

An Intraoperative Sub-Anesthetic Dose of Esketamine on Postoperative Depressive Symptoms in Perimenopausal Women with Breast Cancer Undergoing Modified Radical Mastectomy: Protocol for a Randomized, Triple-Blinded, Controlled Trial

Lin-Lin Liu^{1,2,*}, Jing-Hui Hu^{1,2,*}, Jing-Jing Pan^{1,3,*}, Hong Liu⁴, Fu-Hai Ji^{1,2}, Ke Peng^{1,2}

¹Departments of Anesthesiology, First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, People's Republic of China; ²Institute of Anesthesiology, Soochow University, Suzhou, Jiangsu, People's Republic of China; ³Department of Anesthesiology, Guanyun People's Hospital, Lianyungang, Jiangsu, People's Republic of China; ⁴Department of Anesthesiology and Pain Medicine, University of California Davis Health, Sacramento, CA, USA

*These authors contributed equally to this work

Correspondence: Ke Peng, Department of Anesthesiology, First Affiliated Hospital of Soochow University, 188 Shizi Street, Suzhou, Jiangsu, 215006, People's Republic of China, Tel +86-159-6215-5989, Email pengke0422@163.com

Background: Depressive symptoms are common among perimenopausal women with breast cancer having modified radical mastectomy. Esketamine exerts antidepressant effects. This study aims to assess whether an intraoperative sub-anesthetic dose of esketamine prevents postoperative depressive symptoms in these patients.

Methods: In this randomized, triple-blinded, placebo-controlled trial, we will enroll 130 perimenopausal women (aged 45–60 years) with breast cancer undergoing unilateral modified radical mastectomy. Patients will be randomly assigned with a 1:1 ratio to receive either esketamine (0.25 mg/kg i.v.) or normal saline after anesthesia induction and before skin incision. The primary outcome is the incidence of depressive symptoms at day 30 postoperatively, assessed using the Beck's Depression Inventory (BDI). Secondary outcomes include incidence of depressive symptoms and BDI scores at day 1, 3, and 180 postoperatively, anxiety symptoms and scores at day 1, 3, 30, and 180 postoperatively, pain intensity and quality of recovery at day 1 and 2 postoperatively, nausea and vomiting within 48 hours postoperatively, length of postoperative hospital stay, and cancer-specific outcomes. Data will be analyzed in the modified intention-to-treat population.

Discussion: This is the first trial to evaluate the effects of a sub-anesthetic dose of esketamine on depressive symptoms in perimenopausal women after modified radical mastectomy. The results of this study will help to improve their mental health and recovery after breast cancer surgery.

Trial Registration: Chinese Clinical Trial Registry (ChiCTR2200064348).

Keywords: esketamine, perimenopausal women, depressive symptoms, breast cancer, modified radical mastectomy

Introduction

According to the recent cancer statistics, breast cancer has become the most commonly diagnosed cancer in the world and continues to have significant impacts on public health.¹ With advances in treatment, the mortality rate of breast cancer has declined; however, survivors often suffer from adverse mental health outcomes, such as depression and anxiety.² Recent studies showed that the prevalence rate of depressive symptoms ranged from 9% to 66% and of anxiety

from 18% to 33% in breast cancer survivors.^{3,4} For perimenopausal women undergoing surgery, they are more likely to experience these symptoms, leading to increased risk of health problems and reduced quality of life.⁵

Ketamine, a noncompetitive antagonist of N-methyl-D-aspartic acid (NMDA) receptors, is commonly used for sedation, analgesia, and anesthesia. The antidepressant effect of ketamine has been studied in recent years.^{6–8} Esketamine is the more potent S-enantiomer of racemic ketamine.⁹ The Food and Drug Administration has approved the use of esketamine for treatment-resistant depression (TRD).¹⁰ According to a recent international consensus, intranasal esketamine demonstrates efficacy and safety for up to 1 year in patients with TRD, but long-term evidence of ketamine in TRD is insufficient.¹¹ A recent study suggested that esketamine alleviated postoperative depression after laparoscopic total hysterectomy, which was more effective compared to the racemic ketamine.¹² Two meta-analyses have reported the benefits of perioperative ketamine or esketamine on postoperative depressive symptoms.^{13,14} Our recent work also suggested that a perioperative low-dose esketamine infusion reduced postoperative depressive symptoms in patients after thoracoscopic lung cancer surgery.¹⁵ However, as far as we know, there is no study on perioperative use of esketamine in perimenopausal women with breast cancer.

The main purpose of this study is to explore the effects of an intraoperative sub-anesthetic dose of esketamine on depressive symptoms in perimenopausal women after modified radical mastectomy. We hypothesize that the use of esketamine would prevent depressive symptoms in our patients.

Methods

Ethics and Registration

The protocol of this trial was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University (Approval No. 2022-204) on August 4, 2022. This trial was registered at the Chinese Clinical Trial Registry (<http://www.chictr.org.cn>, identifier: ChiCTR2200064348) on October 3, 2022. This study will be conducted in accordance with the Declaration of Helsinki. Written informed consent will be obtained from all patients. This protocol follows the guidelines of Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.¹⁶

Study Design

This is an investigator-initiated, randomized, triple-blinded, controlled trial, including a total of 130 perimenopausal women undergoing unilateral modified radical mastectomy at the First Affiliated Hospital of Soochow University, Suzhou, China. The study is ongoing by the time of this manuscript submission. [Figure 1](#) presents the study flow diagram. [Table 1](#) shows the schedule of patient enrollment, study interventions, and measurements complying with the SPIRIT statement.

Eligibility Criteria

The inclusion criteria of this study are as follows: (1) perimenopausal women aged 45–60 years; (2) American Society of Anesthesiologists (ASA) physical status I–III; (3) preoperative diagnosis of breast cancer and scheduled for unilateral modified radical mastectomy under general anesthesia; and (4) providing a written informed consent.

Patients will be excluded if they meet the following criteria: (1) unplanned or emergent surgery; (2) left ventricular ejection fraction <30% or respiratory failure; (3) serious liver or renal dysfunction (Child-Pugh grade C or need for renal replacement therapy); (4) mental illness (any DSM-V diagnosis, eg, depressive disorders, anxiety disorders, and personality disorders), long-term use of antipsychotics or drug addict; (5) having allergies or contraindications to study medications; (6) illiteracy or inability to understand the scales in this study.

Randomization and Blinding

An independent statistician generates a randomization list using an online tool (<https://www.sealedenvelope.com>), with an allocation ratio of 1:1 and permuted block sizes of 2 and 4. Eligible patients will be randomized to an esketamine group or a normal saline group. The details of allocation are concealed using opaque sealed envelopes. An independent anesthesia nurse prepares the study medications (esketamine or normal saline) according to the randomization results,

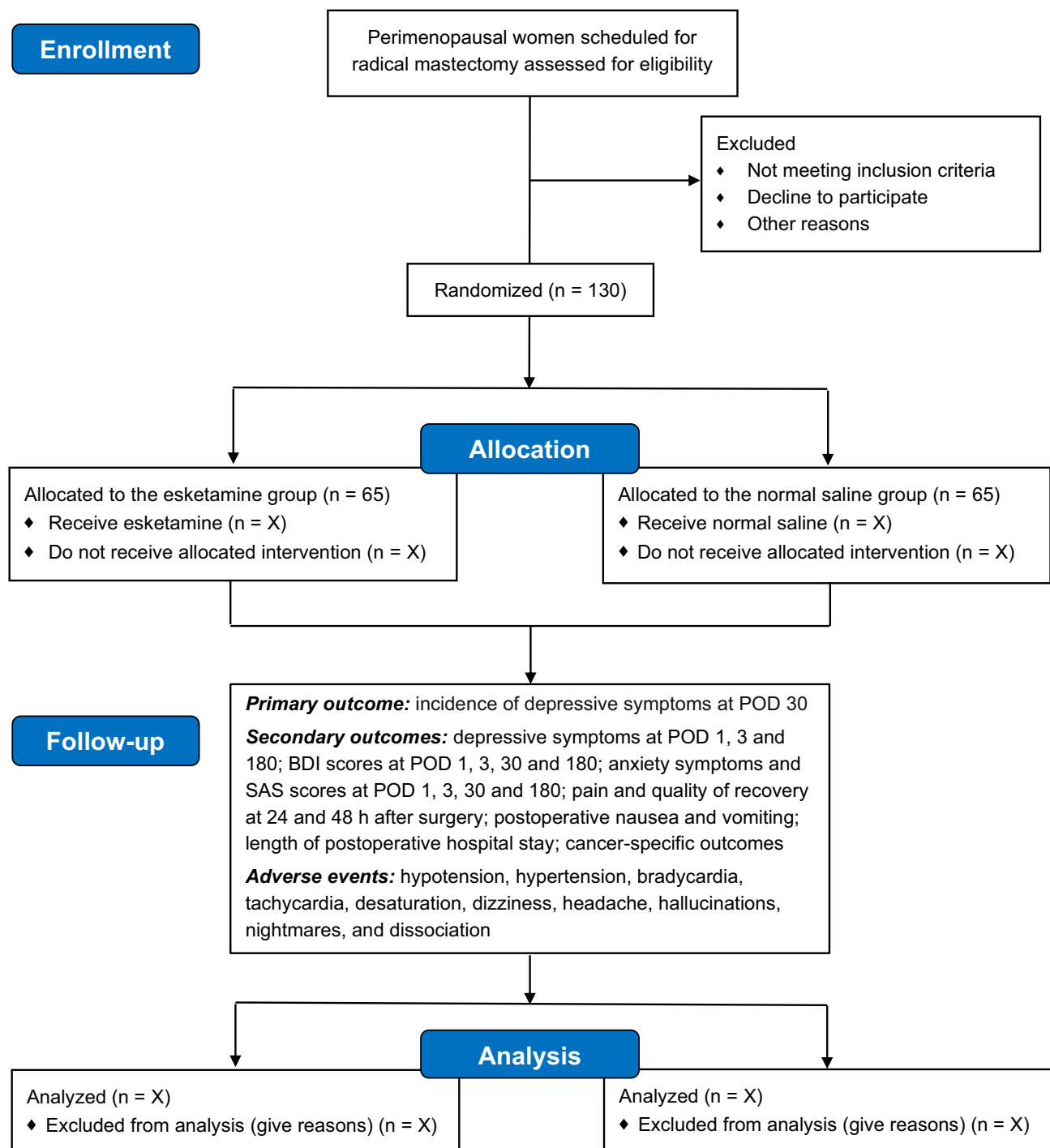


Figure 1 Study flow diagram.

Abbreviations: BDI, Beck's Depression Scale; SAS, Self-rating Anxiety Scale; POD, postoperative day.

and then the medications will be distributed to independent attending anesthesiologists. It is impossible to distinguish esketamine and normal saline because both of them are colorless and transparent solutions. Patients, anesthesiologists, surgeons, investigators responsible for data collection and outcome assessment, and statisticians will be blinded to the group allocation.

Table 1 Schedule of Patient Enrollment, Study Interventions, and Measurements

Timepoint	Study Period									
	Enrollment	Allocation	Post-Allocation					Close-Out		
	Preanesthetic Visit	Before Surgery	During Surgery	POD 1	POD 2	POD 3	Hospital Discharge	POD 30	POD 180	
Enrollment										
Eligibility screening	x									
Written informed consent	x									
Randomization		x								
Allocation		x								
Interventions										
Esketamine			x							
Normal saline			x							
Measurements										
Baseline characteristic	x									
Depressive symptoms	x			x		x		x	x	
BDI score	x			x		x		x	x	
Anxiety symptoms	x			x		x		x	x	
SAS score	x			x		x		x	x	
Pain intensity				x	x					
Quality of recovery				x	x					
PONV					x					
Postoperative hospital stay							x			
Cancer-specific outcomes								x	x	
Adverse events ^a			x	x	x					

Notes: According to SPIRIT statement of defining standard protocol items for clinical trials. ^aIncluding hypotension, hypertension, bradycardia, tachycardia, desaturation, dizziness, headache, hallucinations, nightmares, and dissociation.

Abbreviations: BDI, Beck's Depression Scale; SAS, Self-rating Anxiety Scale; PONV, postoperative nausea and vomiting; POD, postoperative day.

Anesthesia and Study Interventions

All patients will fast for 6–8 h with no premedication. Patients will be monitored following the ASA monitoring standards. Anesthesia will be induced with intravenous propofol 1.5–2 mg/kg, sufentanil 0.3 µg/kg, and cisatracurium 0.2 mg/kg. After anesthesia induction, dexamethasone 5 mg and palonosetron 0.075 mg will be given to prevent postoperative nausea and vomiting (PONV). After endotracheal intubation, the lungs will be mechanically ventilated (tidal volume of 8–10 mL/kg, frequency of 12–18 breaths/mins, and inspired oxygen fraction of 50–80%) according to the clinical practice at our institution. Ventilation will be adjusted to maintain the peripheral oxygen saturation \geq 95% and the end-tidal carbon dioxide at 35–40 mmHg.

For the administration of study medications, patients will receive intravenous injection of 0.25 mg/kg esketamine (the esketamine group) or an equivalent volume of normal saline (the normal saline group), after anesthesia induction and before surgical incision.

Anesthesia will be maintained with 1–3% sevoflurane inhalation targeting minimal alveolar concentration of 0.7–1.3. Intermittent intravenous boluses of sufentanil 0.1 µg/kg and cisatracurium 0.1 mg/kg will be administered when needed. Nasopharyngeal temperature will be maintained at 36–37°C using a warming blanket. Patients will receive Lactated Ringer solution for fluid repletion. Flurbiprofen axetil 50 mg will be given intraoperatively. After surgery, patients will be extubated and transferred to a post-anesthesia care unit (PACU). Patients with a modified Aldrete score \geq 9 will be discharged to their surgical ward.

Study Outcomes

The primary outcome of this study is the incidence of depressive symptoms at day 30 postoperatively, assessed using the Beck's Depression Inventory (BDI). The BDI includes 13 self-rating items consisting of cognitive, affective, and somatic contents. Each item is rated on a 4-point scale (0–3), and the total BDI scores range from 0 to 39. Higher scores indicate a more severe depression (0–4, no depression; 5–7, mild depression; 8–15, moderate depression; ≥ 16 , severe depression).^{17,18}

The secondary outcomes include (1) incidence of depressive symptoms at day 1, 3, and 180 postoperatively, (2) BDI scores at day 1, 3, 30, and 180 postoperatively, (3) incidence of anxiety symptoms at day 1, 3, 30, and 180 postoperatively, assessed using the Self-rating Anxiety Scale (SAS), (4) SAS scores at day 1, 3, 30, and 180 postoperatively, (5) pain intensity at rest and on coughing at day 1 and 2 postoperatively, assessed using the Visual Analogue Scale (VAS), (6) quality of recovery at day 1 and 2 postoperatively, assessed using the Quality of Recovery (QoR)-15, (7) PONV within 48 hours, (8) length of postoperative hospital stay, and (9) cancer-specific outcomes including overall survival, disease-free survival and progression-free survival.

The SAS is a validated anxiety scale that includes 20 items covering a variety of anxiety symptoms. Responses are given for each item on a 4-point scale (1–4), and raw total scores range from 20 to 80. The final SAS score is calculated as the raw total scores multiplied by 1.25. The total SAS scores range from 25 to 100. Higher scores represent a more severe anxiety (0 to 49, no anxiety; 50 to 59, mild anxiety; 60 to 69, moderate anxiety; ≥ 70 , severe anxiety).^{19–21}

The VAS is widely used to measure pain intensity in clinical settings, ranging from 0 (no pain) to 10 (the most severe pain).²² The QoR-15 is a convenient patient-reported tool, including 15 items of five domains (pain, comfort, physical independence, psychological support, and emotional state) with each item ranging from 0 to 10. Higher scores suggest better quality of recovery (0–89, poor recovery; 90–121, moderate recovery; 122–135, good recovery; 136–150, excellent recovery).^{23–25}

Perioperative adverse events include intraoperative hemodynamic events (hypotension, hypertension, bradycardia, and tachycardia) and postoperative events (desaturation, dizziness, headache, hallucinations, nightmares, and dissociation) within the first 2 days postoperatively.

Data Collection and Monitoring

A trained independent investigator will collect patients' demographic data and baseline characteristics preoperatively (including age, body mass index, marital status, education years, ASA physical status, surgical site, hypertension, diabetes, and preoperative medications). The BDI, SAS and Social Support Rating Scale (SSRS) scores will be measured via the WeChat application. The SSRS is a self-reported scale to assess patients' social support over the past year, including subjective support, objective support and utilization of social support. Higher SSRS scores indicate a higher level of social support.²⁶

Perioperative data include duration of anesthesia, duration of surgery, time to extubation, length of stay in PACU, and adverse events. The BDI and SAS scores will be collected on day 1, 3, 30, and 180 postoperatively via the WeChat application. The VAS and QoR-15 scores will be collected at 24 and 48 h after surgery via ward visit. The cancer-specific outcomes will be collected on day 180 via telephone.

All data will be recorded using case report forms and registered on an electronic database. Upon completing data registration, the database will be locked. After deidentification, the database will be sent to an independent statistician at the Department of Epidemiology and Biostatistics, Soochow University. An independent data monitoring committee will supervise the whole process of this study to ensure patients' safety.

Sample Size

According to the previous studies, the incidence of depressive symptoms after modified radical mastectomy is approximately 30%.^{3,4} We expect that the use of esketamine would lead to a 20% reduction in this incidence. Based on this assumption, 59 patients are needed in each group with a power of 80% and an α level of 0.05. To take into account

a possible drop-out rate of 10%, a total of 130 patients ($n = 65$ in each group) will be recruited. The sample size is calculated using the PASS software (version 15.0.5, NCSS, LCC, Kaysville, UT).

Statistical Analysis

For continuous data, means (standard deviations) or medians (interquartile ranges) will be reported depending on data distribution. For categorical data, numbers (percentages) will be reported. Data will be analyzed using the independent *t*-test, repeated measures analysis of variance, or Mann Whitney rank sum test, Chi-squared test, or Fisher's exact test, as appropriate.

The demographic data and baseline characteristics will be presented using the descriptive statistics only. For the study outcomes, the between-group differences will be assessed using mean difference or odds ratio with 95% confidence intervals. For the primary outcome, a multivariate logistic regression model will be applied to adjust for the baseline covariates (preoperative BDI, SAS, and SSRS scores). Moreover, subgroup analyses will be conducted according to preoperative depressive symptoms, anxiety symptoms, and social support levels. For the secondary outcomes, no corrections for multiple comparisons will be used, and these outcomes should be considered exploratory. Disease progression will be included as a confounder in analyzing the long-term outcomes.

All analyses will be conducted based on the modified intention-to-treat population. There are no plans for missing data imputation or interim analysis. Statistical analysis will be performed using the SPSS 26.0 software (SPSS Inc, Chicago, IL, USA). A two-sided $P < 0.05$ is considered statistically significant.

Discussion

This randomized triple-blind controlled trial will recruit 130 perimenopausal women undergoing modified radical mastectomy to evaluate the effects of a single intraoperative sub-anesthetic dose of esketamine on postoperative depressive symptoms. The main hypothesis is that the use of esketamine would prevent depressive symptoms up to 30 days after surgery. We also hypothesize that esketamine would improve anxiety symptoms and quality of recovery after surgery, without increasing adverse events. The results of this trial will be reported conforming to the Consolidated Standards of Reporting Trials guidelines.²⁷

Perimenopause is a special and inevitable period which represents the final reproductive transition stage in a woman's life.^{28,29} Women in the perimenopausal period have increased prevalence of depressive symptoms compared with women in the premenopausal period.²⁸ With the influence of breast cancer and surgery on mental health, perimenopausal women undergoing modified radical mastectomy are more prone to mental problems.⁴ However, based on the available evidence, there is lack of effective prophylactic or therapeutic approaches for depressive or anxiety symptoms in these vulnerable patients.

A sub-anesthetic dose of esketamine may improve postoperative depression symptoms. For patients with colorectal cancer, esketamine 0.3 mg/kg reduced the incidence of depressive symptoms after colorectal surgery.³⁰ For patients undergoing laparoscopic total hysterectomy, esketamine at a dose of 0.25 or 0.5 mg/kg alleviated postoperative depression during the first 3 days after surgery, which was more effective than the racemic ketamine.¹² For patients with Crohn's disease, esketamine 0.25 mg/kg during anesthesia induction followed by continuous infusion at 0.12 mg/kg/h for 30 min reduced mild-to-moderate depressive symptoms after bowel resection.³¹ A recent study suggested that esketamine reduced the average depression scores for breast cancer patients, but that study did not report or compare the incidence of depressive symptoms.³² Therefore, our study will test the antidepressant effects of esketamine in perimenopausal women undergoing modified radical mastectomy.

The administration of esketamine may cause several side effects, such as headache, nausea and vomiting, excessive salivation, dissociation, and elevated blood pressure and heart rate, which are often dose-dependent and transient.^{33,34} In our study, we use a sub-anesthetic dose of esketamine (0.25mg/kg) and we expect that this dose is unlikely to cause significant adverse effects.

There are some possible mechanisms of the antidepressant action of the NMDA receptor antagonist ketamine or esketamine. Brain-derived neurotrophic factor (BDNF) plays a crucial role in depression.^{35,36} Previous studies suggested that ketamine reduced the levels of serum inflammatory factors, alleviated neuroinflammation, and increased the

expression of BDNF.^{37,38} In addition, Li et al showed that increased synaptic signaling proteins and new spine synapses through the activation of the rapamycin pathway underlay the rapid antidepressant effects of ketamine in rats.³⁹

The strengths of this study include the patient population (perimenopausal women with breast cancer who are extremely vulnerable to depressive symptoms), the explicit primary outcome of 30-day depressive symptoms, and the randomized triple-blind controlled study design. This study has some limitations. First, our patients will receive an intraoperative sub-anesthetic dose of 0.25 mg/kg esketamine, and the optimal dose needs further investigations. Second, this study would have been more influential if we designed this study comparing three arms: ketamine, esketamine, and placebo. Whether or not ketamine and esketamine are superior to placebo and whether or not they are superior to each other need to be assessed in future studies. Last, it is likely that many patients with preoperative mental disorders do not voluntarily participate in epidemiological studies,⁴⁰ so our patients included in this study may not be representative of the whole patient population.

In conclusion, this trial aims to explore whether an intraoperative sub-anesthetic dose of esketamine reduces the incidence of postoperative depressive symptoms in perimenopausal women undergoing modified radical mastectomy. The results will help to improve postoperative mental health and recovery for these patients.

Abbreviations

ASA, American Society of Anesthesiologists; BDI, Beck's Depression Inventory; PACU, Post-anesthesia care unit; PONV, Postoperative nausea and vomiting; QoR-15, Quality of Recovery-15; SAS, Self-rating Anxiety Scale; SPIRIT, Standard Protocol Items: Recommendations for Interventional Trials; SSRS, Social Support Rating Scale; VAS, Visual Analogue Scale.

Data Sharing Statement

Data available at chictr.org.cn (ChiCTR2200064348). All data relevant to the study is included in this manuscript. The prospective listing of the study on the Chinese Clinical Trial Registry can be found at <https://www.chictr.org.cn/showproj.html?proj=179003>.

Ethics Approval and Consent to Participate

The trial protocol was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University (Approval No. 2022-204) on August 4, 2022. This trial was registered at the Chinese Clinical Trial Registry (<http://www.chictr.org.cn>, identifier: ChiCTR2200064348) on October 3, 2022. This study will be conducted in accordance with the Declaration of Helsinki. Written informed consent will be obtained from all patients.

Acknowledgments

We would like to thank all patients, therapists, supervisors and research assistants who will participate in the study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work is supported by the Suzhou Medical Health Science and Technology Innovation Project (SKY2022136 to KP), Jiangsu Medical Association Anesthesia Research Project (SYH-32021-0036 (2021031) to KP), College Students' Extracurricular Academic Research Project of Soochow University (KY2023101A to JHH), National Natural Science Foundation of China (82072130 to FHJ), Key Medical Research Projects in Jiangsu Province (ZD2022021 to FHJ), and Suzhou Clinical Medical Center for Anesthesiology (Szlcyxzxj202102 to FHJ). The funders have no role in study design,

management, data collection, analysis, data interpretation, writing of the report, or the decision to submit the report for publication.

Disclosure

The authors declare that they have no competing interests in this work.

References

1. Arnold M, Morgan E, Runggay H, et al. Current and future burden of breast cancer: global statistics for 2020 and 2040. *Breast*. 2022;66:15–23. doi:10.1016/j.breast.2022.08.010
2. Carreira H, Williams R, Funston G, Stanway S, Bhaskaran K. Associations between breast cancer survivorship and adverse mental health outcomes: a matched population-based cohort study in the United Kingdom. *PLoS Med*. 2021;18(1):e1003504. doi:10.1371/journal.pmed.1003504
3. Kim SY, Kim SW, Shin IS, et al. Changes in depression status during the year after breast cancer surgery and impact on quality of life and functioning. *Gen Hosp Psychiatry*. 2018;50:33–37. doi:10.1016/j.genhosppsych.2017.09.009
4. Maass SW, Roorda C, Berendsen AJ, Verhaak PF, de Bock GH. The prevalence of long-term symptoms of depression and anxiety after breast cancer treatment: a systematic review. *Maturitas*. 2015;82(1):100–108. doi:10.1016/j.maturitas.2015.04.010
5. Tang R, Luo M, Li J, et al. Symptoms of anxiety and depression among Chinese women transitioning through menopause: findings from a prospective community-based cohort study. *Fertil Steril*. 2019;112(6):1160–1171. doi:10.1016/j.fertnstert.2019.08.005
6. Yang Y, Cui Y, Sang K, et al. Ketamine blocks bursting in the lateral habenula to rapidly relieve depression. *Nature*. 2018;554(7692):317–322. doi:10.1038/nature25509
7. Smith-Apeldoorn SY, Veraart JK, Spijker J, Kamphuis J, Schoevers RA. Maintenance ketamine treatment for depression: a systematic review of efficacy, safety, and tolerability. *Lancet Psychiatry*. 2022;9(11):907–921. doi:10.1016/S2215-0366(22)00317-0
8. Hirota K, Lambert DG. Ketamine and depression. *Br J Anaesth*. 2018;121(6):1198–1202. doi:10.1016/j.bja.2018.08.020
9. Johnston JN, Henter ID, Zarate CA Jr. The antidepressant actions of ketamine and its enantiomers. *Pharmacol Ther*. 2023;246:108431. doi:10.1016/j.pharmthera.2023.108431
10. Kim J, Farchione T, Potter A, Chen Q, Temple R. Esketamine for treatment-resistant depression - first FDA-approved antidepressant in a new class. *N Engl J Med*. 2019;381(1):1–4. doi:10.1056/NEJMp1903305
11. McIntyre RS, Rosenblat JD, Nemeroff CB, et al. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: an international expert opinion on the available evidence and implementation. *Am J Psychiatry*. 2021;178(5):383–399. doi:10.1176/appi.ajp.2020.20081251
12. Wang J, Wang Y, Xu X, Peng S, Xu F, Liu P. Use of various doses of S-ketamine in treatment of depression and pain in cervical carcinoma patients with mild/moderate depression after laparoscopic total hysterectomy. *Med Sci Monit*. 2020;26:e922028. doi:10.12659/MSM.922028
13. Guo J, Qiu D, Gu HW, et al. Efficacy and safety of perioperative application of ketamine on postoperative depression: a meta-analysis of randomized controlled studies. *Mol Psychiatry*. 2023. doi:10.1038/s41380-023-01945-z
14. Wang J, Sun Y, Ai P, et al. The effect of intravenous ketamine on depressive symptoms after surgery: a systematic review. *J Clin Anesth*. 2022;77:110631. doi:10.1016/j.jclinane.2021.110631
15. Gan SL, Long YQ, Wang QY, et al. Effect of esketamine on postoperative depressive symptoms in patients undergoing thoracoscopic lung cancer surgery: a randomized controlled trial. *Front Psychiatry*. 2023;14:1128406. doi:10.3389/fpsy.2023.1128406
16. Calvert M, Kyte D, Mercieca-Bebber R, et al. Guidelines for inclusion of patient-reported outcomes in clinical trial protocols: the SPIRIT-PRO extension. *JAMA*. 2018;319(5):483–494. doi:10.1001/jama.2017.21903
17. Beck AT, Beamesderfer A. Assessment of depression: the depression inventory. *Mod Probl Pharmacopsychiatry*. 1974;7:151–169. doi:10.1159/000395074
18. Fan N, Xu K, Ning Y, et al. Profiling the psychotic, depressive and anxiety symptoms in chronic ketamine users. *Psychiatry Res*. 2016;237:311–315. doi:10.1016/j.psychres.2016.01.023
19. Zung WW. A rating instrument for anxiety disorders. *Psychosomatics*. 1971;12(6):371–379. doi:10.1016/S0033-3182(71)71479-0
20. Dunstan DA, Scott N. Norms for Zung's Self-rating Anxiety Scale. *BMC Psychiatry*. 2020;20(1):90. doi:10.1186/s12888-019-2427-6
21. Geng Y, Gao T, Zhang X, Wang Y, Zhang Z. The association between disease duration and mood disorders in rheumatoid arthritis patients. *Clin Rheumatol*. 2022;41(3):661–668. doi:10.1007/s10067-021-05967-2
22. Genc C, Kaya C, Bilgin S, Dost B, Ustun YB, Koksak E. Pectoserratus plane block versus erector spinae plane block for postoperative opioid consumption and acute and chronic pain after breast cancer surgery: a randomized controlled trial. *J Clin Anesth*. 2022;79:110691. doi:10.1016/j.jclinane.2022.110691
23. Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. *Anesthesiology*. 2013;118(6):1332–1340. doi:10.1097/ALN.0b013e318289b84b
24. Wessels E, Perrie H, Scribante J, Joama Z. Quality of recovery in the perioperative setting: a narrative review. *J Clin Anesth*. 2022;78:110685. doi:10.1016/j.jclinane.2022.110685
25. Kleif J, Gogenur I. Severity classification of the quality of recovery-15 score-an observational study. *J Surg Res*. 2018;225:101–107. doi:10.1016/j.jss.2017.12.040
26. Tao Y, Yu H, Liu S, et al. Hope and depression: the mediating role of social support and spiritual coping in advanced cancer patients. *BMC Psychiatry*. 2022;22(1):345. doi:10.1186/s12888-022-03985-1
27. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c869. doi:10.1136/bmj.c869
28. de Kruif M, Spijker AT, Molendijk ML. Depression during the perimenopause: a meta-analysis. *J Affect Disord*. 2016;206:174–180. doi:10.1016/j.jad.2016.07.040

29. Grub J, Suss H, Willi J, Ehlert U. Steroid hormone secretion over the course of the perimenopause: findings from the swiss perimenopause study. *Front Glob Womens Health*. 2021;2:774308. doi:10.3389/fgwh.2021.774308
30. Ren Q, Hua L, Zhou X, et al. Effects of a single sub-anesthetic dose of ketamine on postoperative emotional responses and inflammatory factors in colorectal cancer patients. *Front Pharmacol*. 2022;13:818822. doi:10.3389/fphar.2022.818822
31. Zhang Z, Zhang WH, Lu YX, et al. Intraoperative low-dose S-ketamine reduces depressive symptoms in patients with crohn's disease undergoing bowel resection: a randomized controlled trial. *J Clin Med*. 2023;12(3):1152.
32. Liu P, Li P, Li Q, et al. Effect of pretreatment of S-ketamine on postoperative depression for breast cancer patients. *J Invest Surg*. 2021;34(8):883–888. doi:10.1080/08941939.2019.1710626
33. Correia-Melo FS, Leal GC, Vieira F, et al. Efficacy and safety of adjunctive therapy using esketamine or racemic ketamine for adult treatment-resistant depression: a randomized, double-blind, non-inferiority study. *J Affect Disord*. 2020;264:527–534. doi:10.1016/j.jad.2019.11.086
34. Gastaldon C, Raschi E, Kane JM, Barbui C, Schoretsanitis G. Post-marketing safety concerns with esketamine: a disproportionality analysis of spontaneous reports submitted to the FDA adverse event reporting system. *Psychother Psychosom*. 2021;90(1):41–48. doi:10.1159/000510703
35. Chen B, Dowlatsahi D, MacQueen GM, Wang JF, Young LT. Increased hippocampal BDNF immunoreactivity in subjects treated with antidepressant medication. *Biol Psychiatry*. 2001;50(4):260–265. doi:10.1016/s0006-3223(01)01083-6
36. Martinowich K, Manji H, Lu B. New insights into BDNF function in depression and anxiety. *Nat Neurosci*. 2007;10(9):1089–1093. doi:10.1038/nn1971
37. Medeiros GC, Gould TD, Prueitt WL, et al. Blood-based biomarkers of antidepressant response to ketamine and esketamine: a systematic review and meta-analysis. *Mol Psychiatry*. 2022;27(9):3658–3669. doi:10.1038/s41380-022-01652-1
38. Lepack AE, Fuchikami M, Dwyer JM, Banasr M, Duman RS. BDNF release is required for the behavioral actions of ketamine. *Int J Neuropsychopharmacol*. 2014;18(1):pyu033.
39. Li N, Lee B, Liu RJ, et al. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science*. 2010;329(5994):959–964. doi:10.1126/science.1190287
40. Carreira H, Williams R, Muller M, Harewood R, Stanway S, Bhaskaran K. Associations between breast cancer survivorship and adverse mental health outcomes: a systematic review. *J Natl Cancer Inst*. 2018;110(12):1311–1327. doi:10.1093/jnci/djy177

International Journal of General Medicine

Dovepress

Publish your work in this journal

The International Journal of General Medicine is an international, peer-reviewed open-access journal that focuses on general and internal medicine, pathogenesis, epidemiology, diagnosis, monitoring and treatment protocols. The journal is characterized by the rapid reporting of reviews, original research and clinical studies across all disease areas. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/international-journal-of-general-medicine-journal>