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

Qingfeng Wei, Cen Chen, Jiajia Zhu, Bin Mei, Xuesheng Liu

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).

INTRODUCTION

Breast cancer remains one of the most prevalent forms of cancer among women. 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. Patients diagnosed at an early stage display a relative 5-year survival rate approaching 100%. 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. Depression, a prevalent negative emotion, often shadows the lives of patients with breast cancer. 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. 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. A meta-analysis involving 282,203 patients revealed that depression escalates the risk of recurrence, all-cause mortality and breast cancer-specific death. 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. 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. 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. 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. 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. Esketamine, introduced in 2019, is the S-enantiomer of ketamine and similarly functions as an NMDA receptor antagonist. Compared with ketamine, esketamine exhibits higher potency, enhanced receptor affinity and a reduced prevalence of adverse reactions in the nervous system. Furthermore, it maintains a rapid antidepressant response, making it a subject of intense focus in current antidepressant treatment drug research. 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. 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. 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. 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. 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.

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. Additionally, disconnection between the dmPFC and anterior cingulate cortex was observed 24 hours post-ketamine infusion, which has been postulated to represent a manipulation of plastic adaptation within the brain. 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. 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. Despite the focus of current studies on functional brain connectivity during the acute phase of depression, 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. The findings will be reported in alignment with the Consolidated Standards of Reporting Trials Statement. The workflow of the study is depicted in figure 1.
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/m².
⇒ 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.

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**Patient and public involvement**

Patients or the public were not involved in the design, 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.
These events include nausea, vomiting, symptoms of psychosis (assessed by a non-0 score on select items of the Brief Psychiatric Rating Scale35 (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 Scale36), oversedation, manic states (defined by scores equal to or exceeding 5 on the 11-item Young Mania Rating Scale37), 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 al8 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 χ² 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).
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.

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Competing interests None declared.

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

Patient consent for publication Not required.
Supplemental material
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REFERENCES
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Provenance and peer review
Not commissioned; externally peer reviewed.
Participant's Informed Consent

Protocol name: The influence of low-dose ESketamine on postoperative depressive symptoms in breast cancer patients (EASE): study protocol for a randomised controlled trial

Program version number version date: 03, March 17, 2023
Informed Consent Version Number Version Date: 01, March 17, 2023
Affiliation: The First Affiliated Hospital of Anhui Medical University
Principal Investigator (Physician in Charge): Xuesheng Liu

You are being invited to participate in a clinical research study. This information sheet gives you information to help you decide whether or not to participate in this clinical research study. This information sheet gives you information to help you decide whether or not to participate in this clinical study. Please read it carefully and if you have any questions, please ask the investigator in charge of the study.

Your participation in this study is voluntary. This study has been reviewed by the Ethics Review Board of this research institution.

Research Aim: Escitalopram is a commonly used intravenous anesthetic drug, which has been approved for the treatment of clinically refractory depression and major depressive disorder. Studies have shown that esketamine has a rapid onset of action, can rapidly eliminate suicidal intent in patients, and low-dose maintenance therapy can help stabilize patients' conditions with fewer adverse effects, making it a hot topic in current research on antidepressant medications. Studies have shown that brain-derived neurotrophic factors and alterations in resting brain functional connectivity may respond to the efficacy of antidepressant treatment. The purpose of this study is to investigate the effect of prophylactic administration of esketamine on postoperative depression in breast cancer patients and its effect on brain-derived neurotrophic factor and resting state brain functional connectivity.

Study Process: If you agree to participate in this study, we will number you and
create a medical record file. During the study we will need to collect some of your specimens, MRI information, etc., which will be sampled and collected for you by a professional.

**Blood Collection:** 3 mL of venous blood will be drawn from your arm, once before surgery and once early in the morning of Day 1, for a total of 2 samples. Your sample will only be used in this study to measure the level of brain-derived neurotrophic factor.

**Magnetic Resonance Data Collection:** You will be taken to the MRI room by the investigator for a 10-minute procedure, once before and once on Day 1, for a total of 2 times. Your data will only be used to analyze the functional status of the brain for this study.

**Scale Assessment:** We will ask you about your pain and depression status before surgery, at 3 day postoperative, at 5 day postoperative or at discharge, at 4 week postoperative, and at 12 week postoperative, either face-to-face or by phone contact.

**Risks and Discomfort:** All information will be confidential to you. Your specimen collection will be performed in strict accordance with strict aseptic requirements. There may be some very minor risks associated with specimen collection, including transient pain, localized bruising, and in a few cases mild dizziness, or very rare needle infections.

**Benefit:** The use of a commonly used intravenous general anesthetic drug in this study may be beneficial in improving your mood after surgery as well as reducing the occurrence of adverse times such as your level of postoperative pain. Therefore, you may potentially benefit by participating in this study.

**Costs:** Propofol, sufentanil, remifentanil, ropivacaine, and esketamine are drugs that are already available in China and are routinely used for anesthesia, so you will be responsible for the cost of the study medications and related treatment. The study medications and associated costs will be your responsibility, and routine treatments and investigations for other co-morbidities will not be covered. Resting-state MRI and blood tests for brain-derived neurotrophic factors will be free of charge.

**Compensation:** There is no additional compensation to you for this study.
As a research participant, you have the following responsibilities: to be truthful about your medical history and current physical condition; to tell the study doctor about any discomfort you experience during this study; and to tell the study doctor if you have recently participated in other research studies or are currently participating in other research studies.

Privacy Issues: If you decide to participate in this study, your participation in the study and your personal information during the study will be kept confidential. Your biospecimen will be identified by the study number and not by your name. Information that identifies you will not be shared with anyone outside of the research team unless you give your permission. All study members and the study sponsor are asked to keep your identity confidential. Your file will be kept in a locked filing cabinet and will be accessible only to researchers. If necessary to ensure that the study is conducted in accordance with the regulations, members of the government regulatory or ethical review committee will be given access to your personal data at the research unit as required. No personal information about you will be disclosed when the results of this study are published.

If you are harmed as a result of participating in this study: You may be entitled to free treatment and/or compensation for damages related to this clinical study.

You may choose not to participate in this study, or you may request to withdraw from the study at any time by notifying the investigator that your data will not be included in the results of the study, and any of your medical treatment and rights will not be affected as a result.

Disposal of Biological Specimens and Information at the End of the Study: The investigator will retain essential documents related to the clinical trial for 5 years after completion of the study. Blood specimens will be disposed of in accordance with the Medical Waste Management Regulations.

The research physician may terminate your continued participation in this study if you need other treatment, or if you do not follow the study plan, or if a study-related injury occurs or for any other reason.

You will be kept informed of the information and progress of the study, and we
will notify you of any new safety information related to the study. If you have questions about this study, or if you experience any discomfort or injury during the study, or if you have questions about the rights and interests of participants in this study, you may contact Xuesheng Liu at 0551-62922304.

If you have any questions or claims regarding your rights and health from participating in this study, you may contact the Institutional Ethics Committee at 62923537; Contact: Tao Zhou
Informed consent signature page

I have read this informed consent form.
I had the opportunity to ask questions and all of them were answered.
I understand that participation in this study is voluntary.
I can choose not to participate in the study or withdraw at any time by notifying the researcher without discrimination or retaliation, and any of my medical treatment and rights will not be affected as a result.
The study physician may terminate my continued participation in this study if I need other treatment, or if I do not comply with the study plan, or if a study-related injury occurs or for any other reason.
I will receive a signed copy of the Informed Consent Form.

Subject's Name:________________________
Subject's signature:________________________
Date:________________________

I have accurately communicated this document to the subject, requesting that he/she has carefully read this informed consent form and that any questions or issues raised are carefully answered.

Researcher's Name:________________________
Researcher's signature:________________________
Date:________________________