Effect of esketamine on perioperative depressive symptoms in major surgery patients (PASSION II)

STATISTICAL ANALYSIS PLAN

Protocol Version 2.0

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1. Introduction

This statistical analysis plan (SAP) explains the established statistical analyses for a multicenter, randomized, placebo-controlled study (the PASSION II study) to evaluate the impact of esketamine on moderate-to-severe depressive symptoms in major surgery patients. This SAP is in accordance with the published protocol [1] (Zhou et al., Effect of esketamine on perioperative depressive symptoms in major surgery patients (PASSION II): study protocol for a randomized controlled trial. BMJ Open 2022;12: e056713. DOI:10.1136/bmjopen-2021-056713), together with any following amendments.

This SAP is special for the use of research members within Beijing Tiantan Hospital and should be implemented in combination with the PASSION II protocol. This SAP was written by the Principal Statistician and approved by the Principal Investigator. Additional statistical analysis not planned in the protocol will be performed and considered carefully in line with the principles of this analysis plan.

2. Study objective and endpoints

Study objective

The primary objective of this study is to assess the effects of esketamine administered intraoperatively at 0.2 mg/kg within 40 min versus an equal speed of placebo on 3-day depressive symptoms after intervention in patients with depressive symptoms patients undergoing major surgery.

All the secondary objectives in the protocol will be exploratory and list as follows:

To assess the effectiveness of esketamine administrated for depressive symptoms during the perioperative period.

Other objectives are as follows:

To compare moderate-to-severe pain after ketamine and placebo were administered during the first 3 postoperative days.

To compare all the safety events of surgery and study drugs administered intraoperatively in terms of psychiatric symptoms, dissociative symptoms and manic

symptoms, and adverse and serious adverse events during the study period.

Further exploratory objectives were to evaluate the postoperative 1-, 3-, and 6-month quality of life (WHODAS 2.0) and depressive symptoms.

Study endpoints

Primary efficacy

The remission rate of depressive symptoms at 3 days postoperatively was defined as a Montgomery-Åsberg Depression Rating Scale (MADRS) score less than or equal to 10. [2]

Secondary efficacy

The remission rate of depressive symptoms at discharge was defined as MADRS scores less than or equal to 10.

The response rates of depressive symptoms 3 days after surgery and at discharge.

The rate of moderate-to-severe pain during the first postoperative 3 days and severe pain were defined as numeric analogue scale (NAS) scores greater than 3.

Changes in further efficacy: Changes in depressive symptom scores at 1 month, 3 months, and 6 months postoperative; and the WHODAS 2.0.

Safety efficacy

Psychiatric complications: drug-related manic, psychotic, and dissociative symptoms during the first 3-day postoperative period. [3,4]

Surgery-related complications

3. Study overview

This study is a multicenter, randomized, placebo-controlled and double-blinded clinical trial. The primary null hypothesis of this study is that there is no difference in the 3-day postoperative remission rate between 0.2 mg/kg esketamine administered intraoperatively for 40 min and placebo administered at the same time in the same volume.

Patients undergoing major surgery, combined with moderate-to-severe depressive symptoms defined as those with a Patient Health Questionnaire 9 (PHQ-9) [5] score

of 10 or greater for the initial diagnosis of depressive symptoms and a MADRS score of 22 or greater for the assessment of severity, with ages ranging from 18--65 years. Major surgeries, including neurosurgical tumor resection, coronary artery bypass grafting, total hip or keen arthroplasty, breast cancer surgery, pneumonectomy or hepatectomy, are estimated to exceed 2 hours. Participants who meet the exclusion criteria will be excluded. Patients who signed the informed consent will be randomized into the esketamine group or the placebo group. In the esketamine group, esketamine will begin to be administered intravenously at a total dose of 0.2 mg/kg per weight and will continue for 40 min. In the placebo group, the same volume of normal saline will be administered at the same infusion rate. All patients will be followed during the perioperative period for depressive symptoms and drug-related complications.

The participants will be randomly assigned to the esketamine group or placebo group at a 1:1 ratio. Randomization results will be achieved via a real-time, online system before surgery. A randomized four-block design stratified patients by depressive severity (severe depressive symptoms are defined by MADRS scores equal to or greater than 30). The randomization sequence was created by independent engineers who will keep the allocation blinded, and all study-related investigators will be blinded to the randomization results. Randomization will be performed after informed written consent has been obtained.

Validation of endpoints

The data will be validated according to the preprescribed rules. A research manager at each center will determine that all the data are complete, consistent and up-to-date. The research managers are also responsible for retrieving original data and checking and tracking the key endpoint data at the specified time.

Planned analyses

The detailed procedure of analysis in this SAP will be performed only after the database is frozen. The intent-to-treat and per-protocol populations will be determined before unblinding the treatment allocation.

Treatment comparisons

The comparison of interest in this trial is between esketamine and placebo administered intraoperatively over the 3-day period of depressive symptom remission after surgery.

4. Statistical hypotheses

The primary endpoint of this study is the remission rate 3 days after surgery in patients with moderate-to-severe depressive symptoms.

The null hypothesis of no difference in remission rate between the two arms of intervention will be analysed by a two-sided test at the 5% level of significance.

$H0: \lambda1/\lambda2 = 1$

$H1: \lambda1/\lambda2 \neq 1$

where $\lambda1$ is the remission rate at postoperative day 3 in the group treated with esketamine and where $\lambda2$ is the same timepoint in the group treated with placebo.

5. Sample size determination

The difference in the remission rates of antidepressant effects between esketamine and ketamine was reported to be 3.8% in patients with treatment-resistant depression. 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 on the basis of the PASSION study at our research site. We assumed that the remission rate in the esketamine group would be 19.3% and that in the placebo group would be 10%. A sample size of 506 participants provided 80% power to show the difference between the esketamine group and the placebo group (with a ratio of 1:1), including 1 interim analysis with a two-sided significance level of 0.05. Considering a 10% attrition rate, the total sample size is planned to be 564.

6. Interim analysis

The planned interim analysis will be performed after 424 patients (75% of the total sample size) have completed the follow-up. This interim analysis is based on the

intention-to-treat principle, and the p value is set at 0.019 following adjustment by the O'Brien-Fleming method. [6] The trial will be stopped after interim analysis if a significant difference between the groups is detected.

7. Population analysis

Total population

This population will comprise all the subjects screened and for whom a record exists in the study database. This population will be used for listing adverse events occurring prior to randomization and reasons for withdrawal occurring prior to randomization.

Modified Intent-to-Treat Population

The intent-to-treat (ITT) population will include all the subjects after randomization and who received esketamine or placebo during surgery. After randomization, it is assumed that all participants have been administered a placebo or esketamine. The modified intent-to-treat population will be excluded from the analysis after randomization situations no longer meet the eligibility criteria, patients who do not have surgery, or patients who cannot undergo follow-up due to surgery-related combinations, such as aphasia or coma. The modified ITT population will be tested for demographic characteristics and efficacy and safety outcomes. The population will be used for primary analysis of the efficacy and safety outcomes.

Per-Protocol population

The per protocol (PP) population will comprise all participants except subjects who are confirmed as protocol transgressors. The subjects excluded from the PP population will be confirmed before being blind. This population was used for sensitivity analysis to determine the effect of missing data. In the PP population, subjects will be analysed according to the treatment received and the real events after postoperative assessments.

8. Statistical considerations

The data will be analyzed by Stata 16.0 software (Stata Corp LP, College Station, TX,

USA) and all significance tests will be two-sided , with an alpha setting of 0.05 and 95% confidence intervals confirmed.

Subgroup analysis

The rate of postoperative 3-day remission will be presented at each level of the variables listed below. The degree of change in the treatment effect of each subgroup at different levels will be evaluated via an interaction test.

Multiplicity

The single primary outcome was defined in the protocol, and all other efficacy variables were treated as secondary or other. The only comparison of interest in this study was between esketamine and placebo, and there was no need to adjust for multiple comparisons. All estimates of treatment effects for secondary endpoints will be presented with 95% confidence intervals, no inferential tests will be performed, and only exploratory tests with simple descriptions of these endpoints will be performed.

Missing Data

If the amount of missing data is lower than the prescribed attrition rate, which is 10%, the data will drop out. Missing data during the assessment period will be replaced with negative results before breaking blind. Sensitivity analysis will be applied for the different imputation methods, such as imputation with means or medians or dropouts or negative results. The missing data will be reported and analysed to determine their effects on primary efficacy.

9. Statistical analysis

General statistical calculations

For binary outcomes, the summary statistics are reported as the number and proportion, and the $\chi 2$ test was used for hypothesis testing. For outcomes measured on a continuous scale, the summary statistics are reported as the mean and standard deviation (SD) or median and interquartile range (IQR) depending on normality according to the Shapiro-Wilk test. Statistical inference to evaluate the effect of

treatment was presented as absolute mean differences and 95% CIs via the independent t test and linear regression for continuous variables, except skewed variables, for which the absolute difference and 95% CIs were calculated via the Mann-Whitney U test and the Hodges-Lehmann method. All the summarized descriptive statistics will be presented to one further decimal place unless otherwise specified. P values are rounded to 3 decimal places (those less than 0.001 are displayed as <0.001).

Follow-up data

The CONSORT flow chart will be used to summarize the follow-up of patients throughout the trial. Each center records the details of all randomization, intervention, and missing data.

Demographic and baseline characteristics

The demographic information, such as age, sex, weight, height, and body mass index, will be summarized and presented to the participants in the two intervention groups. Other variables included education level, marital status, American Society of Anesthesiologists physical status classification, Charlson's comorbidity index, smoking history, and comorbidity history. Baseline data for operation characteristics, such as delayed extubation, type and extent of resection, and time to spontaneous respiration, will also be obtained.

Efficacy analyses

All statistical analyses for the main effects were two-sided at P values less than 0.05.

Primary efficacy analysis

The primary outcome was postoperative 3-day remission events assessed by the MADRS scale after intervention.

Main Model

The remission rate of depressive symptoms at 3 days postoperative will be summarized by treatment group via the chi-square test or Fisher's exact test to compare the differences between groups in the m-ITT population. The risk ratio for the intervention comparison is presented, and the 95% CI is reported. The results are

also displayed graphically on a histogram plot.

Secondary efficacy analysis

All secondary endpoints are based on the m-ITT population. For categorical variables, which are presented as frequency counts and percentages, a two-sided Pearson's $\chi 2$ test or Fisher's exact test will be used, as appropriate. The odds ratios and 95% CIs were calculated. For continuous variables, prior to performing the statistical analysis, the assumptions of normality and homogeneity of variance of the residuals of quantitative variables were tested via the Shapiro-Wilk test and Levene's test, respectively. For efficacy analysis, a t test (normal variables) or the Mann-Whitney U test (skewed variables) will be used, as appropriate. The absolute difference and 95% CIs were calculated via the Mann-Whitney U test and the Hodges-Lehmann method.

Safety analysis

Safety endpoints will be assessed in the total population. The related variables are presented as frequency counts and percentages in both the esketamine group and the control group, odds ratios and 95% CIs.

Interaction with subgroups

A summary forest plot will be presented on the basis of the predefined subgroups, and interactions between them will be investigated for the primary endpoint. Exploratory subgroup-specific summary statistics and p values for interactions are presented. A separated logistic model was applied for interaction to identify its effect significance. The subgroup analysis included the following covariates: unbalanced baseline variables, age, sex, severity of depressive symptoms and pain severity after surgery.

Main results with Tables

Table 1. Demographic and preoperative characteristics of the total population.

Characteristics	Esketamine group	Control group
Sex		
Female	n (%)	n (%)
Male	n (%)	n (%)
Age, yr,	Mean (SD)/median (IQR)	Mean (SD)/median (IQR)
Height, cm,	Mean (SD)/median (IQR)	Mean (SD)/median (IQR)
Weight, kg,	Mean (SD)/median (IQR)	Mean (SD)/median (IQR)
Education	n (%)	n (%)
Married	n (%)	n (%)
Living state (alone)	n (%)	n (%)
Employed	n (%)	n (%)
Currently smoke	n (%)	n (%)
Alcohol intake		
Never	n (%)	n (%)
Occasional	n (%)	n (%)
Patient-reported duration of illness		
< 1 month	n (%)	n (%)
1-3 months	n (%)	n (%)
Coexisting medical condition		
Diabetes	n (%)	n (%)
Hypertension	n (%)	n (%)
Stroke	n (%)	n (%)
Heart disease	n (%)	n (%)
Chronic pain	n (%)	n (%)
MDD	n (%)	n (%)
Motor dysfunction	n (%)	n (%)
Surgical history	n (%)	n (%)
ASA physical status	n (%)	n (%)
Charlson's comorbidity scores	Mean (SD)/median (IQR)	Mean (SD)/median (IQR)
Severe depressive symptoms	n (%)	n (%)
Recurrent malignancy	n (%)	n (%)
Preoperative assessment		
PHQ-9	Mean (SD)/median (IQR)	Mean (SD)/median (IQR)

MADRS	Mean (SD)/median (IQR)	Mean (SD)/median (IQR)
GAD-7	Mean (SD)/median (IQR)	Mean (SD)/median (IQR)
HADS	Mean (SD)/median (IQR)	Mean (SD)/median (IQR)
WHODAS 2.0 scores	Mean (SD)/median (IQR)	Mean (SD)/median (IQR)
Z-WHODAS 2.0	Mean (SD)/median (IQR)	Mean (SD)/median (IQR)
Type of surgery	n (%)	n (%)
Other[a]	n (%)	n (%)

Data are shown as the mean (SD)/median (interquartile range) and numbers (%).

Table 2. Primary outcome and Secondary outcomes.

Characteristics	Esketamine group	Control group	OR/Difference (95%CI)	P value
Primary Outcome				
Remission on day 3	n (%)	n (%)	OR (95% CIs)	x
Secondary Outcomes				
NRS Pain scores >3, 0-48 Hours	n (%)	n (%)	OR (95% CIs)	x
Rescue analgesia, 0-48 Hours	n (%)	n (%)	OR (95% CIs)	x
Assessments on POD3				
MADRS	median (IQR)	median (IQR)	D (95% CIs)	x
GAD-7	median (IQR)	median (IQR)	D (95% CIs)	x
HADS	median (IQR)	median (IQR)	D (95% CIs)	x
PHQ-9≥10	n (%)	n (%)	OR (95% CIs)	x
Response	n (%)	n (%)	OR (95% CIs)	x
Assessments on discharge				
MADRS	median (IQR)	median (IQR)	D (95% CIs)	x
GAD-7	median (IQR)	median (IQR)	D (95% CIs)	x
HADS	median (IQR)	median (IQR)	D (95% CIs)	x
PHQ-9≥10	n (%)	n (%)	OR (95% CIs)	x
Response	n (%)	n (%)	OR (95% CIs)	x
Remission	n (%)	n (%)	OR (95% CIs)	x
Length of hospital stay	median (IQR)	median (IQR)	D (95% CIs)	x
Adverse events				
PONV, 0-48 Hours	n (%)	n (%)	OR (95% CIs)	x
Dissociative symptoms (CADSS≥5)	n (%)	n (%)	OR (95% CIs)	x
Psychotic side effects (BPRS 4 items≥5)	n (%)	n (%)	OR (95% CIs)	x
Manic symptoms (YMRS≥5)	n (%)	n (%)	OR (95% CIs)	x
Delirium	n (%)	n (%)	OR (95% CIs)	x
Infection after surgery	n (%)	n (%)	OR (95% CIs)	x
Bleeding events	n (%)	n (%)	OR (95% CIs)	x
Thrombus events	n (%)	n (%)	OR (95% CIs)	x

Figure 1 Flow chart and consort diagram of the study

Figure 2 Primary outcomes and MADRS scores

Figure 3 Subgroup analysis and interactions

10. Reference

[1] Zhou Y, Ma B, Sun W, et al Effect of esketamine on perioperative depressive symptoms in major surgery patients (PASSION II): study protocol for a randomised controlled trial BMJ Open 2022;12:e056713.

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