomy for breast cancer, esketamine combined with SAPB can reduce the acute postoperative pain, alleviate the anxiety and depression of patients, and do not increase the adverse reactions after the operation.

Keywords: Esketamine; Serratus anterior plane block; Anesthesia; Breast cancer; Anxiety; Depression

According to the latest data, breast cancer ranks first in the incidence of female malignant tumors in China[1]. Surgical excision is the primary treatment, and modified radical mastectomy for breast cancer is currently the most commonly used surgical procedure. Modified radical mastectomy for breast cancer involves the breast and axillary region, which can cause significant acute pain, with 19.5% to 21.0% of patients experiencing persistent moderate to severe pain[2-4]. Patients are highly susceptible to negative emotions such as anxiety and depression without adequate pain relief, which, in turn, affects the quality of life. Esketamine is a new type of antidepressant with few adverse effects, good tolerability, and low addictiveness. A single infusion can reduce the degree of depression in patients with bipolar disorder[5]. Esketamine also has good analgesic effects and can reduce the dosage of perioperative opioids and non-steroidal anti-inflammatory drugs (NSAIDs) and the adverse effects caused by them[6]. With the gradual popularization of multimodal analgesia, ultrasound-guided nerve block is widely used in clinical practice. The serratus anterior plane block (SAPB) mainly blocks the lateral cutaneous branch of the ipsilateral second to sixth intercostal nerves, the long thoracic and thoracic dorsal nerves, and it can provide good analgesia for modified radical mastectomy.

Moreover, the rib cage is used as the localization for the SAPB, and the puncture position is tabulated. As a localization, SAPB has the advantages of having a superficial puncture location and a high safety factor[7-8]. This study aims to investigate the effects of esketamine combined with SAPB on postoperative analgesia and mood in patients undergoing modified radical mastectomy with general anesthesia.

1 Information and methodology

1.1 General information

This study was approved by the Ethics Committee of the hospital (20230101), and an informed consent form was signed by the patients and their families before surgery. Patients of the First People's Hospital of Suqian City who underwent elective modified radical mastectomy for breast cancer under general anesthesia from January 2023 to January 2024, aged 18-65 years old, American Society of Anesthesiologists (ASA) class I-II, body mass index (BMI) 19-28 kg/m^2 were selected.

Exclusion criteria:

(1) contraindications to the use of esketamine (hyperthyroidism, allergy, etc.);
(2) history of severe cardiovascular disease, chest surgery, alcohol abuse, psychiatric disorders;
(3) history of opioid or other addictive drug abuse;
(4) recent use of antidepressants or β-receptor antagonists;
(5) allergy to the use of drugs in the perioperative period;
(6) inability to read and write Chinese, hearing impairment, and communication difficulties;
(7) incomplete clinical data and refusal to participate in the study.

Elimination criteria:

(1) intraoperative pathological findings of benign lesions;
(2) intraoperative knowledge;
(3) massive intraoperative bleeding;
(4) unplanned postoperative admission to the ICU;
(5) unconsciousness or death during the follow-up period;
(6) reoperation during the follow-up period;
(7) patients or clients requesting to withdraw from the study during the follow-up period;
(8) failure of nerve block.

1.2 Sample size

The sample size was estimated using G*Power 3.1 software. According to the results of the pre-test, the test level α=0.05, the test efficacy 1-β=0.9, and the mean anxiety score by the hospital anxiety and depression scale (HADS) in esketamine combined with SAPB group (KS group) was (6.54±2.26), in SAPB group (S group) was (8.12±2.47), and in blank control group (C group) was (8.84±3.33) 1 week after surgery. The two-sided test was used to determine the minimum sample size of each group, which was 26 patients. Considering a 20% loss to follow-up rate, the final number of patients to be included in this study was 96, with 32 patients in each group.

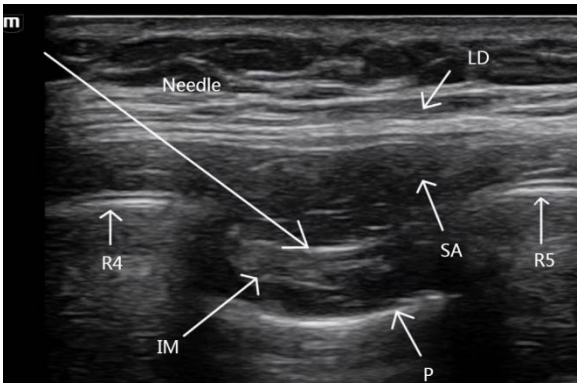
1.3 Grouping and intervention

The random number table method was used; the 96 patients were randomly divided into esketamine combined with the KS, S, and C groups, each with 32 cases. Among them, one patient in group S with intraoperative rapid pathology was benign, and one patient in group C with intraoperative hemorrhage >500 ml was excluded. Thus, the study was finally completed with 94 patients: 32 in group KS, 31 in group S, and 31 in group C. There was no statistically significant difference in age, gender, height, weight, BMI, ASA classification, and operation time among the three groups (P>0.05). **[Table 1]**

In the KS group, after the induction of general anesthesia, the patient's upper arm on the affected side was abducted and, the elbow was flexed, and the operator wore sterile gloves. After disinfecting the skin at the puncture site with iodine vapors, a sterile towel was spread, the ultrasound probe with a sterile luminal sleeve was wrapped, and a Mylab Alpha model ultrasound instrument (Esaote, Italy) with a 5-13 MHz high-frequency probe was used under the guidance of the axillary midline fifth intercostal space. Adjusting the probe angle, gain and other parameters, identifying the latissimus dorsi and serratus anterior muscle, and using the in-plane approach to puncture, when the tip of the needle reaches the deep layer of the serratus anterior muscle **[Figure 1]**, the serratus anterior interspace was confirmed by injecting physiological saline, and after no blood was withdrawn, 20 mL of 0.375% ropivacaine (ropivacaine hydrochloride injection, 10 ml:75 mg, Zhejiang Xianju Pharmaceutical Co., Ltd., batch No.: EE2252) was injected. After the nerve block was completed, general anesthesia was administered, and a slow intravenous injection of 0.25 mg/kg esketamine (esketamine hydrochloride injection, 2 ml:50 mg, Jiangsu Hengrui Pharmaceuticals Co., Ltd., batch No.: 221018BL) was administered before skin incision. The intraoperative continuous pumping dose was 0.12 mg • kg^{-1} • h^{-1}, and SAPB was performed on the affected side in group S after induction of general anesthesia. Only general anesthesia was administered in group C. Groups S and C were given the same dose of saline as group KS after induction of anesthesia and intraoperatively.

Tab. 1 Comparison of general data among three groups ($\bar{x}\pm s$)

Group	Case	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	Surgical time (min)
Group KS	32	47.38±6.03	157.81±1.69	57.50±1.76	23.06±0.89	127.19±5.18
Group S	31	50.06±5.54	157.61±1.58	57.68±1.66	23.19±0.90	127.16±4.95
Group C	31	49.03±5.90	156.97±1.80	57.39±1.86	23.26±0.93	128.68±4.40
F value		1.709	2.126	0.214	0.403	0.994
P value		0.187	0.125	0.808	0.669	0.374



Note:R is rib; IM is intercostal muscle; P is pleura; SA is serratus anterior; LD is latissimus dorsi muscle.

Fig.1 Ultrasoundgraphic images of serratus anterior plane

1.4 Anesthesia methods

The patients were routinely fasted for 8 hours before surgery and forbidden to drink for 4 hours. After entering the room, the peripheral venous access was opened, electrocardiogram (ECG), blood pressure (BP), pulse oximetry (SpO_2), and heart rate (HR) were routinely monitored, and radial arteries of the healthy side were punctured for tubing placement, and systolic blood pressure (SBP) was continuously monitored. The Anesthesia method was selected as static-aspiration compound anesthesia, anesthesia induction: preoxygenation for 5 min, according to the defatted body weight, three groups were given injections of sufentanil 0.5 μg/kg, etomidate injection 0.3 mg/kg, cis-atracurium 0.2 mg/kg, midazolam 0.05 mg/kg, and the appropriate type of airway tube was inserted through the mouth, mechanical ventilation was carried out, the setting of the tidal volume of 6-8 ml/kg, the ventilation The frequency was 10-14 times/min, the inspiratory/expiratory ratio was 1:2, the inhalation oxygen flow rate was 2 L/min, and the ETCO2 was maintained at 35-45 mmHg. Anesthesia maintenance: 0.3 $ug \cdot kg^{-1} \cdot min^{-1}$ remifentanil, 4-12 $mg \cdot kg^{-1} \cdot h^{-1}$ propofol and 0.1 $mg \cdot kg^{-1} \cdot h^{-1}$ cis-atracurium. Intraoperative rehydration volume and rehydration scheme were performed in accordance with the rule of 421. Adjustments were made for changes in SBP of no more than 30 % of the basal value. A total of 8 mg intravenous ondansetron was administered at the beginning of skin suturing, and all medications were stopped 10 min before the end of the procedure. In all three groups, the electronic analgesic pump was opened for intravenous self-controlled analgesia (PCIA) within 30 min after the operation, with the following formula: sufentanil of 2 μg/kg + ondansetron of 8 mg + 0.9 % saline to 100 ml, with a background dose of 2.0 mL/h, bolus of 1.5 ml, and a locking time of 15 min. When the patients in all three groups had VAS scores of ≥ 4, they pressed the PCIA self-control button and observed for 10 min; if the pain could not be relieved, 2 mg oxycodone was slowly pushed intravenously.

1.5 Observing indexes

(1) The resting/active visual analogue scale (VAS) scores were recorded at 2, 6, 12, and 24 hour after the end of surgery. (2) The same trained nurse assessed the patient's anxiety and depression by using the HADS 1 day before surgery, 3 days after surgery, and 1 week after surgery. The HADS consists of two parts, anxiety (HADS-A) and depression (HADS-D), with seven questions each. Each option is scored as 0, 1, 2, or 3 points, with a total of 21 points, and a score of >8 points is considered anxiety or depression. The higher the score, the worse the anxiety or depression[9]. (3) The number of analgesic pump presses and the incidence of adverse reactions were evaluated for 48 hours postoperatively.

1.6 Statistical methods

SPSS 26.0 software was used to analyze the data. Measurement information was subjected to Kolmogorov-Smirnov test, and did not coincided with normal distribution was expressed by M (P_{25}, P_{75}), and comparisons between multiple groups were made by Kruskal-Wallis H rank sum test, and two-by-two comparisons between groups were made by Bonferroni method of more positive; measurement information conforming to the normal distribution was expressed by $\bar{x}\pm s$, and comparisons between three groups were made by one-way ANOVA or ANOVA for repeated measures information, and two-by-two comparisons were made using the LSD-t test. Count data were expressed as cases (%), and the differences between groups were compared using the χ^2 test or Fisher's exact test. All were two-sided tests, and $P<0.05$ was considered a statistically significant difference.

2 Results

2.1 Resting/exercise VAS scores

The KS and S groups had lower resting/exercise VAS scores than the C group at 6 and 12 h postoperatively, and the difference was statistically significant ($P<0.05$). The KS group's postoperatively 12-hour exercise VAS score was lower than that of the C and S groups ($P<0.05$); and the difference in the 3 groups' postoperatively 2-hour and 24-hour resting/exercise VAS scores was not statistically significant ($P>0.05$). **[Table 2]**

2.2 HADS scores

HADS scores of group KS were lower than those of groups S and C at postoperative day 3 and postoperative week 1 ($P < 0.05$). The differences in HADS-A and HADS-D scores among the three groups at preoperative day 1 were not statistically significant ($P > 0.05$). **[Table 3]**

Tab.2 Comparison of VAS scores among three groups after rest and exercise (point, $\bar{x}\pm s$)

Groups	Case	Resting state (physics)				Exercise state			
		Postoperative 2 hours	Postoperative 6 hours	Postoperative 12 hours	Postoperative 24 hours	Postoperative 2 hours	Postoperative 6 hours	Postoperative 12 hours	Postoperative 24 hours
Group KS	32	1.13±0.71	1.47±0.51[a]	2.03±0.78[a]	3.81±1.09	1.53±0.51	2.41±0.50[a]	2.81±0.64[ab]	5.66±1.23
Group S	31	1.35±0.55	1.61±0.50[a]	2.03±0.71[a]	3.55±1.18	1.61±0.50	2.48±0.51[a]	3.61±0.95[a]	5.87±1.36
Group C	31	1.42±0.50	2.58±0.81	3.84±0.69	4.16±0.78	1.68±0.48	3.77±0.88	5.74±0.93	6.00±0.89
$F/P_{(group)}$ Value		34.902/<0.001				42.836/<0.001			
$F/P_{(time)}$ Value		159.939/<0.001				388.283/<0.001			
$F/P_{(interaction)}$ Value		11.452/<0.001				18.046/<0.001			

Note:[a] P<0.05 compared with group C;[b] P<0.05 compared with group S.

Tab.3 Comparison of HADS scores among three groups in different time points (point, $\bar{x}\pm s$)

Groups	Case	HADS-A scores			HADS-D score		
		Postoperative 1 day	Postoperative 3 days	Postoperative 1 week	Postoperative 1 day	Postoperative 3 days	Postoperative 1 week
Group KS	32	9.00±3.29	6.63±2.30[ab]	6.53±2.46[ab]	6.47±2.54	7.06±2.76[ab]	5.97±1.93[ab]
Group S	31	8.84±3.39	9.19±3.27	8.52±2.87	7.58±2.96	9.29±2.97	8.87±3.16
Group C	31	8.71±3.41	9.10±3.59	9.19±3.17	7.13±2.75	8.84±2.71	8.87±2.94
$F/P_{(group)}$ Value		3742/0.027			8.222/0.001		
$F/P_{(time)}$ Value		2.500/0.088			10.344/<0.001		
$F/P_{(interaction)}$ Value		4.520/0.002			2.716/0.031		

Note:a P<0.05 compared with group C;b P<0.05 compared with group S.

2.3 Number of analgesic pump presses at 48 hour postoperatively

The number of analgesic pump presses at 48 hour postoperatively in patients of groups KS, S and C were 1 (1, 2), 1 (1, 2) and 3 (1,4), respectively, and the difference between the three groups was statistically significant (H=16.974, P<0.01). A two-by-two comparison showed that the number of analgesic pump presses in groups KS and S was significantly lower than group C (P<0.05).

2.4 Incidence of adverse reactions in the 48 hour-postoperative period

The prevalance of insomnia in the KS group was lower than that in the S and C groups among the postoperative adverse reactions (P<0.05), and the difference was statistically significant.There was no statistically significant difference in the comparison of other adverse reactions (P>0.05). **[Table 4]**

Tab.4 Comparison of adverse reactions among three groups within 48 hours after surgery [case (%)]

Groups	Case	Nausea and vomiting	Respiratory depression	Suffer from insomnia	Cognitive impairment
Group KS	32	6 (18.8%)	1 (3.1%)	0[ab]	1 (3.1%)
Group S	31	6 (19.4%)	0	6 (19.4%)	0
Group C	31	7 (22.6%)	0	7 (22.6%)	0
χ^2 value		0.946			
P value		0.623	>0.999	0.008	>0.999

Note: [a] P<0.05 compared with Group C;[b] P<0.05 compared with Group S;[c] using Fisher's exact test.

3 Discussion

Modified radical mastectomy for breast cancer has a wide range of incisions, is highly traumatic, and involves mastectomy and axillary lymph node dissection, which can damage part of the cutaneous nerves, as well as postoperative negative pressure suction of the wound, compression bandage, hematoma and fluid accumulation compression and stimulation of the nerves leading to moderate or severe pain in this type of surgery. Patients undergoing modified radical mastectomy for breast cancer are prone to negative emotions such as anxiety and depression as they have to overcome the fear of cancer during treatment, as well as physiological changes brought about by changes in the appearance of the breast and postoperative pain stimulation. In this study, esketamine combined with SAPB was applied during general anesthesia surgery in patients undergoing modified radical mastectomy for breast cancer in order to prevent central sensitization, reduce opioid tolerance, alleviate postoperative pain, and alleviate patients' postoperative anxiety and depression. The results showed that patients' postoperative pain was effectively alleviated, postoperative anxiety and depression were improved, and the incidence of postoperative insomnia could be reduced without increasing the nausea and vomiting, and other adverse reactions The results showed that the patients' postoperative pain was effectively relieved and postoperative anxiety and depression were improved.

Opioids are widely used for intraoperative and postoperative analgesia. However, high doses of opioids

can lead to acute tolerance and induction of nociceptive hypersensitivity[10]. They can also lead to nausea and vomiting, respiratory depression, and other adverse effects in patients. Therefore, this study chose esketamine combined with SAPB for multimodal analgesia. Esketamine has a high affinity for NMDA receptors, which can inhibit the afferent NMDA receptors in the spinal cord from receiving injurious stimuli, reduce opioid-induced nociceptor sensitization[11], thus inhibiting central sensitization[12], and also act on opioid δ-receptors to improve the function of δ-receptors[13]. SAPB can be used to target the pain locus to prevent nociceptive signals at an early stage, avoiding central sensitization, which can lead to nausea, respiratory depression and other adverse effects. SAPB mainly targets the pain sites, blocking the transmission of nociceptive signals as early as possible, avoiding central sensitization, and reducing the transition from acute pain to chronic pain [14]. SAPB can provide good intraoperative and postoperative analgesia for patients undergoing modified radical mastectomy for breast cancer. In this study, after SAPB, the resting/exercise VAS scores were significantly lower at 6 and 12 hours. This may be because SAPB has an excellent analgesic effect on the surgical area in the early postoperative period, and the duration of action of ropivacaine is about 6-8 hours. When local anesthetics act on the peripheral nerve block, the analgesic time is significantly prolonged, and some of them can be up to 24 hours [15]. After the addition of acephate, the exercise VAS scores of the KS group were significantly lower than those of group S and group C. The analgesic effect was better than that of SAPB alone. The combination of esketamine had a better analgesic effect after the weakening effect of SAPB, which was consistent with the results of previous studies [16]. The decrease in the number of postoperative presses of the analgesic pumps in groups KS and S compared with group C is because both esketamine and SAPB have the effect of relieving postoperative pain.Wang *et al.*[17] conducted a systematic review and meta-analysis on the treatment of acute postoperative pain in adults with esketamine sedation and concluded that the perioperative application of esketamine is effective in assisting analgesia, which can reduce the intensity of pain and the need for opioids in a short period after the operation. In this study, 2-hour postoperative pain was reduced by the use of esketamine. In this study, the difference in resting/exercise VAS scores among the three groups at 2 hours postoperatively was not statistically significant because the analgesic effect of the opioids used intraoperatively was still at its peak; the difference in resting/exercise VAS scores among the three groups at 24 hours postoperatively was not statistically significant, because on the one hand, SAPB can exert analgesic effects in a short period postoperatively, and on the other hand, the improvement of the patient's postoperative pain scores by using a small dosage of esketamine in the perioperative period Improvement may be time-limited, and prolonging the use of esketamine may be more meaningful for patients' postoperative pain relief.

In this study, HADS was chosen as an indicator for evaluating the mood of patients undergoing modified radical mastectomy for breast cancer. HADS is one of the commonly used tools to screen for anxiety and depression in oncology patients[18]. Ozalp *et al.*[19] have confirmed that the HADS scale is effective in screening the presence of anxiety and depressive negative emotions in breast cancer patients. The results of this study showed that the patients were mainly anxious one day before surgery, and the anxiety subsided and changed mainly to depression after surgery. The HADS-A and HADS-D scores in the KS group were lower than those in the S and C groups at 3 days and 1 week after surgery ($P<0.05$). Similar to the results of Franz *et al*. [20], patients with refractory depression who were given 0.2-0.4 mg/kg esketamine intravenously for 2 hours showed relief of depressive symptoms that persisted until 3 days postoperatively.This may be due to the fact that esketamine exerts antidepressant effects by sustained blockade of the NMDA receptor[21] and by improvement of neuroplasticity and synapse formation[22]. Escrivastigmine also leads to increased levels of neurotransmitters such as dopamine in the ventral striatum and caudate nucleus, leading to increased excitability of limbic structures and good mood[23]. Studies have also shown that the antidepressant effects of esketamine can last up to 1 week or even 1 month[24].

The results of this study showed that the incidence of postoperative insomnia was lower in the KS group than in the S and C groups. Consistent with the results of Qiu *et al.*[25], whose study found that continuous infusion of 0.3 $mg\cdot kg^{-1}\cdot h^{-1}$ esketamine during gynecologic laparoscopic surgery prevented postoperative sleep disorders. It may be because esketamine rapidly improves mood and produces a favorable sleep response compared to conventional antidepressants. The mechanisms by which esketamine improves postoperative sleep are not fully understood and may be due to its antidepressant effects, interaction with the circadian system, and positive neurocognitive effects[26]. It may also be due to the fact that esketamine in combination with SAPB provides patients with good postoperative analgesia and reduces discomfort due to pain, which in turn improves sleep. The present study also confirmed that esketamine combined with SAPB did not increase other adverse effects.

There are some limitations in this study: only the effect on anxiety and depression in the early postoperative period was observed. In contrast, the effect on long-term mood needs to be further investigated. In addition, only a single dose of esketamine was studied in the perioperative period. The conclusions of this study need to be further confirmed by multicenter studies with larger sample sizes.

In conclusion, esketamine combined with SAPB for general anesthesia in patients undergoing modified radical mastectomy for breast cancer can optimize anesthesia effects, reduce patients' postoperative pain, decrease the number of postoperative analgesic pump presses, alleviate anxiety and depression in the early postoperative period, and reduce the incidence of insomnia.

Conflict of interest: None

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·论　著·

艾司氯胺酮联合前锯肌平面阻滞对乳腺癌改良根治术后镇痛的影响

从文博[1]，朱伟[2]，仲明杰[1]，申帅[1]，孙悦[1]
1. 南京医科大学附属宿迁第一人民医院麻醉与围术期医学科，江苏 宿迁 223800；
2. 南京医科大学第一附属医院麻醉科，江苏 南京 210000

摘要：目的　探讨艾司氯胺酮联合前锯肌平面阻滞（SAPB）对乳腺癌改良根治术患者术后镇痛及焦虑抑郁情绪的影响。**方法**　选取宿迁市第一人民医院 2023 年 1 月至 2024 年 1 月乳腺癌改良根治术患者 96 例，按随机数字表法分为 3 组（n=32）：艾司氯胺酮联合 SAPB 组（KS 组）、SAPB 组（S 组）、空白对照组（C 组）。KS 组在全身麻醉诱导后行患侧 SAPB，在切皮前缓慢静脉注射 0.25 mg/kg 艾司氯胺酮，术中持续泵注剂量为 0.12 mg/（kg·h），手术结束前 30 min 停药；S 组在全身麻醉诱导后行患侧 SAPB；C 组实施全身麻醉。S 组和 C 组在麻醉诱导后和术中给予 KS 组同等剂量生理盐水。记录患者术后 2、6、12、24 h 的静息/运动视觉模拟评分（VAS）；记录患者术前 1 d、术后 3 d 及术后 1 周医院焦虑抑郁量表（HADS）评分；记录患者术后 48 h 内镇痛泵的按压次数和不良反应发生情况。**结果**　与 C 组相比，KS 组和 S 组在术后 6、12 h 静息/运动 VAS 评分降低，术后 48 h 内镇痛泵的按压次数较少（P<0.05）；与 C 组和 S 组相比，KS 组术后 12 h 运动 VAS 评分较低（P<0.05），术后 3 d、1 周的 HADS 评分低（P<0.05），术后失眠发生率低（KS 组为 0，S 组为 19.4%，C 组为 22.6%，P=0.008）；其他不良反应比较差异无统计学意义（P>0.05）。**结论**　在乳腺癌改良根治术中，艾司氯胺酮联合 SAPB 可减轻患者术后的急性疼痛，缓解患者焦虑抑郁情绪，且不增加术后不良反应。

关键词：艾司氯胺酮；前锯肌平面阻滞；麻醉；乳腺癌；焦虑；抑郁
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Effect of esketamine combined with serratus anterior plane block on postoperative analgesia after modified radical mastectomy for breast cancer

CONG Wenbo*, ZHU Wei, ZHONG Mingjie, SHEN Shuai, SUN Yue
** Department of Anesthesiology and Perioperative Medicine, The Affiliated Suqian First People's Hospital of Nanjing Medical University, Suqian, Jiangsu 223800, China*
Corresponding author: ZHU Wei, E-mail: zhuweijsph@163.com

Abstract: Objective　To explore the effects of esketamine combined with serratus anterior plane block (SAPB) on postoperative analgesia, anxiety and depression in patients with breast cancer undergoing modified radical mastectomy. **Methods**　From January 2023 to January 2024, 96 patients with breast cancer underwent modified radical mastectomy in Suqian First Hospital were selected and randomly divided into three groups (n = 32): esketamine combined with SAPB group (KS group), SAPB group (S group), and blank control group (C group). The KS group underwent SABP on the affected side after induction of general anesthesia, 0.25 mg/kg of esketamine was slowly injected intravenously before skin incision, with a continuous infusion dose of 0.12 mg·kg^{-1}·h^{-1} during surgery. The medication was stopped 30 minutes before the end of the surgery; S group underwent SABP on the affected side after induction of general anesthesia; C group received general anesthesia. The S group and C group were given the same dose of normal saline to the KS group after anesthesia induction and during surgery. The resting/exercise visual analogue scale (VAS) scores of

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通信作者：朱伟，E-mail: zhuweijsph@163.com
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patients at 2, 6, 12, 24 hours post-surgery and the hospital anxiety and depression scale (HADS) for patients 1 day before surgery, 3 days after surgery, and 1 week after surgery were recorded. The number of compressions of the analgesic pump and the occurrence of adverse reactions within 48 hours after surgery were compared. **Results** Compared with C group, KS and S groups had lower resting/exercise VAS scores at 6 and 12 hours postoperatively, and fewer number of compressions of the analgesic pump within 48 hours postoperatively ($P<0.05$). Compared with C group and S group, the KS group had lower exercise VAS scores at 12 hours post-surgery and HADS scores at 3 days and 1 week post-surgery ($P<0.05$), as well as a lower incidence rate of insomnia within 48 hours post-surgery (KS group 0, S group 19.4%, C group 22.6%, $P<0.05$). However, there was no statistically significant incidence of adverse reactions among three groups ($P>0.05$). **Conclusion** In the modified radical mastectomy for breast cancer, esketamine combined with SAPB can reduce the acute postoperative pain, alleviate the anxiety and depression of patients, and do not increase the adverse reactions after the operation.

Keywords: Esketamine; Serratus anterior plane block; Anaesthesia; Breast cancer; Anxiety; Depression

目前,乳腺癌居我国女性恶性肿瘤的发病首位[1]。手术切除仍是其主要的治疗手段,乳腺癌改良根治术是目前最常用的手术方式。乳腺癌改良根治术涉及乳腺和腋窝区域,可造成明显的急性疼痛,其中 19.5%~21.0%的患者经历了持续的中度至重度疼痛[2-4]。疼痛使患者极易出现焦虑、抑郁等负面情绪,进而影响生活质量。艾司氯胺酮是一种新型抗抑郁药,不良反应少,耐受性良好,成瘾性低,单次输注可减轻双相障碍患者的抑郁程度[5]。艾司氯胺酮还具有良好的镇痛作用,可以减少围术期阿片类和非甾体抗炎药物的用量及其引起的不良反应[6]。随着多模式镇痛逐渐普及,超声引导下神经阻滞技术广泛用于临床。前锯肌平面阻滞(serratus anterior plane block, SAPB)主要阻滞同侧第 2~6 肋间神经外侧皮支、胸长神经和胸背神经,可对乳腺癌改良根治术起到良好的镇痛效果;且 SAPB 操作时以肋骨作为定位,具有穿刺位置表浅,安全系数高的优势[7-8]。本研究探讨艾司氯胺酮联合 SAPB 对于全麻乳腺癌改良根治术患者术后镇痛及情绪的影响。

1　资料与方法

1.1　一般资料　本研究经医院伦理委员会批准[伦审第(20230101)号],术前与患者及家属签署知情同意书。选取宿迁市第一人民医院 2023 年 1 月至 2024 年 1 月在全麻下择期行乳腺癌改良根治术患者,年龄 18~65 周岁,美国麻醉师协会(ASA)Ⅰ~Ⅱ级,身体质量指数(BMI)19~28 kg/m^2。排除标准:艾司氯胺酮使用禁忌(甲状腺功能亢进症、过敏等);严重的心血管疾病胸部手术史、酒精滥用史、精神疾病史;阿片类药物或者其他成瘾性药物滥用史;近期服用抗抑郁药或 β 受体拮抗剂者;对围术期使用药物过敏者;不会读写中文,听力障碍,沟通困难者;临床资料不完整,拒绝参与研究。剔除标准:术中病理结果为良性病变;有术中知晓;术中大量出血;术后非计划入 ICU;随访期间意识不清或死亡;随访期间再次手术;患者或委托人随访期间要求退出研究,神经阻滞失败。

1.2　样本量计算　运用 G*Power 3.1 软件估算样本量,根据预试验结果,检验水准 $\alpha=0.05$,检验效能 $1-\beta=0.9$,采用双侧检验确定每组最小样本量为 26 例,考虑 20%的失访率,最终本次研究拟纳入患者 96 例,每组 32 例。

1.3　分组及干预　采用随机数字表法,将纳入的 96 例患者随机分为艾司氯胺酮联合 SAPB 组(KS 组)、SAPB 组(S 组)、空白对照组(C 组),各 32 例。其中 S 组 1 例患者术中快速病理为良性,C 组 1 例患者术中出血量>500 mL,予以剔除,最终有 94 例患者完成本研究,KS 组 32 例,S 组 31 例,C 组 31 例。三组患者年龄、性别、身高、体重、BMI、ASA 分级及手术时间等差异均无统计学意义($P>0.05$)。见表 1。

KS 组在全身麻醉诱导后将患者患侧上臂外展,肘部屈曲,操作者戴无菌手套,用碘伏对穿刺部位皮肤进行消毒,铺无菌巾,用无菌腔镜套包裹超声探头,采用 Mylab Alpha 型超声仪(Esaote 公司,意大利)5~13 MHz 高频探头引导下在腋中线第五肋间处,调整探头角度、增益等参数,平移辨别背阔肌和前锯肌,采用平面内进针法穿刺,当针尖到达前锯肌深层(见图 1),通过注射生理盐水确认前锯肌间隙,回抽无血液后注入 0.375%罗哌卡因(盐酸罗哌卡因注射液,10 mL∶75 mg,浙江现琅制药,批号:EE2252)20 mL。神经阻滞完成后行全身麻醉,在切皮前缓慢静脉注射艾司氯胺酮(盐酸艾司氯胺酮注射液,2 mL∶50 mg,江苏恒瑞医药,批号:221018BL)0.25 mg/kg,术中持续泵注剂量为 0.12 mg·kg^{-1}·h^{-1},S 组在全身麻醉

诱导后行患侧 SAPB；C 组仅实施全身麻醉。S 组和 C 组在麻醉诱导后和术中给予 KS 组同等剂量生理盐水。

表 1　三组患者一般资料比较　($\bar{x}\pm s$)

Tab. 1　Comparison of general data among three groups　($\bar{x}\pm s$)

组别	年龄(岁)	身高(cm)	体重(kg)	BMI(kg/m²)	手术时间(min)
KS 组(n=32)	47.38±6.03	157.81±1.69	57.50±1.76	23.06±0.89	127.19±5.18
S 组(n=31)	50.06±5.54	157.61±1.58	57.68±1.66	23.19±0.90	127.16±4.95
C 组(n=31)	49.03±5.90	156.97±1.80	57.39±1.86	23.26±0.93	128.68±4.40
F 值	1.709	2.126	0.214	0.403	0.994
P 值	0.187	0.125	0.808	0.669	0.374

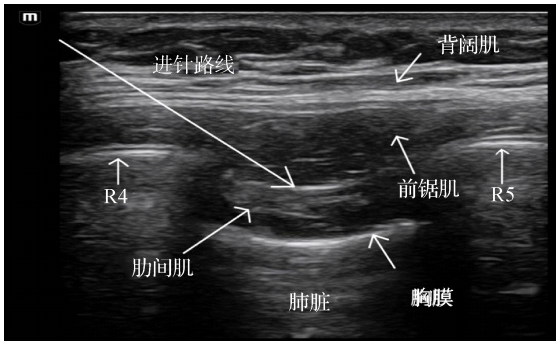

图 1　前锯肌平面超声声像图

Fig. 1　Ultrasonographic images of serratus anterior plane

1.4　*麻醉方法*　患者术前常规禁食 8 h，禁饮 4 h，入室后开放外周静脉通路，常规监测心电图(ECG)、血压(BP)、脉搏血氧饱和度(SpO_2)、心率(HR)，行健侧桡动脉穿刺置管，连续监测收缩压(SBP)。麻醉方法选用静吸复合麻醉，麻醉诱导：预充氧 5 min，根据去脂体重给予三组注射舒芬太尼 0.5 μg/kg，依托咪酯注射液 0.3 mg/kg，顺式阿曲库铵 0.2 mg/kg，咪达唑仑 0.05 mg/kg，经口插入合适型号气管导管，机械通气，设置潮气量 6～8 mL/kg，通气频率 10～14 次/min，吸呼比为 1∶2，吸入氧流量 2 L/min，维持 $ETCO_2$ 35～45 mmHg。麻醉维持：瑞芬太尼 0.3 μg·kg^{-1}·min^{-1}，丙泊酚 4～12 mg·kg^{-1}·h^{-1}，顺式阿曲库胺 0.1 mg·kg^{-1}·h^{-1}，术中补液量和补液方案按照“421 法则”进行补液。调整 SBP 及 HR 变化幅度不超过基础值的 30%。当三组患者的 SBP 下降超过基础值的 30%或小于 90 mmHg 时，给予去氧肾上腺素 0.1～0.5 mg；SBP 升高超过基础值的 30%或大于 180 mmHg 时，给予乌拉地尔 12.5～25 mg；HR＜50 次/min 时，给予阿托品 0.01 mg/kg；HR＞100 次/min 时，给予艾司洛尔 0.5 mg/kg，必要时可重复给药。开始缝合皮肤时静脉注射昂丹司琼 8 mg，于手术结束前10 min停止给予所有药物。三组患者均于术毕 30 min 内开放电子镇痛泵行静脉自控镇痛(PCIA)，配方：舒芬 2 μg/kg+昂丹司琼 8 mg+0.9%生理盐水至 100 mL，背景剂量为 2.0 mL/h，bolus 为 1.5 mL，锁定时间为 15 min。当三组患者 VAS 评分≥4 分时，按压 PCIA 自控按钮，观察 10 min，如果疼痛不能缓解，静脉缓慢推注羟考酮 2 mg。

1.5　*观察指标*　(1) 记录手术结束后 2、6、12、24 h 的静息/活动时视觉模拟量表(VAS)评分。(2) 由同一名经过培训的护士于手术前 1 d、术后 3 d 及术后1 周采用医院焦虑量表(HADS)评估患者焦虑、抑郁情绪。HADS 由焦虑(HADS-A)和抑郁(HADS-D)两部分组成，各 7 个问题，每个选项按 0～3 分计分，共21 分，评分＞8 分为伴有焦虑或抑郁情绪，分值越高提示焦虑或抑郁情绪越重[9]。(3) 评估术后48 h镇痛泵按压次数和不良反应发生情况。

1.6　*统计学方法*　采用 SPSS 26.0 软件分析数据。计量资料进行 Kolmogorov-Smirnov 正态性检验，不服从正态分布以 $M(P_{25}, P_{75})$ 来表示，多组间比较采用 Kruskal-Wallis H 秩和检验，组间两两比较采用 Bonferroni 法较正；符合正态分布的计量资料用 $\bar{x}\pm s$ 表示，三组间比较采用单因素方差分析或重复测量资料的方差分析，两两比较采用 LSD-t 检验；计数资料以例(%)表示，比较采用 χ^2 检验或 Fisher 确切概率法。均为双侧检验，P＜0.05 为差异有统计学意义。

2　结　果

2.1　*静息/运动后 VAS 评分*　KS 组和 S 组在术后 6、12 h 静息/运动 VAS 评分低于 C 组(P＜0.05)；KS 组术后 12 h 运动 VAS 评分低于 C 组和 S 组(P＜0.05)；而三组术后 2 h、24 h 静息/运动 VAS 评分差异无统计学意义(P＞0.05)。见表 2。

2.2　*HADS 评分*　KS 组在术后 3 d、术后 1 周时 HADS-A 和 HADS-D 评分低于 S 组和 C 组(P＜0.05)；术前 1 d 时三组 HADS-A 和 HADS-D 评分差异无统计学意义(P＞0.05)。见表 3。

2.3　*术后 48 h 镇痛泵按压次数*　KS、S 组与 C 组患者术后 48 h 镇痛泵按压次数分别为 1(1,2)、1(1,2)和 3(1,4)，三组比较差异有统计学意义(H=16.974，P＜0.01)；两两比较显示，KS 组和 S 组镇痛泵按压次数显著低于 C 组(P＜0.05)。

2.4　*术后 48 h 内不良反应发生情况*　KS 组在术后不良反应中失眠比率低于 S 组和 C 组，差异有统计学意义(P＜0.05)；其他不良反应比较差异无统计学意义(P＞0.05)。见表 4。

表 2　三组患者静息/运动后 VAS 评分比较　（分，$\bar{x}\pm s$）

Tab. 2　Comparison of VAS scores among three groups after rest and exercise　（point，$\bar{x}\pm s$）

组别	例数	静息状态				运动状态			
		术后 2 h	术后 6 h	术后 12 h	术后 24 h	术后 2 h	术后 6 h	术后 12 h	术后 24 h
KS 组	32	1.13±0.71	1.47±0.51[a]	2.03±0.78[a]	3.81±1.09	1.53±0.51	2.41±0.50[a]	2.81±0.64[ab]	5.66±1.23
S 组	31	1.35±0.55	1.61±0.50[a]	2.03±0.71[a]	3.55±1.18	1.61±0.50	2.48±0.51[a]	3.61±0.95[a]	5.87±1.36
C 组	31	1.42±0.50	2.58±0.81	3.84±0.69	4.16±0.78	1.68±0.48	3.77±0.88	5.74±0.93	6.00±0.89
$F/P_{组间}$ 值		34.902/<0.001				42.836/<0.001			
$F/P_{时间}$ 值		159.939/<0.001				388.283/<0.001			
$F/P_{交互}$ 值		11.452/<0.001				18.046/<0.001			

注：与 C 组比较，[a]P<0.05；与 S 组比较，[b]P<0.05。

表 3　三组各时点 HADS 评分比较　（分，$\bar{x}\pm s$）

Tab. 3　Comparison of HADS scores among three groups at different time points　（point，$\bar{x}\pm s$）

组别	例数	HADS-A 评分			HADS-D 评分		
		术前 1 d	术后 3 d	术后 1 周	术前 1 d	术后 3 d	术后 1 周
KS 组	32	9.00±3.29	6.63±2.30[ab]	6.53±2.46[ab]	6.47±2.54	7.06±2.76[ab]	5.97±1.93[ab]
S 组	31	8.84±3.39	9.19±3.27	8.52±2.87	7.58±2.96	9.29±2.97	8.87±3.16
C 组	31	8.71±3.41	9.10±3.59	9.19±3.17	7.13±2.75	8.84±2.71	8.87±2.94
$F/P_{组间}$ 值		3742/0.027			8.222/0.001		
$F/P_{时间}$ 值		2.500/0.088			10.344/<0.001		
$F/P_{交互}$ 值		4.520/0.002			2.716/0.031		

注：与 C 组比较，[a]P<0.05；与 S 组比较，[b]P<0.05。

表 4　三组患者术后 48 h 内不良反应发生情况比较　［例(%)］

Tab. 4　Comparison of adverse reaction among three groups within 48 hours after surgery　［case(%)］

组别	例数	恶心呕吐	呼吸抑制	失眠	认知障碍
KS 组	32	6(18.8)	1(3.1)	0[ab]	1(3.1)
S 组	31	6(19.4)	0	6(19.4)	0
C 组	31	7(22.6)	0	7(22.6)	0
χ^2 值		0.164			
P 值		0.921	>0.999[c]	0.008[c]	>0.999[c]

注：与 C 组比较，[a]P<0.05；与 S 组比较，[b]P<0.05；[c] 使用 Fisher 确切概率法。

3　讨　论

乳腺癌改良根治术切口范围广，创伤大，术中涉及乳腺切除及腋窝淋巴结清扫，会损伤部分皮神经，以及术后伤口负压吸引、加压包扎、血肿及积液压迫刺激神经导致该类手术呈中、重度疼痛。乳腺癌改良根治术患者在治疗中既要克服对癌症的恐惧心理，又要面对乳房外观改变带来的生理变化，以及受术后疼痛刺激，容易出现焦虑、抑郁等负面情绪。本研究在乳腺癌改良根治术患者全麻手术中应用艾司氯胺酮联合 SAPB 以预防中枢敏化，降低阿片类药物耐受，减轻术后疼痛，缓解患者术后焦虑抑郁情绪。结果显示，患者术后疼痛有效缓解，术后焦虑抑郁情绪得到改善，并且可以降低术后失眠的发生率，同时不增加恶心呕吐等不良反应的发生率。

阿片类药物广泛应用于术中及术后的镇痛，但是大剂量的阿片类药物会导致急性耐受和诱导痛觉过敏[10]，还会导致患者产生恶心呕吐、呼吸抑制等不良反应。因此，本研究选择艾司氯胺酮联合 SAPB 进行多模式镇痛。艾司氯胺酮与 N-甲基-D-天冬氨酸（NMDA）受体亲和力较高，可以抑制脊髓内 NMDA 受体接受伤害性刺激的传入，减少阿片类药物引发的痛觉过敏[11]，从而抑制中枢敏化[12]，还可以作用于阿片 δ 受体，改善 δ 受体功能[13]，具有良好的镇痛作用。SAPB 主要针对疼痛位点进行靶点干预，尽可能早期阻断痛觉信号的传递，避免发生中枢敏化，可减少急性疼痛向慢性疼痛的转变[14]，SAPB 可为乳腺癌改良根治术患者提供良好的术中及术后镇痛。本研究中患者行 SAPB 后，6、12 h 静息/运动 VAS 评分明显降低，可能是因为 SAPB 在术后早期对手术区域有良好的镇痛效果，罗哌卡因作用时间大约为 6~8 h，局部麻醉药作用于外周神经阻滞时，镇痛时间延长，部分可到 24 h[15]。在加用艾司氯胺酮后，KS 组术后 12 h 运动 VAS 评分明显低于 S 组和 C 组，镇痛效果优于单独应用 SAPB，考虑在 SAPB 效果减弱后，联合艾司氯胺酮有更好的镇痛效果。与既往研究结果一致[16]。与 C 组比较，KS 组和 S 组术后按压镇痛泵次数减少，是因为艾司氯胺酮和 SAPB 都具有缓解术后疼痛的作用。Wang 等[17] 对艾司氯胺酮静注治疗成人术后急性疼痛进行了系统综述和荟萃分析，认为围手术期应用艾司氯胺酮能够有效地辅助镇痛，可降低

成人术后短时间内疼痛的强度和对阿片类药物的需求。本研究中，术后 2 h 的静息/运动 VAS 评分三组差异无统计学意义，由于术中使用的阿片类药物的镇痛作用还处于峰值；术后 24 h 三组的静息/运动 VAS 评分差异无统计学意义，一方面 SAPB 可在术后短时间内发挥镇痛作用；另一方面围术期使用小剂量艾司氯胺酮对患者术后疼痛评分的改善可能具有时限性，延长艾司氯胺酮的使用时间可能会对患者术后疼痛的缓解更有意义。

本研究选择 HADS 作为评价乳腺癌改良根治术患者情绪的指标，HADS 是筛查肿瘤患者焦虑抑郁常用的工具之一[18]。Ozalp 等[19]研究证实，HADS 量表可有效筛查出乳腺癌患者存在的焦虑和抑郁负性情绪。本研究结果显示，术前 1 d 患者主要以焦虑情绪为主，术后焦虑情绪有所缓解，主要转变为抑郁情绪。KS 组在术后 3 d、术后 1 周时 HADS-A 和 HADS-D 评分低于 S 组和 C 组。与 Singh 等[20]结果相似，给予难治性抑郁症患者 0.2～0.4 mg/kg 艾司氯胺酮静滴 2 h 后，患者抑郁症状缓解，并持续到术后 3 d。这可能是因为艾司氯胺酮可持续阻断 NMDA 受体[21]，改善神经可塑性和突触的形成[22]，从而发挥抗抑郁作用。艾司氯胺酮还可导致腹侧纹状体和尾状核中多巴胺等神经递质水平升高，进而边缘结构兴奋性增强，产生良好的情绪[23]。也有研究显示艾司氯胺酮的抗抑郁作用可持续 1 周甚至 1 个月[24]。

本研究结果显示，KS 组术后失眠发生率低于 S 组和 C 组。与 Qiu 等[25]结果一致，其研究发现，在妇科腹腔镜手术中持续输注 0.3 $mg \cdot kg^{-1} \cdot h^{-1}$ 艾司氯胺酮，可以预防术后睡眠障碍。可能是因为艾司氯胺酮相较于传统的抗抑郁药可以快速改善情绪和产生良好的睡眠反应。艾司氯胺酮改善术后睡眠的机制尚未完全清楚，可能是由于它的抗抑郁作用，及其与昼夜节律系统的相互作用，以及它的积极神经认知作用[26]。还可能因为艾司氯胺酮联合 SAPB 为患者提供了良好的术后镇痛，减轻因疼痛引起的不适，进而改善睡眠。本研究也证实艾司氯胺酮联合 SAPB 并不增加其他不良反应。

本研究存在一定的局限性：仅观察术后早期对于焦虑抑郁情绪的影响，而对远期情绪的影响有待进一步研究；仅研究了单一剂量的艾司氯胺酮在围术期的应用。本研究所得到的结论还需要开展多中心、更大样本量的研究予以进一步证实。

综上所述，艾司氯胺酮联合 SAPB 用于全麻乳腺癌改良根治术患者可优化麻醉效果，减轻患者术后疼痛，减少术后镇痛泵按压次数，缓解术后早期焦虑抑郁情绪，降低失眠的发生率。

利益冲突　无

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