Randomized Controlled Trial

Sub-Anesthesia Dose of S-Ketamine Reduces Postoperative Pain and Anxiety in Patients Receiving Breast and Thyroid Surgery: A Randomized, Controlled Trial

Dongxu Zhou, MSc[1], Fan Liu, MSc[1], Fei Jiang, MSc[1], Xihong Ye, MD, PhD[1], Xingrui Gong, MD, PhD[1], and Mazhong Zhang, MD, PhD[2]

From: [1]Department of Neuroscience and Brain Disease, Department of Anesthesiology, Xiangyang Central Hospital, Affiliated Hospital of Hubei University of Arts and Science, Xiangyang, Hubei, China; [2]Department of Anesthesiology and Pediatric Clinical Pharmacology Laboratory, Shanghai Children's Medical Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China

Address Correspondence: Xingrui Gong, MD, PhD Department of Neuroscience and Brain Disease, Department of Anesthesiology, Xiangyang Central Hospital, Affiliated Hospital of Hubei University of Arts and Science Xiangyang, Hubei, China E-mail: gongxrhbxy@sohu.com

Disclaimer: Dongxu Zhou and Fan Liu contributed equally to the article. The present study was supported by a grant from the National Natural Science Foundation of Xiangyang (Grant No. 2021YL17).

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 10-12-2022
Accepted for publication: 12-20-2022

Free full manuscript: www.painphysicianjournal.com

Background: Postoperative pain and anxiety affect patients' recovery and increase the family burden. S-ketamine presents analgesic effects and anti-depressive effects in clinics. The effect of a sub-anesthesia dose of S-ketamine on postoperative pain and anxiety remains to be clarified.

Objectives: This study aimed to evaluate the analgesic and anxiolytic effects of a sub-anesthesia dose of S-ketamine on postoperative pain and anxiety and explored the risk factors for postoperative pain in patients receiving breast or thyroid surgery under general anesthesia.

Study design: A randomized, double-blind, controlled trial.

Setting: A university hospital.

Methods: One hundred twenty patients receiving breast or thyroid surgery, stratified by surgery type, were randomized to S-ketamine and control groups in a 1:1 ratio. S-ketamine (0.3 mg/kg) or an equal volume of normal saline was administrated after anesthesia induction. Visual analog scale (VAS) of pain and self-rating anxiety scale (SAS) were tested before surgery and on postoperative day 1, 2, and 3. VAS and SAS score between the 2 groups were compared, and the risk factors for postoperative moderate to severe pain were explored with logistic regression analysis.

Results: Intraoperative S-ketamine decreased VAS and SAS scores on postoperative day 1, 2, and 3 ($P < 0.05$, 2-way ANOVA for repeated measurements followed by Bonferroni post-analysis). Subgroup analysis showed S-ketamine decreased VAS and SAS scores both in breast surgery and thyroid surgery patients on postoperative day 1, 2, and 3. Logistic regression identified S-ketamine and regular exercise are protective factors, and anxiety before surgery is a risk factor for postoperative moderate to severe pain ($P < 0.05$).

Limitations: The anxiety score in our study is not so high, which may under-evaluate the anxiolytic effect of S-ketamine. However, S-ketamine decreased the SAS scores postoperatively in our study.

Conclusions: Intraoperative sub-anesthesia dose of S-ketamine reduces postoperative pain and anxiety intensity. Anxiety before surgery is a risk factor, and S-ketamine and regular exercise are protective factors for postoperative pain.

The study was registered at www.chictr.org.cn with the number: ChiCTR2200060928.

Key words: S-ketamine, pain, anxiety, breast, thyroid

Pain Physician 2023: 26:257-264

Postoperative pain is very common and disturbing after surgery. Inadequate pain management is associated with increased postoperative complications, prolonged hospital stay, and chronic postoperative pain (1). In addition, perioperative anxiety is a frequent co-morbidity as patients' excessive worry about the safety of the surgery and complications (2). Nearly one in 2 patients present perioperative anxiety behaviors, which result in increased perioperative complications (3). The anxiety and pain are often intertwined and accentuate each other, making the treatment and postoperative recovery more difficult (4). Opioids have been the most frequently used for postoperative analgesia after surgery, but the adverse effects, including tolerance, addiction, respiratory depression, and hyperalgesia frequently result in pursuing opioid-sparse anesthesia and analgesia (5). Thus, developing an ideal strategy to decrease postoperative pain and anxiety has been a challenge for postoperative care.

S-ketamine is a N-methyl-D-aspartate (NMDA) receptor antagonist; it could attenuate pain signals transduction, spinal dorsal horn wind-up, and central sensitization (6). S-ketamine has been used for treating acute and chronic pain in clinics and has been approved by Food and Drug Administration for treating depression or major depressive disorders (7). Recently, S-ketamine has been proven to reverse anxiety-like behaviors in animals (8); whether it is also effective against postoperative anxiety remains to be clarified. Considering a high dose would increase the side effects of S-ketamine, we used a sub-anesthesia dose of the drug. Thus, we explored the analgesic and anxiolytic effects of a sub-anesthesia dose of S-ketamine on patients receiving breast and thyroid surgery, and the risk factors of acute postoperative pain in these patients.

Methods

The study was carried out obeying the Declaration of Helsinki (October 2000), and the research protocol was approved by the Ethics Committee of Xiangyang Central Hospital, Affiliated Hospital of Hubei University of Arts and Science, Xiangyang, China. All of the female patients aged 18-65 years, with American Society of Anesthesiologists (ASA) anesthesia grade I-III, and planned to receive breast or thyroid surgery in our hospital were included. Exclusion criteria were as follows: patients with any schizophrenia, mania, and any other mental illness; any serious allergy to S-ketamine; any contraindication to midazolam, fentanyl, rocuronium, remifentanil, and propofol; and those who will discharge less than 3 days after surgery.

Written informed consent was acquired from patients and their families. The baseline clinical characteristics of all the patients were collected: age, weight, height, smoking, drinking, previous disease, education, economic level, work status, marital status, fertility status, exercise habit, previous surgery history, ASA classification, white blood cell (WBC) count; neutrophil (NEUT) count, preoperative pathology of the tumor, visual analog scale of pain (VAS), self-rating anxiety scale (SAS) (9). Regular exercise was defined as 75-150 minutes of vigorous-intensity physical exercise per week or 150-300 min moderate-intensity physical exercise per week (10).

Before the experiment, a biostatistician generated randomized numbers with a computer in a 1:1 ratio, stratified by surgery type, and then allocated patients into 2 groups: group S (0.3 mg/kg of S-ketamine, No.20060403; Jiangsuhengrui Pharmaceutical Co., Ltd., Jiangsu, China) or group C (same volume of normal saline). A biostatistician prepared the drug according to the number sequence. After the patient's admission to an operating room, a non-invasive blood pressure, standard 5-lead electrocardiograph, and pulse oxygen saturation were placed for hemodynamic monitoring. For anesthesia induction, 0.05 mg/kg midazolam, 0.2 mg/kg etomidate, 0.4 μg/kg sufentanil, 0.6 mg/kg rocuronium were used. Endotracheal intubation was performed by an experienced anesthetist, and mechanical ventilation was followed immediately after induction. Then, an anesthesia assistant took the S-ketamine from the biostatistician and injected it after intubation.

Anesthesia was maintained with continuous infusions of propofol (50-150 μg/kg/min), remifentanil (0.2-0.5 μg/kg/min), and sevoflurane (1%). The anesthesia depth of induction and maintenance was guided by bispectral index (BIS) monitoring, and the BIS was controlled between 40-55 by increasing or decreasing the propofol injection rate. Rocuronium was added intermittently according to the operation progress. The end-respiratory partial pressure of carbon dioxide ($PetCO_2$) was monitored and maintained within 35-40 mmHg. During the anesthesia, the noninvasive mean blood pressure was maintained within 20% of its baseline value and above 60 mmHg, which was achieved either by infusion of 20 μg phenylephrine or by 20 μg nitroglycerin each time to increase or decrease the blood pressure, respectively. After the surgery, the endotracheal tube was removed, and the patient was

sent to the post-anesthesia care unit before returning to the ward. All of the surgeries were conducted by the same team, and the anesthesiologists were blinded to the patient and drug allocation.

Perioperative Pain and Anxiety Measurement

SAS and VAS scores are primary outcome measures, and adverse events are secondary outcome measures. The SAS was used to evaluate the patients' anxiety score before surgery and on postoperative day (POD) 1, 2, and 3 after surgery. The VAS score was used to evaluate the patients' pain scores on POD 1, 2, 3. Adverse events, including nausea, vomiting, sore throat, headache, delirium, illusion, pruritus, Ramsay sedation score, and recovery time, were recorded on POD 1.

Statistical Analysis

The sample size calculation used PASS11 software (NCSS, LLC. Kaysville, Utah). The primary outcomes were postoperative pain and anxiety score on postoperative day one. From our preliminary test, the mean VAS score was 3 and 2 in the C and S groups, respectively, and the standard division of 1.5. Based on a 2-sided alpha error of 0.05 and power of 90%, n = 49 per group was required in each group of the experiment. Considering there might be a 10% dropout, we included 60 patients in each group. The data were expressed as mean ± standard deviation (SD), and for the comparison between the 2 groups, we used 2-sample independent t-tests if they were normally distributed. The chi-square test or Fisher's exact test was used for categorical data. Comparisons of pain and anxiety data recorded over time between the groups or subgroups were analyzed using 2-way ANOVA for repeated measurements. If an overall significant difference between the groups was found, Bonferroni posthoc tests were conducted. Logistic regression was performed to explore the risk factors of postoperative moderate to severe pain (VAS $\geq$ 3). *P*-value < 0.05 was considered statistically significant. The statistical analyses were done using the GraphPad Prism software (GraphPad Prism 5.0, GraphPad Software Inc., San Diego, CA). The study was registered at www.chictr.org.cn with the number: ChiCTR2200060928.

Results

Patients' Baseline Characteristics

The patient characteristics are shown in Table 1. Sixty-two breast surgery and 68 thyroid surgery patients were scrutinized in this study. Ten patients were excluded: 3 patients were excluded because of cerebral infarction history, 4 patients were men, and 3 patients refused to participate. Finally, 120 patients were included; 60 breast surgery patients were randomized to the C (n = 30) and S (n = 30) groups, and 60 thyroid surgery patients were randomized to the C (n = 30) and S (n = 30) groups. The trial flow chart is shown in Fig 1. There was no significant difference between the 2 groups in terms of age, height, weight, WBC and NEUT count, and preoperative pain intensity ($P > 0.05$, t-test). Their smoking, drinking, exercise habit, history of heart, pulmonary, liver, renal, cerebrovascular disease, diabetes mellitus, hypertension, previous surgery, education, economic level, working and marital status, with child, ASA classification, preoperative pathology results, radiotherapy, and chemotherapy history were not different between groups ($P > 0.05$, chi-square).

Comparison of Postoperative Outcomes and Complications

The results showed no patients presented pain before surgery. The VAS score was significantly lower in the S group compared to the C group on postoperative day one, 2, and 3 ($P < 0.05$, 2-way ANOVA for repeated measurements followed by Bonferroni post-analysis, Table 2). Similarly, the SAS scores were not different between groups before surgery and were remarkably lower in the S group compared to the C group on postoperative day 1, 2, and 3 ($P < 0.05$, 2-way ANOVA for repeated measurements followed by Bonferroni post-analysis, Table 2).

The postoperative complications, recovery time, and Ramsay sedation score were also observed between the 2 groups within 24 hours after surgery. No significant difference was observed in the incidence of nausea or vomiting, and no patients reported delirium, illusion, pruritus, and recovery time ($P > 0.05$, t-test, Table 3). The incidence of sore throat, headache ($P < 0.05$, chi-square, Table 3), and the Ramsay sedation score ($P < 0.05$, t-test, Table 3) in the S group was lower compared to the C group.

Subgroup Analysis of VAS Scores and SAS Scores in the Breast Surgery or Thyroid Groups

The VAS score decreased with time and was lower in the S group compared to the C group in both breast and thyroid surgery groups on postoperative day 1, 2, and 3 ($P < 0.05$, 2-way ANOVA for repeated measurements followed by Bonferroni post-analysis, Fig. 2A and

Table 1. *Patients' baseline characteristics*.

	C group	S group	*P* value
Breast disease/thyroid disease	30/30	30/30	
Age (years)	47.33 ± 12.12	48.30 ± 11.49	0.66
Height (cm)	159.28 ± 5.75	159.63 ± 5.17	0.72
Weight (kg)	61.75 ± 10.54	60.28 ± 10.20	0.44
Smoking (Y/N)	0/60	0/60	NA
Drinking (Y/N)	0/60	0/60	NA
Heart disease (Y/N)	1/59	0/60	0.49
Pulmonary disease (Y/N)	0/60	4/56	0.13
Liver disease (Y/N)	0/60	0/60	NA
Renal disease (Y/N)	1/59	1/59	1
Cerebrovascular disease (Y/N)	3/57	0/60	0.24
Hypertension (Y/N)	11/49	9/51	0.62
Diabetes mellitus (Y/N)	1/59	3/57	0.61
Education			0.51
Primary school	5	8	
Junior school	26	21	
Senior school	18	23	
University	11	8	
Economic level			0.19
Low	2	4	
Middle	57	56	
High	2	0	
Employed (Y/N)	42/18	41/19	0.84
Marital status (single/ married)	4/56	1/59	0.36
With child (Y/N)	56/4	58/2	0.68
Exercise habit (Y/N)	15/45	13/47	0.66
Previous surgery history (Y/N)	25/35	19/41	0.27
ASA classification (II/III)	34/26	38/22	0.46
Heart function (I/II, NYHA)	60/0	60/0	NA
WBC count (*1012/ L)	5.83 ± 1.50	5.41 ± 1.48	0.13
NEUT count (*109/L)	3.48 ± 1.14	3.27 ± 1.21	0.32
Preoperative pathology			0.25
Benign	8	3	
Malignant	38	39	
Not clear	14	18	
Preoperative VAS score	0/60	0/60	NA
Preoperative SAS score	39.47 ± 5.65	40.92 ± 4.15	0.112
Preoperative radiotherapy (Y/N)	0/60	0/60	NA
Preoperative chemotherapy (Y/N)	8/52	4/56	0.2

Results are expressed as mean ± SD. American Society of Anesthesiologists, ASA; Neutrophile, NEUT; White Blood cell, WBC; Self-Rating Anxiety Scale, SAS; Standard deviation, SD; Visual analog scale, VAS; Control, C; S-ketamine, S.

B). The results of the SAS score in the breast and thyroid surgery groups showed a similar time course as VAS. The SAS score decreased with time and was lower in the S group compared to the C group of both breast and thyroid surgery groups on postoperative day 1, 2, and 3 ($P < 0.05$, 2-way ANOVA for repeated measurements followed by Bonferroni post-analysis, Fig. 2C and D).

Multivariate Logistic Regression Analysis of Factors of Postoperative Pain and Anxiety in the 2 Groups

The data of the C group and S group were combined and analyzed with a multivariate logistic regression method to identify the risk factors of moderate to severe postoperative pain. The results showed that S-ketamine and regular exercise are protective factors and preoperative anxiety is a risk factor for moderate to severe postoperative pain, analyzed using a stepwise back-ward likelihood ratio (Table 4). The *P*-value, adjusted OR, and 95% confidence interval was ($P = 0.000$, $\beta = 0.029$, 95%CI [0.009 to 0.093]) for S-ketamine, ($P = 0.014$, $\beta = 0.232$, 95%CI [0.072 to 0.744]) for regular exercise, and ($P = 0.007$, $\beta = 1.167$, 95%CI [1.044 to 1.301]) for preoperative anxiety.

Discussion

Our randomized, double-blind, controlled study evaluated the effect of intraoperative S-ketamine on postoperative pain and anxiety. Our results demonstrated that patients who received a sub-anesthesia dose of S-ketamine had lower pain and anxiety scores compared with normal saline. The analgesic and anxiolytic effects of S-ketamine can last more than 3 days after surgery. Multivariate logistic regression analysis showed that S-ketamine and regular exercise are protective factors and anxiety before surgery is a risk factor for moderate to severe postoperative pain.

Previous studies have demonstrated that S-ketamine decreases postoperative pain; the mechanism can be explained by the antagonism of the NMDA receptors (6,11). A recent meta-analysis evaluated the effect of

perioperative S-ketamine for analgesia, which included 12 studies (6), and the results showed that S-ketamine decreases acute postoperative pain both in the rest and movement and morphine consumption. Another recent study further demonstrated that postoperative low-dose ketamine reduced hydromorphone requirements during the first 24 hours after lumbar surgery in opioid-tolerant patients (12). The opioid-saving effect of S-ketamine may not only attribute to its intrinsic analgesic effect but also to reduce acute opioid tolerance and hyperalgesia (13,14). In addition, a recent study has demonstrated that intraoperative S-ketamine reduces analgesic use and pain after surgery (15). In our study, intraoperative sub-anesthesia dose of S-ketamine decreased acute postoperative pain; the reason may be attributed to the inhibition of pain transduction by blocking NDMA receptors. Surprisingly, our results showed that the analgesic effect lasts several days after surgery in our study; the reason for this may be due to its anti-allodynic effect of NMDA receptor antagonism, which prevents long-term central sensitization formation (16).

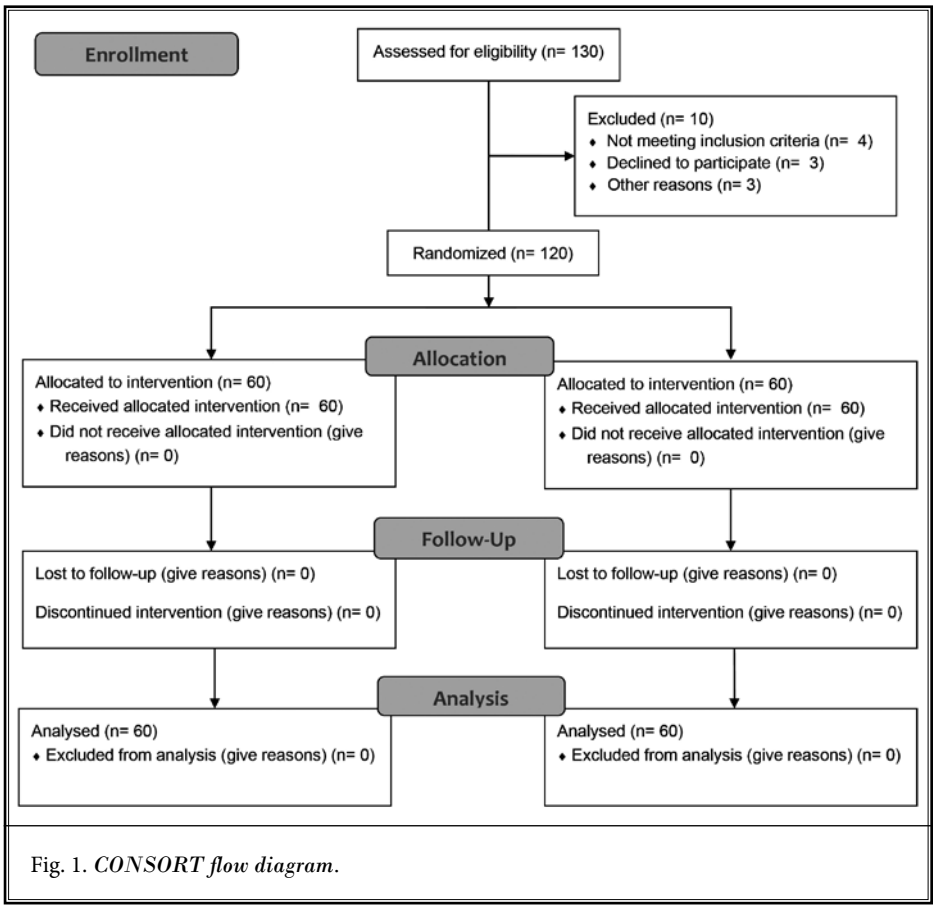

Fig. 1. *CONSORT flow diagram.*

Table 2. *Perioperative pain and anxiety scores.*

Variables	Group	Before	POD 1	POD 2	POD 3
VAS	C group	0	3.18 ± 1.10	2.57 ± 0.79	2.15 ± 0.84
	S group	0	1.00 ± 1.14*	0.40 ± 0.66*	0.06 ± 0.25*
SAS	C group	39.49±5.65	35.20 ± 5.08	32.08 ± 3.43	30.58 ± 3.31
	S group	40.92±4.15	27.18 ± 2.36*	26.00 ± 1.25*	25.03 ± 0.18*

Results are expressed as mean ± SD. Postoperative day POD; Self-Rating Anxiety Scale, SAS; Standard deviation, SD; Visual Analogue Scale, VAS; Control, C; S-ketamine, S. *$P <$ 0.05 compared with the C group.

Psychiatric diseases, including anxiety and depression, are a worldwide public health problem that cause disability and result in personal suffering and economic loss. Intranasal (S)-ketamine has recently been approved for treating depression by the Food and Drug Administration. Postpartum depression is a frequent complication after delivery, and S-ketamine improved the depressive score postoperatively (17,18). However, in the acute postoperative period, anxiety is a major symptom that affects the patients, and a higher anxiety score is a risk factor for poor sleep quality, more severe pain, and prolonged postoperative hospital stay (3,19). Further, previous studies have demonstrated that even treatment-resistant anxiety spectrum disorders were improved within an hour of ketamine dosing and persisted for up to one week (20-22). A dose-response profile was noticed for anxiolytic effects after ketamine dosing. Although the anxiolytic effect of S-ketamine has been observed in animals (23), the anxiolytic effect of S-ketamine on patients, to our knowledge, has not

Table 3. *Comparison of adverse responses, recovery time, and Ramsay sedation score between the 2 groups within 24 hours after surgery.*

	C group	S group	*P*
Nausea	4	4	0.64
Vomiting	2	3	0.50
Sore throat	23	9*	0.004
Headache	9	1*	0.008
Delirium	0	0	NA
Illusion	0	0	NA
Pruritus	0	0	NA
Recovery time (min)	7.08 ± 1.44	6.98 ± 1.03	0.66
Ramsay sedation score	2.05 ± 0.22	2.25 ± 0.44*	0.002

Results are expressed as mean ± SD; Control, C; S-ketamine, S.
*$P < 0.05$ compared with the C group.

Table 4. *Multivariate logistic regression analysis of factors of postoperative pain and anxiety in the 2 groups.*

	β	95% Confidential interval	*P*
S-ketamine	0.029	(0.009, 0.093)	0.000
Regular exercise	0.232	(0.072, 0.744)	0.014
Anxiety before surgery	1.167	(1.044, 1.301)	0.007

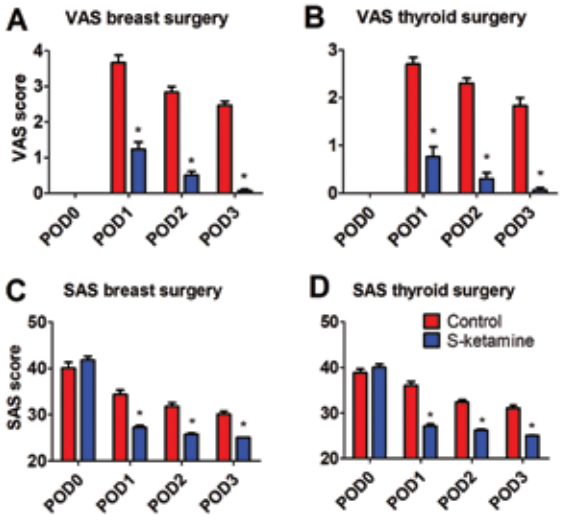

Fig. 2. *Comparison of VAS scores between the C group and S group in the breast (A) and thyroid (B) surgery groups. Comparison of SAS scores between the C group and S group in the breast (C) and thyroid (D) surgery groups. *$P < 0.05$, 2-way ANOVA for repeated measurements followed by Bonferroni post-analysis; control group, C; S-ketamine group, S; Visual analog scale, VAS; Self-rating anxiety scale, SAS; Postoperative day, POD.*

been reported. Our results showed that the intraoperative sub-anesthesia dose of S-ketamine also presents a postoperative anxiolytic effect, which is verified by the lower SAS score. Although only a few patients showed SAS scores > 50 before surgery, the SAS score was lower in the C group after surgery compared to the S group, which confirmed the anxiolytic effect of S-ketamine.

A recent review systematically reviewed 288 published reports of studies and identified the main side effects related to ketamine (24). The most common side effects reported were headache, dizziness, dissociation, elevated blood pressure, and blurred vision. These side effects occur immediately after a single-dose administration, especially if the drug was given intravenously, and most side effects were resolved shortly after administration. High doses and repeated administration have been associated with potentially serious and persistent toxic effects, including urological, hepatic, craving or dependence, and cognitive changes, which limit its clinical utilization (24,25). S-ketamine has a similar spectrum of side-effect as ketamine; however, S-ketamine has less incidence of these side effects compared to ketamine. S-ketamine has 4 times the affinity for NMDA receptors as R-ketamine, and a lower dose of S-ketamine could result in similar effects without such side effects (6). Our results confirmed that a sub-anesthesia dose of S-ketamine prevented postoperative hypersensitivity formation and anxiety without increasing the side effects when compared to normal saline. Nausea, vomiting, delirium, illusion, pruritus, and recovery time were not different between the 2 groups; even the incidence of sore throat and headache were lower in the S group, which may be attributed to the analgesic effect of S-ketamine. The Ramsay sedation score was slightly higher than the normal saline group. The low incidence of side effects of S-ketamine provides new options in future perioperative multi-modal analgesia, and larger sample size studies are needed to assess the side effects of this medication.

We finally combined the data and explored the risk factors of moderate to severe pain after breast and thyroid surgery. Our results identified that S-ketamine and regular exercise are protective factors, and anxiety score before surgery is a risk factor for moderate to severe postoperative pain. A recent review study indicated that about one in 2 patients undergoing surgery suffers from preoperative anxiety (26); and preoperative anxiety has been verified to be a critical risk factor for postoperative pain and longer hospital stay (27-29). Consistent with the previous studies, our results con-

firmed that conclusion and the reasons for this might be attributed to the fact that anxiety activates some brain regions related to pain (30). Thus, patients with higher preoperative anxiety scores are preconditioned and more prone to develop postoperative pain. Surprisingly, our results identified that regular exercise is a protective factor for postoperative pain. Previous studies have demonstrated that regular exercise-based treatment results in improvements in chronic pain and function by improving anti-inflammatory properties (31,32). However, in our study, preoperative exercise decreased the acute postoperative pain, which may be due to the exercise-induced preconditioning effect (33,34).

Limitations

Our study has several limitations. Firstly, our research is a small sample size study, some side effects may not be observed, and logistic regression results may not be potent enough to identify some risk factors of postoperative pain in patients receiving breast and thyroid surgery. In addition, the anxiety score in our study is not so high, and this may under-evaluate the anxiolytic effect of S-ketamine. Thirdly, the optimal dosage of S-ketamine for postoperative pain and anxiety should be further examined. Lastly, this study was only conducted at a single center. In the future, we will coordinate with different hospitals to evaluate the effects of S-ketamine on postoperative pain and anxiety. However, our results verified intraoperative sub-anesthesia dose S-ketamine may be a promising method for treating postoperative pain sensitization and anxiety.

Conclusions

Intraoperative S-ketamine presents analgesic and anxiolytic effects in patients receiving breast and thyroid surgery. Intraoperative S-ketamine and regular exercise are protective factors, and anxiety before surgery is a risk factor for acute postoperative moderate to severe pain.

Authors' Contributions

Fan Liu and Dongxu Zhou did the experiments. Fei Jiang did the statistical analysis. Xingrui Gong and Xihong Ye designed the experiment. Mazhong Zhang revised the manuscript. All authors read and approved the final manuscript.

References

1. Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. *Lancet* 2019; 393:1537-1546.
2. Bates GE, Mostel JL, Hesdorffer M. Cancer-related anxiety. *JAMA Oncol* 2017; 3:1007.
3. Li XR, Zhang WH, Williams JP, et al. A multicenter survey of perioperative anxiety in China: Pre- and postoperative associations. *J Psychosom Res* 2021; 147:110528.
4. Hassett AL, Marshall E, Bailey AM, et al. Changes in anxiety and depression are mediated by changes in pain severity in patients undergoing lower-extremity total joint arthroplasty. *Reg Anesth Pain Med* 2018; 43:14-18.
5. Hollmann MW, Rathmell JP, Lirk P. Optimal postoperative pain management: Redefining the role for opioids. *Lancet* 2019; 393:1483-485.
6. Wang X, Lin C, Lan L, Liu J. Perioperative intravenous S-ketamine for acute postoperative pain in adults: A systematic review and meta-analysis. *J Clin Anesth* 2021; 68:110071.
7. Daly EJ, Singh JB, Fedgchin M, et al. Efficacy and safety of intranasal esketamine adjunctive to oral antidepressant therapy in treatment-resistant depression: A randomized clinical trial. *JAMA Psychiat* 2018; 75:139-148.
8. Yang S, Xu K, Xu X, et al. S-ketamine pretreatment alleviates anxiety-like behaviors and mechanical allodynia and blocks the pro-inflammatory response in striatum and periaqueductal gray from a post-traumatic stress disorder model. *Front Behav Neurosci* 2022; 16:848232.
9. Olatunji BO, Deacon BJ, Abramowitz JS, Tolin DF. Dimensionality of somatic complaints: Factor structure and psychometric properties of the self-rating anxiety scale. *J Anxiety Disord* 2006; 20:543-61.
10. Ding D, Mutrie N, Bauman A, Pratt M, Hallal PRC, Powell KE. Physical activity guidelines 2020: Comprehensive and inclusive recommendations to activate populations. *Lancet* 2020; 396:1780-1782.
11. Brinck EC, Tiippana E, Heesen M, et al. Perioperative intravenous ketamine for acute postoperative pain in adults. *Cochrane Database Syst Rev* 2018; 12:D12033.
12. Boenigk K, Echevarria GC, Nisimov E, et al. Low-dose ketamine infusion reduces postoperative hydromorphone requirements in opioid-tolerant patients following spinal fusion: A randomised controlled trial. *Eur J Anaesthesiol*. 2019; 36:8-15.
13. Qi F, Liu T, Zhang X, et al. Ketamine reduces remifentanil-induced postoperative hyperalgesia mediated by CaMKII-NMDAR in the primary somatosensory cerebral cortex region in mice. *Neuropharmacology* 2020; 162:107783.
14. Ilkjaer S, Petersen KL, Brennum J, Wernberg M, Dahl JB. Effect of systemic N-methyl-D-aspartate receptor antagonist (ketamine) on primary and secondary hyperalgesia in humans. *Br J Anaesth* 1996; 76:829-834.
15. Nielsen RV, Fomsgaard JS, Nikolajsen L, Dahl JB, Mathiesen O. Intraoperative S-ketamine for the reduction of opioid consumption and pain one year after spine surgery: A randomized clinical trial of opioid-dependent patients. *Eur*

J Pain 2019; 23:455-460.

16. Xu X, Tao X, Huang P, al. N-methyl-d-aspartate receptor subunit 2B on keratinocyte mediates peripheral and central sensitization in chronic post-ischemic pain in male rats. *Brain Behav Immun* 2020; 87:579-590.
17. Wang Q, Xiao M, Sun H, Zhang P. A Study on the preventive effect of esketamine on postpartum depression (PPD) after Cesarean section. *Comput Math Methods Med* 2022; 2022:1524198.
18. Machado C, Lacerda ALT, Bressan RA, Noto C. Esketamine for Postpartum Suicidality. *Biol Psychiatry* 2021; 89:e35-e36.
19. Schaal NK, Hepp P, Heil M, et al. Perioperative anxiety and length of hospital stay after caesarean section - A cohort study. *Eur J Obstet Gynecol Reprod Biol* 2020; 248:252-256.
20. Glue P, Neehoff S, Sabadel A, et al. Effects of ketamine in patients with treatment-refractory generalized anxiety and social anxiety disorders: Exploratory double-blind psychoactive-controlled replication study. *J Psychopharmacol* 2020; 34:267-272.
21. Tully JL, Dahlen AD, Haggarty CJ, Schioth HB, Brooks S. Ketamine treatment for refractory anxiety: A systematic review. *Br J Clin Pharmacol* 2022; 88:4412-4426.
22. Whittaker E, Dadabayev AR, Joshi SA, Glue P. Systematic review and meta-analysis of randomized controlled trials of ketamine in the treatment of refractory anxiety spectrum disorders. *Ther Adv Psychopharmacol* 2021; 11:1926974055.
23. Yang S, Xu K, Xu X, et al. S-ketamine pretreatment alleviates anxiety-like behaviors and mechanical allodynia and blocks the pro-inflammatory response in striatum and periaqueductal gray from a post-traumatic stress disorder model. *Front Behav Neurosci* 2022; 16:848232.
24. Short B, Fong J, Galvez V, Shelker W, Loo CK. Side-effects associated with ketamine use in depression: A systematic review. *Lancet Psychiatry* 2018; 5:65-78.
25. Acevedo-Diaz EE, Cavanaugh GW, Greenstein D, et al. Comprehensive assessment of side effects associated with a single dose of ketamine in treatment-resistant depression. *J Affect Disord*. 2020; 263:568-575.
26. Bedaso A, Mekonnen N, Duko B. Prevalence and factors associated with preoperative anxiety among patients undergoing surgery in low-income and middle-income countries: A systematic review and meta-analysis. *BMJ Open* 2022; 12:e58187.
27. Gravani S, Matiatou M, Nikolaidis PT, et al. Anxiety and depression affect early postoperative pain dimensions after bariatric surgery. *J Clin Med* 2020; 10:53.
28. Gu D, Zhou M, Han C, et al. Preoperative anxiety induces chronic postoperative pain by activating astrocytes in the anterior cingulate cortex region. *Rev Assoc Med Bras* (1992) 2019; 65:1174-1180.
29. Stamenkovic DM, Rancic NK, Latas MB, et al. Preoperative anxiety and implications on postoperative recovery: What can we do to change our history. *Minerva Anestesiol* 2018; 84:1307-17.
30. Zhuo M. Neural mechanisms underlying anxiety-chronic pain interactions. *Trends Neurosci* 2016; 39:136-145.
31. Borisovskaya A, Chmelik E, Karnik A. Exercise and chronic pain. *Adv Exp Med Biol* 2020; 1228:233-253.
32. Owen PJ, Miller CT, Mundell NL, et al. Which specific modes of exercise training are most effective for treating low back pain? Network meta-analysis. *Br J Sports Med* 2020; 54:1279-1287.
33. Gong X, Jiang J, Zhang M. Exercise preconditioning reduces neonatal incision surgery-induced enhanced hyperalgesia via inhibition of P38 mitogen-activated protein kinase and IL-1β, TNF-α release. *Int J Dev Neurosci* 2016; 52:46-54.
34. Powers SK, Bomkamp M, Ozdemir M, Hyatt H. Mechanisms of exercise-induced preconditioning in skeletal muscles. *Redox Biol* 2020; 35:101462.