BMJ Open

Influence of low-dose esketamine on postoperative depressive symptoms in patients with breast cancer (EASE): study protocol for a randomised controlled trial

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To cite: Wei Q, Chen C, Zhu J, *et al*. Influence of low-dose esketamine on postoperative depressive symptoms in patients with breast cancer (EASE): study protocol for a randomised controlled trial. *BMJ Open* 2023;**13**:e075767. doi:10.1136/bmjopen-2023-075767

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-075767).

Received 18 May 2023
Accepted 01 September 2023

Check for updates

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ABSTRACT

Introduction Depressive symptoms have surfaced as the principal mental health concern among patients with breast cancer, with surgical interventions potentially exacerbating these symptoms and adversely influencing clinical outcomes. This study protocol is designed to investigate the efficacy of low-dose esketamine administered perioperatively on depressive symptoms in patients with breast cancer. It also aims to illuminate the potential neurobiological underpinnings of this effect.

Methods and analysis This research represents a single-centre, prospective, randomised, double-blind, placebo-controlled study. The trial anticipates enrolling 108 female patients exhibiting mild-to-severe depressive symptoms who are slated for radical mastectomy. Through stratified randomisation, eligible patients will be systematically assigned to either the esketamine group (0.25 mg/kg) or placebo group (0.9% saline) in a 1:1 ratio. The primary outcome is the response rate at the third postoperative day. Secondary outcomes encompass the remission rate, depression-related scores, depression severity and safety-related endpoints. Tertiary (exploratory) outcomes involve alterations in brain-derived neurotrophic factor and resting-state functional brain connectivity.

Ethics and dissemination The Clinical Trial Ethics Committee at The First Affiliated Hospital of Anhui Medical University has conferred ethical approvals for this trial (approval number: PJ2023-05-25). Results from this trial will be disseminated in peer-reviewed journals and presented at professional symposiums.

Trial registration number Chinese Clinical Trials Registry (ChiCTR2300071062).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study represents a randomised, double-blind, placebo-controlled investigation into the potential therapeutic effects of esketamine on depressive symptoms in patients undergoing breast cancer surgery.
⇒ The study leverages neuroimaging techniques (resting-state functional MRI) to provide a preliminary and objective appraisal of esketamine's antidepressant mechanism.
⇒ As a single-centre study focusing on patients with breast cancer with depressive symptoms, the external validity of the findings might be constrained.

INTRODUCTION

Breast cancer remains one of the most prevalent forms of cancer among women.[1] Emerging data indicate that over 300 000 new cases of breast cancer are diagnosed annually in China, with the age of onset demonstrating a progressively declining trend.[2] Patients diagnosed at an early stage display a relative 5-year survival rate approaching 100%.[3] Given that breast cancer survival rates are among the highest for cancers, ensuring quality of life for survivors is a primary concern, warranting consideration from the initial clinical consultation and treatment planning.[4] Depression, a prevalent negative emotion, often shadows the lives of patients with breast cancer.[5] Following a breast cancer diagnosis, a significant majority of patients will undergo surgical intervention. Surgery, as a potent stressor, can profoundly affect a patient's physical and psychological state, potentially predisposing them to depression or other negative emotions.[6] Persistent postoperative depression can undermine the body's immune system, enhance sympathetic nervous system activity and alter neurotransmitter levels. These changes may exacerbate the side effects of treatment, potentially diminishing its effectiveness. Additionally, postoperative depression may heighten the risk of cancer recurrence and metastasis, and in severe instances, can even precipitate mortality, thereby impacting patient prognosis and quality of life profoundly.[6] A meta-analysis involving 282 203 patients revealed that depression escalates the risk of recurrence, all-cause mortality and breast cancer-specific death.[7] Hence, ameliorating

postoperative depressive symptoms in patients with breast cancer is an imperative clinical issue that requires urgent attention.

General antidepressants necessitate extended treatment duration, and the scheduling of surgery may lead to inadequate preoperative antidepressant intervention in these patients. Moreover, antidepressants exert specific influences on anaesthesia and surgical outcomes.[8] Consequently, there is an emergent need to investigate straightforward and effective antidepressant strategies for patients experiencing perioperative depression.

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, possesses sedative and analgesic pharmacological properties, rendering it suitable for the induction and maintenance of general anaesthesia in clinical practice.[9] Recent research has illuminated that ketamine can elicit swift and sustained antidepressant effects, particularly in patients grappling with treatment-resistant depression, bipolar disorder and depression accompanied by suicidal ideation.[10 11] The antidepressant properties of ketamine have been substantiated through numerous clinical and preclinical studies, rendering it a fascinating subject in the realm of depression treatment in recent years.[12 13] Given its documented antidepressant effects, ketamine represents a valuable option for patients with preoperative depressive symptoms and for mitigating postoperative depressive mood. However, despite promising clinical and preclinical results, ongoing debates persist regarding the efficacy and safety of perioperative intravenous ketamine.[14] Esketamine, introduced in 2019, is the S-enantiomer of ketamine and similarly functions as an NMDA receptor antagonist.[15] Compared with ketamine, esketamine exhibits higher potency, enhanced receptor affinity and a reduced prevalence of adverse reactions in the nervous system.[16] Furthermore, it maintains a rapid antidepressant response, making it a subject of intense focus in current antidepressant treatment drug research.[17–19] The Food and Drug Administration has approved esketamine for the management of treatment-resistant and suicidal depression. However, the effectiveness of esketamine in preventing and treating depressive symptoms during the perioperative period remains to be evaluated.

Impaired neuronal plasticity and aberrations in dendritic structure represent common pathophysiological features observed in individuals with depression.[20] Recent research suggests that antidepressants have the potential to augment neuronal plasticity, indicating that disruptions in plasticity could detrimentally influence cognitive and emotional regulation, thereby contributing to the onset and progression of depression.[21 22] Brain-derived neurotrophic factor (BDNF), a critical mediator of neuronal plasticity, has been found to be intrinsically linked to the pathogenesis of depression and stress response, and is essential for neuronal growth and survival.[23 24] Prior studies have suggested that BDNF expression in the brains of patients with depression was considerably diminished, and the exogenous administration of BDNF into the hippocampus boosted hippocampal neurogenesis and alleviated depressive symptoms.[25] Furthermore, animal studies have revealed that a deficiency in neurotrophic factors disrupts synaptic plasticity, decreases the survival rate of hippocampal neoblasts and results in a reduction in total brain volume and hippocampal volume.[26]

Resting-state functional MRI (fMRI) connectivity computes the temporal correlation of functional activity between a specific area of interest in the brain and other brain regions during a state of rest, thereby reflecting the functional activity pattern of the brain at the network level. The medial prefrontal cortex (mPFC) is associated with an array of social, emotional and cognitive functions. Neuroimaging studies have revealed that ketamine induces alterations in the dorsomedial prefrontal cortex (dmPFC) of the brain.[27] Additionally, disconnection between the dmPFC and anterior cingulate cortex was observed 24 hours post-ketamine infusion, which has been postulated to represent a manifestation of plastic adaptation within the brain.[28] In 2015, Peng *et al* found that ketamine preferentially targets and modulates mPFC loops in monkeys, as demonstrated through fMRI and graph-theoretic brain network analysis.[29] A recent resting-state fMRI study involving patients with mild-to-moderate depression reported reduced functional connectivity between the mPFC and several other brain regions in the depressed group. In contrast, enhanced functional connectivity was observed with the right inferior frontal gyrus insula.[30] Despite the focus of current studies on functional brain connectivity during the acute phase of depression,[31 32] there remains a deficit of research investigating resting-state functional connectivity in patients with perioperative depression.

To address these gaps, we propose conducting a randomised controlled trial to explore the efficacy of esketamine in mitigating postoperative depression in patients exhibiting preoperative depression. We hypothesise that the intraoperative administration of low doses of esketamine will improve patients' postoperative depressive symptoms. Additionally, we postulate that the antidepressant effects of esketamine may be intimately associated with elevations in BDNF concentrations and alterations in functional brain connectivity.

METHODS AND ANALYSIS

Study design

The EASE Study is a single-centre, prospective, randomised, double-blind, placebo-controlled trial. Participant enrolment is anticipated to commence in August 2023, with the completion of the study expected by December 2024. Participants will be randomised into either the esketamine group or the placebo group. The study design and execution will strictly adhere to the stipulations outlined in the Standard Protocol Items: Recommendations for Interventional Trials.[33] The findings will be reported in alignment with the Consolidated Standards of Reporting Trials Statement.[34] The workflow of the study is depicted in figure 1.

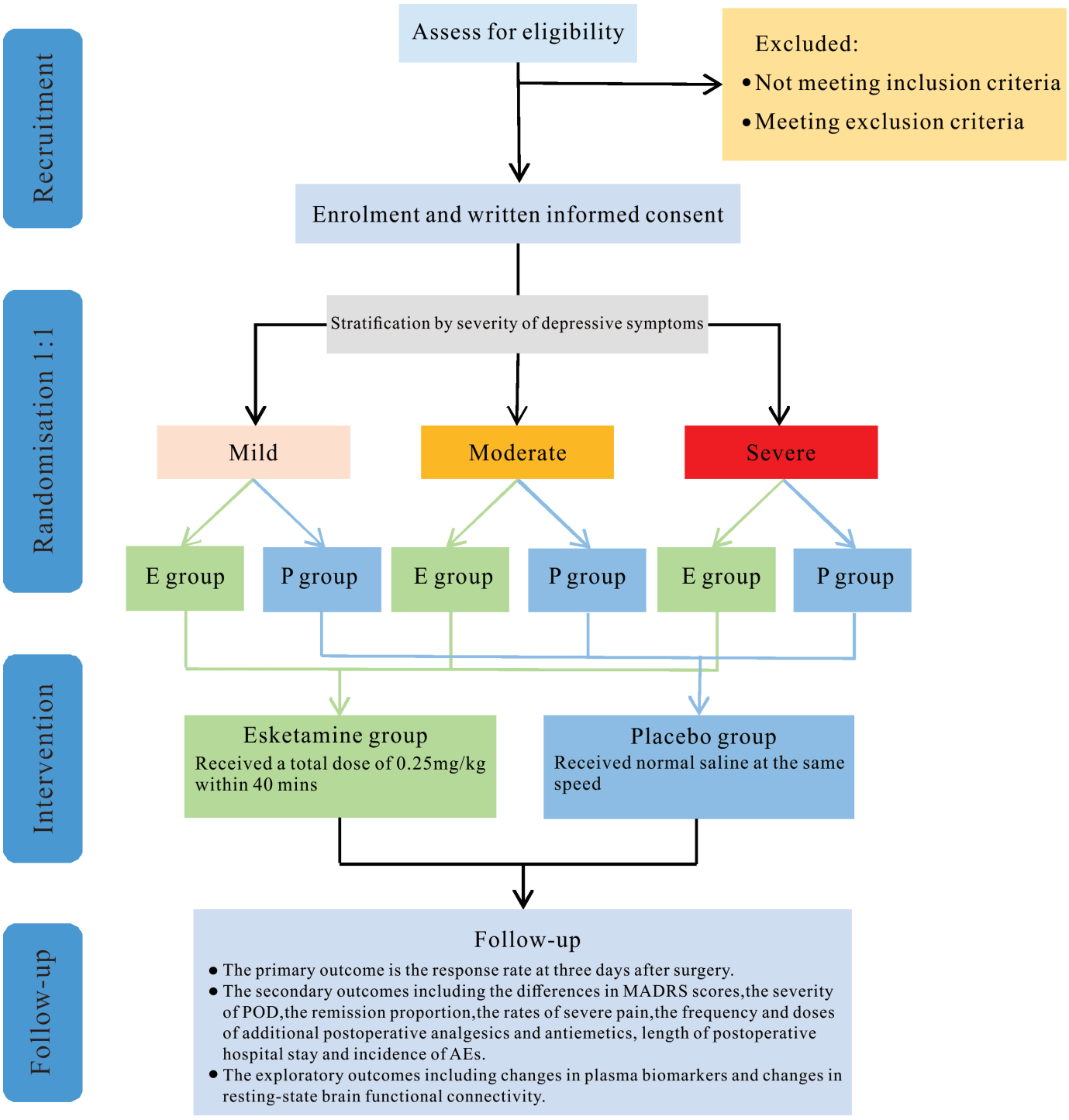

Figure 1 Research flow chart. AEs, adverse events; MADRS, Montgomery-Asberg Depression Rating Scale; POD, postoperative depression.

Study setting

The study will be conducted at The First Affiliated Hospital of Anhui Medical University.

Study objectives and aims

1. Evaluate the impact of low-dose esketamine on postoperative depressive symptoms in patients with breast cancer.
2. Assess the effect of low-dose esketamine on plasma BDNF and resting-state functional connectivity.
3. Investigate the correlation between BDNF, resting-state functional connectivity and the amelioration of depressive symptoms.

Eligibility criteria

Patients will qualify for enrolment if they meet the specified inclusion criteria during screening and exhibit none of the exclusion criteria (box 1). Further, patients retain the right to withdraw from the trial at any point should they choose to retract their informed consent (online supplemental file 1).

Box 1 Inclusion and exclusion criteria

Inclusion criteria
⇒ Age 18–65 years.
⇒ Female patients.
⇒ ASA class I–III.
⇒ Mild-to-severe depressive symptoms (11 scores<MADRS<35 scores).
⇒ Scheduled for elective unilateral radical mastectomy for breast cancer.
⇒ Able to provide written informed consent.

Exclusion criteria
Participants meeting one or more of the following criteria will be excluded from the study:
⇒ Patients with contraindications or allergies to the use of esketamine.
⇒ Patients undergoing preoperative radiotherapy or endocrine therapy and secondary surgery (recurrence or reconstruction).
⇒ BMI >30 kg/m^2.
⇒ History of psychosis, bipolar disorder and recurrent depression.
⇒ History of antidepressant treatment within 2 weeks prescreening.
⇒ Patients with severe preoperative functional abnormalities of the liver and kidneys.
⇒ Patients unable to cooperate with the study for any reason, such as hearing or visual impairment, language comprehension disorder or mental illness.
⇒ History of drug dependence or current pregnancy or breast feeding.
⇒ Preoperative planned ICU admission.
⇒ Individuals already participating in other studies.
⇒ Contraindication for MRI (eg, claustrophobia).

ASA, American Society of Anesthesiologists; BMI, body mass index; ICU, intensive care unit; MADRS, Montgomery-Asberg Depression Rating Scale.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Consent process

Every patient will be approached by a member of the research team who will provide comprehensive information about the trial, its objectives, potential benefits and potential risks prior to surgery (typically during the anaesthesia pre-evaluation visit). Patients will be invited to provide written informed consent. Both the patient and the treating investigator will sign the informed consent form. The original document will be stored in the patient's medical records, and a copy will be provided to the patient.

Randomisation and allocation concealment

An individual not involved in data collection will perform the random allocation of patients into one of two groups: the esketamine group and the placebo group, using the stratified randomisation method at a 1:1 ratio. The severity of preoperative depression will be considered as the stratification factor, with trained investigators assessing depression severity using the Montgomery-Asberg Depression Rating Scale (MADRS). A surgical nurse uninvolved in the study will prepare the medications. The esketamine group will receive a dose of 0.25 mg/kg esketamine, diluted to 20 mL in a syringe, while the placebo group will receive an equivalent volume of normal saline. The syringes will be labelled with the patient's name, preparation date and administration route. Anaesthesiologists, surgeons and perioperative observers will not be able to discern whether the preparation is a control or experimental preparation based on its appearance. For blinding purposes, emergency letters will be prepared, each one assigned a non-transparent emergency envelope containing the medication code number and name, enabling unblinding and individual case rescue in emergency situations. Post-unblinding, the corresponding cases will be considered dropouts. The emergency letter will be dispatched to the research staff along with the blinded drug.

Blinding

A trained anaesthesiologist will assess the overall health of patients before surgery and determine whether they meet the study's inclusion criteria. Patients meeting these criteria will be sequentially assigned to their respective groups. Patients will subsequently be briefed on how to use the relevant scales and questionnaires. Postoperative follow-up and data collection will be conducted by another anaesthesiologist involved in the study. Patients, family members, anaesthesiologists, surgeons, study recorders and evaluators will remain blinded to group assignments and drug compositions. The individual responsible for coordinating and supervising all facets of the study will oversee the execution of the blinding method, ensuring the safety of subjects and the reliability of results, in addition to distributing emergency letters, safeguarding blinding envelopes and unblinding at the conclusion of the study. In the event of a serious adverse event linked to esketamine occurring after intervention and before the end of surgery (such as a hypersensitivity reaction to the investigational drug), the study's principal investigator may opt to disclose drug use. A statistical expert from Anhui Medical University will analyse all data.

Intervention and anaesthesia management

Preoperative evaluation: 1 day prior to the surgery, each patient undergoes a standard clinical visit. The inclusion and exclusion criteria are employed to identify eligible participants for the study. The MADRS is used to ascertain the presence of depressive symptoms before surgery. Afterward, informed consent is obtained, the patient's basic information is documented and a preoperative resting-state fMRI is performed.

Anaesthetic administration: all participants are required to fast routinely before the operation. Upon their arrival in the operating room, they are linked to a multifunctional ECG monitor for continuous tracking of three-lead ECG, non-invasive blood pressure and pulse oxygen saturation. Additionally, peripheral venous access is established. General anaesthesia is induced with 2 mg/kg propofol, 0.05 µg/kg sufentanil and 0.1–0.15 mg/kg cisatracurium. Following the relaxation of the patient's neck muscles, a

laryngeal mask is inserted. The depth of anaesthesia is maintained with total intravenous anaesthesia, featuring a continuous infusion of propofol at 3–7 mg/kg/hour and remifentanil at 0.1 µg/kg/min. The intermittent application of cisatracurium is subject to the clinical experience of the anaesthesiologist. Ten minutes before the conclusion of the surgery, remifentanil is discontinued, and propofol is ceased at the end of the operation. Upon the completion of the surgery, a neostigmine–atropine combination is routinely introduced to counteract the effects of muscle relaxants, and the patient is extubated in the operating room. Non-steroidal anti-inflammatory drugs are used for postoperative pain relief, and opioids are introduced if necessary. Following extubation, patients are transferred to the post-anaesthesia care unit where non-invasive blood pressure, ECG and pulse oximetry are monitored for a minimum of 30 min until a modified Aldrete score of 9 is achieved. The patient is subsequently moved back to the surgical ward, where non-invasive blood pressure and pulse oximetry are intermittently tracked until the following morning. Open-label esketamine is not allowed during the perioperative period, except in compelling circumstances.

Interventions: for the esketamine group, esketamine is administered at a dosage of 0.25 mg/kg, diluted to 20 mL and infused intravenously at a rate of 30 mL/hour. In the placebo group, an equivalent volume of normal saline is infused intravenously at the same rate. The administration of the study drug commences 10 min after the initiation of the procedure. Seasoned anaesthesiologists document vital signs and any adverse reactions during the surgery.

Biological sample collection

Optionally, participants may agree to the collection and storage of two batches of venous blood samples. The initial collection coincides with the baseline assessment, while the second occurs 1 day post-surgery. It should be noted, however, that the analysis of these samples does not serve as a primary goal of this study.

Neuroimaging

If consented by the participants, two resting-state fMRI scans may be performed. The initial scan aligns with the baseline assessment, and the subsequent scan is scheduled for 1 day post-surgery. The analysis of this dataset is not the principal objective of this study. Eligibility for this component of the study requires qualification for the main study and the absence of any contraindications to MRI scanning.

Outcome measures

Primary outcome

The primary outcome is defined by the response rate on the third postoperative day. A 'response' is characterised as a greater than 50% reduction in depressive symptoms, as per the MADRS score, indicative of clinically significant efficacy. A blinded researcher will conduct assessments of the MADRS scores at the patient's bedside between 18:00 and 20:00.

Secondary outcomes

Secondary outcomes are comprised of the following:

- Postoperative MADRS scores, which will be evaluated using a questionnaire on the first, third and fifth postoperative days or at discharge, with follow-up assessments conducted via telephone at 4 and 12 weeks postoperatively.
- Severity of postoperative depressive symptoms, measured using the MADRS. The MADRS total score is 60, with elevated scores signifying more severe depressive symptoms. Scores are classified as follows: 0–11 for remission, 12–21 for mild depression, 22–29 for moderate depression, 30–34 for severe depression and 35–60 for extremely severe depression.
- The remission rate, defined as a MADRS score of 10 or lower.
- The incidence of severe postoperative pain, defined as a Numerical Rating Scale (NRS) score of 7 or higher, within the first 48 hours postoperatively. Postoperative pain will be evaluated using a self-reported NRS score (no pain=0; maximum pain=10).
- The duration of postoperative hospitalisation.

Exploratory outcomes

The exploratory outcomes primarily include alterations in plasma biomarkers and changes in resting-state brain functional connectivity. Venous fasting blood samples, collected pre-surgery and on the morning of postoperative day 1, will be used to measure BDNF concentration. Participants consenting to resting-state fMRI will undergo scans on the day before surgery and 1 day postoperatively, scheduled between 20:00 and 22:00. The timeline for blood sample collection and fMRI is presented in figure 2.

Safety assessment

The safety outcomes of this study are characterised by the incidence of any drug-related adverse events occurring either during the surgery or prior to patient discharge.

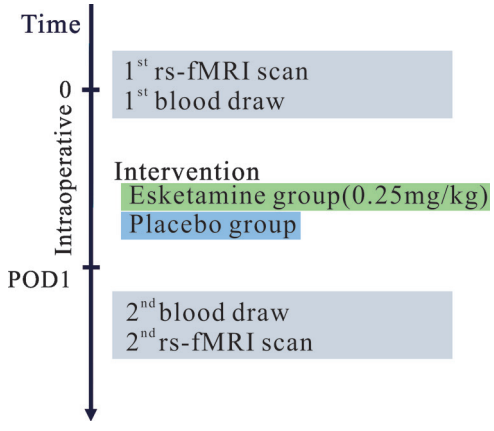

Figure 2 Timeline for collection of blood samples and fMRI examinations. D0, the day of surgery; D1, 1 day after surgery; rs-fMRI, resting-state functional MRI.

These events include nausea, vomiting, symptoms of psychosis (assessed by a non-0 score on select items of the Brief Psychiatric Rating Scale[35] (unusual thought content, suspiciousness, hallucinations and conceptual disorganisation)), elevated secretions, dizziness, dissociative states (evaluated by a non-0 score on the Clinician-Administered Dissociative States Scale[36]), oversedation, manic states (defined by scores equal to or exceeding 5 on the 11-item Young Mania Rating Scale[37]), nightmares, restlessness, pruritus, disorientation, delirium, diplopia, diarrhoea, urinary retention, constipation, chills, hallucinations and so forth.

Adverse events

Any adverse events spontaneously reported by patients or identified by investigators will be meticulously recorded. Detailed information including the time of occurrence, clinical presentation, management and duration of the event, and its regression and relationship to the administered drug will be documented. In cases involving abnormal laboratory tests, patient follow-up will continue until the test results return to normal or are deemed unrelated to the test drug. The association of adverse events with the intervention will be determined and summarised by the investigators. All severe adverse events will be registered and reported to the local Medical Ethics Committee within a 24-hour period.

Training and quality control

The research team has organised training workshops for the testers responsible for the scale assessments involved in this study. Prior to commencing the study assessment procedures, testers received thorough training and standardisation on the MADRS assessment.

Data collection and management

Data collection will be carried out by trained members of the study team. Follow-ups will consist of in-hospital visits (at baseline, and on postoperative days 1, 3, 5, and/or at discharge) and telephone consultations (at 4 and 12 weeks postoperatively), as illustrated in table 1. All collected data will be coded using an anonymous participant ID and compiled in a case report form. While data will not be made publicly available, access may be granted through a formal application process ensuring the privacy and integrity of the data.

Sample size calculation

The primary endpoint of this study is to evaluate the efficacy of mitigating postoperative depression in patients with breast cancer undergoing general anaesthesia. A previous study published in Anesthesia & Analgesia by Zhou *et al*[9] revealed that the perioperative administration of a small dose of ketamine (0.5 mg/kg) as a continuous infusion led to an efficacy rate of 41.5% 3 days postoperatively, in comparison with 16.3% in the saline control group. This study anticipates that esketamine (0.25 mg/kg) will exhibit similar, if not superior, efficacy to ketamine (0.5 mg/kg). Using the PASS V.15.0.5 software for Windows (PASS, USA), a two-sided test was applied with a test efficacy of 0.05 and an assurance of 80% to calculate the required sample size. The computed sample size was 47 patients per group, accounting for a 10% attrition rate; thus, a total of 108 patients with breast cancer are proposed for recruitment in this study.

Statistical analysis

The statistical analysis will be conducted using SPSS V.26.0 software. The Kolmogorov-Smirnov test will be employed to verify if the continuous data conform to a normal distribution. Data adhering to a normal distribution within groups will be expressed as mean and SD, whereas non-normally distributed data will be expressed as median and IQR. Categorical variables will be expressed as rates. Data with normal distribution will be compared between groups using an independent samples t-test, while repeated measures data will be analysed using repeated measures analysis of variance. The Mann-Whitney U test will be used to compare non-normally distributed data between groups, and repeated measures data will be evaluated using the Friedman rank-sum test. Count data will be analysed using the χ^2 test or Fisher's exact probability method. A significance level (α) of 0.05 will be adopted, and p values of <0.05 will be considered indicative of statistically significant differences.

Resting-state functional data will be analysed with SPM V.12 software. Between-group comparisons of differences in resting-state brain functional connectivity pre-surgery and post-surgery will be conducted using an independent samples t-test, while within-group comparisons will use a paired t-test. A combined intensity ($p<0.01$, Alphasim correction) and breadth (minimum cluster >18 voxels) threshold will be applied to quantitatively compare alterations in mPFC functional connectivity. For brain regions demonstrating significant differences in the paired t-test before and after surgery in the esketamine group, the mean Z-values of these brain regions pre-surgery and post-surgery will be extracted for each patient. Subsequently, correlations between the Z-value changes in these differential brain regions and alterations in scale scores and clinical laboratory indices will be examined using Pearson's correlation analysis.

Interim analysis

This study will not include an interim analysis.

Monitoring

The Data Monitoring Committee, composed of two members independent from the study team, will scrutinise the accumulated safety and effectiveness data and provide recommendations on the continuation of the study.

Ethics and dissemination

This study involves the participation of human subjects and has received approval from the Clinical Trial Ethics Committee at The First Affiliated Hospital of Anhui Medical University (approval number: PJ2023-05-25).

Table 1 Summary of study assessments and procedures

	Study period							
	Enrolment	Allocation	Interventions	Follow-up				
Time point	**D-1**	**D0**		**D1**	**D3**	**D5/discharge**	**W4**	**W12**
Enrolment								
Eligibility screen	×							
Informed consent	×							
Clinical interviews	×	×						
Allocation		×						
Interventions								
Esketamine group			×					
Placebo group			×					
Intraoperative and PACU variables			×					
Assessments								
Primary outcome								
MADRS scores					×			
Secondary outcomes								
MADRS scores	×			×		×	×	×
GAD-7 scores	×			×	×	×	×	×
NRS scores				×	×	×	×	×
Use of analgesic drugs				×	×	×		
Use of antiemetic drugs				×	×	×		
Incidence of severe postoperative pain				×	×	×		
Incidence of adverse events				×	×	×		
Days of hospitalisation						×		
Exploratory outcomes								
RSFC	×			×				
BDNF		×		×				

BDNF, brain-derived neurotrophic factor; D0, the day of surgery; D-1, 1 day before surgery; D1, 1 day after surgery; D3, 3 days after surgery; D5, 5 days after surgery; GAD-7, Generalized Anxiety Disorder; MADRS, Montgomery-Asberg Depression Rating Scale; NRS, Numerical Rating Scale; PACU, post-anaesthesia care unit; RSFC, resting-state brain functional connectivity; W4, 4 weeks after surgery; W12, 12 weeks after surgery.

Prior to participating in the study, all participants were required to provide informed consent. The investigator is responsible for providing an annual progress report of the study to the Ethics Committee at a minimum frequency of once per year. In the event of study completion or discontinuation, the Ethics Committee will be duly informed in writing by the investigator. Any modifications to the study (such as revisions to the protocol or the informed consent documentation) must be reported promptly to the Ethics Committee by the investigator. The investigator will not implement any such changes without first obtaining the requisite approval from the Ethics Committee, unless such alterations are necessitated to mitigate a clear and immediate risk to the participant. The Ethics Committee will be promptly notified should such situations arise.

Upon completion of the study, the results corresponding to the primary outcome will be compiled into a manuscript for publication in a peer-reviewed journal. Depending on the context, secondary outcomes may either be included in the primary manuscript or detailed in subsequent manuscripts. All manuscripts will be submitted for publication in peer-reviewed journals. In addition to academic publication, the findings from this trial may also be disseminated through discussions and presentations in various media platforms.

Contributors QW and CC began the research concept. Under the supervision and suggestions of JZ, BM and XL, QW designed the study protocol. With the assistance of all authors, QW prepared, edited and finalised the manuscript. All coauthors critically reviewed and approved the final manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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