Effect of esketamine on perioperative depressive symptoms in major surgery patients (PASSION II): study protocol for a randomised controlled trial

Yang Zhou,1 Bo Ma,1 Wanchen Sun,1 Juan Wang,1 Yuxuan Fu,1 Anxin Wang,2 Gang Wang,3,4 Ruquan Han1

ABSTRACT

Introduction Depressive symptoms are common for patients undergoing major surgery and may worsen their mental health and lead to poor clinical outcomes. It is essential to seek a safe rapid-acting treatment for relieving moderate-to-severe depressive symptoms in patients undergoing major surgery.

Methods and analysis This study is a randomised, placebo-controlled and double-blinded trial aiming to determine the effect of esketamine on moderate-to-severe depressive symptoms in patients undergoing major surgery. Five hundred and sixty-four patients, aged 18–65 years old, undergoing major surgery will be randomly allocated into the esketamine and placebo groups at a 1:1 ratio. Esketamine or placebo will be given intravenously at the same speed on suturing the incision by anaesthesiologists in charge who are blinded to the randomisation. In the esketamine group, the total dosage of esketamine will be 0.2 mg/kg body weight. To estimate the efficacy and safety endpoints, blinded evaluation by trained researchers will be completed at 3 days, 5 days, 1 month, 3 months and 6 months after surgery. The primary outcome is the remission rate at the third postoperative day. The secondary outcomes include depression-related scores, severe pain events and safety-related endpoints such as psychotic symptoms, manic symptoms and dissociative symptoms.

Ethics and dissemination This study was approved by the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University, Beijing, China on 30 October 2020 (KY-2020-058-02). This trial is designed to explore whether the administration of esketamine could improve the mental health of patients with depressive symptoms undergoing major surgery. The conclusions of this study will be published in peer-reviewed journals.

Trial registration number NCT04425473.

INTRODUCTION

Depression is a common mental disorder that has been the primary risk of disability and is an important risk factor associated with a high burden of disease; it is estimated that more than 300 million people suffer worldwide.1,2 Patients undergoing major surgery may have depressive symptoms induced by stress reactions, which could affect mental health in the surgery population. Depressive symptoms are characterised by loss of interest and low mood, during the perioperative period. Although depressive symptoms are different from depression disorder, they could also lead to worse clinical outcomes after surgery, such as cognitive dysfunction, delirium, pain and even shortened survival time.3,4 It has been reported that more than 24% of patients have depressive symptoms during the perioperative period, and this figure is nearly 44% in patients undergoing cardiac surgery or neurosurgery.5,6 However, few interventions resolve the depressive symptoms that occur during the perioperative period, and the influence of antidepressant effects in the early stage on prognosis in the future remains controversial.

Ketamine, a classic anaesthetic for sedation and analgesia, has been reported that could take rapid antidepressant effects in depression patients.10 However, the benefit of ketamine administration in patients with depressive symptoms undergoing major surgery is inconsistent.11-13 To address this problem, our research team developed the PeriOperative depressive Symptoms in patients undergoing Intracranial tumOur resectioN (PASSION)
study to explore the effect of ketamine on depressive symptoms in the neurosurgery population. In the 84 participants that were enrolled, we found that ketamine improved depressive symptoms at the third postoperative day, and the response rate was higher in the ketamine group than in the placebo group (41.5% vs 16.3%), and no adverse events occurred. However, there were several limitations in the PASSION study; for example, the degree of remission did not reach desired levels chiefly because of the relatively small sample size, a single type of surgery was involved in the trial and esketamine has been gradually substituted for ketamine in clinical practice.

Esketamine is a racemic compound of ketamine that has been reported to have rapid and marked antidepressant effects. Based on studies with ketamine, esketamine was developed and has been used for major depression patients since the Food and Drug Administration approved its use in 2019. Compared with traditional antidepressants, which require more than 1 week to take effect in depression patients, esketamine shortens the reaction period to nearly 1 hour after administration with few adverse effects, and the use of esketamine nasal spray has become a novel antidepressant for treatment-resistant depression patients. Compared with ketamine, esketamine shows similar pharmacological characteristics but less side-effect. However, the effects of esketamine administration on depressive symptoms are still unknown. Thus, we should make further efforts to determine the effect of esketamine on depressive symptoms in major surgery patients.

Safety issues associated with the administration of esketamine during surgery are also unclear. It is reported that ketamine could change the intracranial pressure and haemodynamics during drug administration, and increase the risk of psychotic symptoms, hallucinations, or nausea and vomiting after major surgery. For repeated application, ketamine was reported associated with drug abuse and may interact with bladder urothelial cells and induce apoptosis. Due to esketamine and ketamine having similar pharmacological effects, whether the harmful effect mentioned above for single administration of esketamine in major surgery patients is not known for certain.

Based on the previous studies, the depressive symptoms may be a temporary state because of the stress by operation or diseases. Thus, we conducted this trial to explore the effectiveness of esketamine used in surgery patients with depressive symptoms. It is hypothesised that the administration of esketamine intravenously will improve the depressive symptoms in the major surgery population. The primary endpoint is the remission rate at postoperative day 3, and the secondary endpoints consist of other effectiveness and safety-related parameters.

METHODS AND ANALYSIS

Trial design

This study is a multicentre randomised controlled clinical trial to explore the effect of esketamine on depressive symptoms screened during the perioperative period (the flow chart see figure 1). It was approved by the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University, Beijing, China (KY-2020-058-02). All participants or their legal representatives will provide written informed consent after screening and before randomisation. Registration information has been supplied on clinicaltrials.gov.

Participants

The study will be conducted at medical centres in China, and training of the study protocol will be held regularly to guarantee the quality of the trial. Major surgery patients who are 18–65 years old with moderate-to-severe depressive symptoms will be included after informed consent is obtained from their legal representative. Moderate-to-severe depressive symptoms are defined as Patient Health Questionnaire 9 (PHQ-9) scores equal to or more than 10 and Montgomery-Åsberg Depression Rating Scale (MADRS) scores equal to or more than 22. Major surgery is defined as an elective operation with an estimate of more than 2 hours and includes neurosurgical tumour resection, coronary artery bypass grafting operation, total hip or knee arthroplasty surgery, breast cancer surgery, pneumonectomy or hepatectomy. Patients with any of the following conditions will be excluded: aphasia or other conditions that may lead to the inability for mental assessments; diseases requiring maintenance of intubation after surgery; history of psychotic or bipolar disorder; primary diseases that could change hormone levels with laboratory evidence; body mass index more than 30 kg/m²; Child-Pugh grade B or C (defined as Child-Pugh scores more than six points); history of antidepressant therapy in the 2 weeks before screening; repeated suicide attempts (evaluated by a score equal to or more than 3 on the 12-item Quick Inventory of Depressive Symptomatology); history...
Blinding Process

1. Randomisation sequence is prepared by the independent engineers and it will be uploaded in a real-time, online randomisation system.

2. An independent person will prepare the drug according to the randomisation results and the man who prepared the drug will not participate in screening, intervention, and follow-up. The concentration of esketamine will be 0.5 mg/ml and it will be preserved in a syringe (50ml). The normal saline in the placebo group will also be preserved in the same appearance syringe. Both drugs will be labelled with ‘the trial drugs, randomisation code’.

3. The trial drugs will be administrated by the chief anaesthesiologists who are in charge of the surgery. The participants will receive the trial drug intravenously at the speed of 0.6 mL/hour per kilogram of weight for 40 mins. The actual total dosage of esketamine will be 0.2 mg/kg.

4. The certificated accessors will estimate the primary outcome and secondary endpoints of patients at bedside after surgery before discharge. After discharge, the follow-up will be continued by phone.

5. All the research record in paper will be conserved for 2 years after the trials completed.

Figure 2 Schedule of blinding in drug preparation, intervention and follow-up.

of adverse events to ketamine or esketamine; history of drug use disorder or current pregnancy or breastfeeding.

Randomisation and grouping
Participants will be randomly assigned to the esketamine group or placebo group at a 1:1 ratio. Randomisation results will be achieved via a real-time, online system before surgery. A randomised four-blocks design stratified patients by depressive severity (severe depressive symptoms are defined by MADRS scores equal to or more than 30). The randomisation sequence was created by independent engineers who will keep the allocation blind, and all study-related investigators will be blinded to the randomisation results.

Intervention and anaesthesia management
All participants included in this study will receive trial drugs intravenously when the incision is being sutured. In the esketamine group, patients will be administered a total dose of 0.2 mg/kg esketamine (Hengrui Induction, Jiangsu, China) over 40 min. Patients in the placebo group will receive an equivalent volume of normal saline at the same speed. Patients in this study will be under general anaesthesia for major surgery. Anaesthesia management will follow the standard procedure. Total intravenous anaesthesia or balanced anaesthesia will be implemented to maintain appropriate levels of sedation, analgesia and muscle relaxation. Anaesthetics are administered at appropriate dosages based on consideration of the clinical anaesthetists and will include sedatives (propofol or etomidate), analgesics (sufentanil or remifentanil), muscle relaxants (rocuronium or cisatracurium) or inhaled anaesthetics (sevoflurane). Patient-controlled analgesia devices will be applied after surgery by using sufentanil and ondansetron to maintain numerical rating scale scores equal to or less than 4. Other analgesics could be used with the occurrence of severe pain (numerical rating scale score more than 7) during the postoperative period.

Blinding
The trial drugs will be prepared by an independent person who is not participating in screening, intervention and follow-up procedures (see figure 2). Esketamine will be diluted to a concentration of 0.5 mg/mL with normal saline. Both esketamine and normal saline will be kept in syringes (50 mL) with the same appearance and labelled with ‘the trial drugs, randomisation code’. The participants will receive the trial drug at a speed of 0.6 mL/hour per kilogram of weight for 40 min. The intervention will be completed by the anaesthesiologists in charge of the surgery. The anaesthesiologists, accessors and patients will be blinded to the type of drug administered during surgery. The administered drug will be unmasked, with the agreement of the primary investigator, when
esketamine-related severe adverse events occur (such as an allergy to the study drug) after the intervention and before the termination of surgery.

Outcomes
The primary outcome is the proportion of participants attaining remission (defined as a MADRS score less than or equal to 10) 3 days after surgery, based on an evaluation by blinded assessors at the bedside.

Secondary outcomes, including the differences in MADRS scores at 3 days and 5 days (or discharge) after surgery and the rates of patients achieving a response (MADRS scores reduced to or lower than half of the baseline MADRS score), the rate of severe pain within 72-hour postoperative period (severe pain is defined by the numeric rating scale pain scores equal to or more than 7).21

Safety outcomes include manic symptoms evaluated by the 11-item Young Mania Rating Scale (defined by YMRS scores more than or equal to 5) within the 3-day postoperative period,22 psychotic symptoms measured by a non-zero score on four particular items of the Brief Psychiatric Rating Scale (unusual thought content, suspiciousness, hallucinations and conceptual disorganisation) during the 3 days after surgery,23,24 dissociative symptoms accessed by a non-zero score on the Clinician-Administered Dissociative States Scale within 3 days after the operation,25 and all drug-related adverse events during surgery or before discharge.

Data management
The clinical data will be recorded and managed with the electronic database. The paper version materials including the protocol, the case reported forms, informed consent forms and electronic version database will be preserved by the primary investigator and stored in the independently locked strong box in Beijing Tiantan Hospital.

Sample size calculation
It has been reported that the remission rate difference in the antidepressant effects between esketamine and ketamine was 3.8% in treatment-resistant depression patients.26 In the perioperative population with depressive symptoms, the remission rate was reported to be 23.1% in the ketamine group and 9.3% in the placebo group based on the PASSION study at our research site. We assumed that the remission rate in the esketamine group will be 19.3% and that in the placebo group will be 10%. A sample size of 506 participants will provide 80% power to show the difference between the esketamine group and the placebo group (with a ratio of 1:1), including 1 interim analysis by using a two-sided significance level of 0.05.27 With the consideration of a 10% attrition rate, the total sample size is planned to be 564.

Interim analysis
The planned interim analysis will be performed after 424 patients (75% of the total sample size) completed the follow-up. This interim analysis will be based on the intention-to-treat principle, and the p value will be set at 0.019 following adjustment by O’Brien-Fleming methods.28

Statistical analysis
Continuous variables will be reported as the mean (standard deviation) for normally distributed data and the median (IQ ranges) for skewed distributions. Categorical variables will be reported as the number (proportion), and the relative risk with its 95% CI will be calculated. The difference between groups will be reported with 95% CI of absolute differences calculated by independent t-tests for continuous variables and using the Hedges–Lehmann method for skewed variables. The primary endpoint of remission rate at 3 days after surgery will be analysed by using the χ²-test or Fisher’s exact test. The secondary outcomes will be analysed using t-tests, Mann–Whitney U tests and χ² or Fisher’s exact tests as appropriate. The adjusted ORs will be estimated by using a logistic regression model by taking into account the unbalanced baseline variables, age, sex, the severity of depressive symptoms and pain severity after surgery.

For missing values, both imputations with the mean or median or the last observed assessment and multiple imputations will be applied. Sensitivity analysis for different imputation plans will be used to explore the statistical nature of the missing data. All statistical tests will be two-sided at a significance level of 0.05 and the effect sizes will also be reported. Because of the potential for type I errors due to the lack of adjustment for multiple comparisons, the findings for secondary outcomes or sensitivity analysed should be interpreted as exploratory. All analyses will be performed by using Stata V.14.0.

Safety consideration
Once adverse events occurred during drug intervention, the principal investigator will be informed immediately. Based on the severity of the adverse events and the relation to esketamine, the unmasking process will be considered by the principal investigator. All the adverse events that occurred during the trial will be recorded in detail and closely monitored until stabilization or the time of the study intervention is not the cause for adverse events. All the adverse events will be reported to the Institutional Review Board by the principal investigator.

Patient and public involvement
Patients and the public were not involved in the trial design. Participants will have access to the findings of the study on request.

Ethics and dissemination
This study was approved by the Institutional Review Board of Beijing Tiantan Hospital, Capital Medical University, Beijing, China on 30 October 2020 (KY-2020-058-02). It has been registered on clinicaltrials.gov on 11 June 2020. The first participant was recruited on 19 February 2021. The conclusions of this study will be published in peer-reviewed journals.
DISCUSSION

This study is a randomised placebo-controlled double-blinded clinical trial that aims to explore the effect of esketamine on depressive symptoms in the major surgery population. The participants will be administered 0.2 mg/kg esketamine intravenously within 40 min with the suturing of the incision. The efficacy and safety endpoints will be observed during the perioperative period and in the long term after major surgery.

In this study, the patients in the control group will receive normal saline rather than other antidepressants. To the best of our knowledge, traditional antidepressants need to be administrated continuously for more than 1 week before taking effect, which is not suitable for short hospital stays in surgery patients. Besides, traditional antidepressants, such as selective serotonin reuptake inhibitors and tricyclic antidepressants, may lead to a potential risk for bleeding, arrhythmia and anaesthetic metabolism dysfunction during surgery. For ethical concerns, the participants enrolled in this study will be provided with a professional consultation from the psychiatrist as necessary.

Although the PASSION study found that ketamine could alleviate the depressive symptoms assessed by clinician-rating scales to some extent in neurosurgery patients, there are still several concerns about the evidence of clinical trials regarding the resolution for depressive symptoms in the surgery population. First, screening standards for depressive symptoms during the perioperative period are lacking, and assessments in different depressive populations may affect the results of studies. Minor depressive symptoms may induce few adverse outcomes and disappear spontaneously after surgery. However, moderate-to-severe depressive symptoms could lead to worsening moods, enhanced postoperative pain or suicidal ideation, and there is an urgent need to resolve these symptoms. Second, the rating scale tools are subjective. Self-rating scales have commonly been used in previous studies, which also require clinician-rating scales to verify the antidepressant effects. Third, small sample size may have led to false-positive or false-negative results in previously reported studies. Fourth, the long-term effects of ketamine or esketamine on depressive symptoms in patients undergoing major surgery remain unclear. Meanwhile, whether the analgesic effect of esketamine is the key factor considering the antidepressant effects needs to be investigated.

The safety of esketamine as an antidepressant in the context of surgery is unknown. Esketamine, as a novel drug for replacing ketamine, is not approved for intravenous use as an antidepressant. The plasma concentration for the antidepressant dosage of ketamine was reported to be approximately 70–200 ng/mL, which is far lower than the anaesthetic concentration (2000–3000 ng/mL). It is essential to explore an appropriate and safe dosage of esketamine for antidepressant treatment during surgery. Esketamine used in patients undergoing general anaesthesia is theoretically safer than the administration in awake patients. However, different anaesthetics administered during general anaesthesia may induce synergic effects with esketamine or attenuate treatment effectiveness. Thus, it is important to monitor the quality of recovery from general anaesthesia. Similar to ketamine, which could lead to psychotic symptoms, hallucinations, manic symptoms or dissociative symptoms, esketamine given at an antidepressant dosage may also increase these risks after surgery. Determining the safe dosage will also be important for the popularisation of esketamine used as an antidepressant during the perioperative period. Based on the previous study, both 0.2 mg/kg and 0.4 mg/kg of esketamine administrated intravenously were reported with remarkable antidepressant effects and low-dose of esketamine (0.2 mg/kg) with fewer side-effects rate than high-dose of esketamine after drug administration. Thus, we selected 0.2 mg/kg of esketamine as the intervention dosage in this study.

In summary, this study is a randomised controlled trial focusing on the mental health of perioperative patients. The expected result is that esketamine could markedly improve the remission rate after surgery without obvious adverse events, and long-term outcomes may also benefit from the administration of esketamine.

Author affiliations
1 Department of Anaesthesiology, Beijing Tiantan Hospital, Capital Medical University, Beijing, People’s Republic of China
2 Department of Statistics, China National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing, People’s Republic of China
3 China & Beijing Key Laboratory of Mental Disorders, National Clinical Research Center for Mental Disorders, Beijing An Ding Hospital, Capital Medical University, Beijing, People’s Republic of China
4 Department of Psychiatry, Capital Medical University, China & Center of Depression, Beijing Institute for Brain Disorders, Beijing, People’s Republic of China

Contributors YZ and BM were involved in the preparation of the manuscript, and contributed equally to this work. YZ, GW and RH were involved in the study concept and trial design. WS, JW and YF were involved in the data collecting and trial design. AW was involved in the sample size calculation and statistical analysis plan. All authors have read and approved the manuscript.

Funding This study was supported by Beijing Municipal Science & Technology Commission (No. Z19110000619067) and Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support (DFL20180502).

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 Consent obtained from parent(s)/guardian(s).

Provenance and peer review Not commissioned; externally peer reviewed.

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