




# Comparison of Effects of Propofol Combined with Different Doses of Esketamine for ECT in the Treatment of Depression: A Randomized Controlled Trial Protocol

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**Objective:** Major depressive disorder (MDD) is a common mood disorder. Electroconvulsive therapy (ECT) has a significant effect on treatment-resistant MDD. Esketamine may have potential advantages in improving the efficacy of ECT, and the strong affinity of this compound for NMDAR renders it a viable therapeutic option for the management of depression. This study aims to compare the effects of different doses of esketamine combined with propofol anesthesia versus propofol anesthesia alone in ECT, aiming to provide further insights for optimizing ECT and enhancing comprehensive treatment outcomes for depression.

**Study Design and Methods:** This study was a prospective, randomized, controlled, double-blind trial involving subjects and evaluators. One hundred eleven patients scheduled for ECT were randomly assigned to three groups. In Group P, propofol at 1mg/kg was administered intravenously. In Group P+E, propofol at a dosage of 0.5mg/kg and esketamine at a dosage of 0.5mg/kg was administered intravenously. Patients in Group P+SE received propofol at a dosage of 0.75mg/kg and esketamine at a dosage of 0.25mg/kg. The same anesthesia protocol was used for the same patient until the end of the last treatment. The primary outcome measures were the Hamilton depression scale (HAM-D) and the Patient Health Questionnaire-9 (PHQ-9), the Columbia-Suicide Severity Rating Scale (C-SSRS), and the Digit symbol substitution test (DSST). Secondary outcomes included length of hospital stay, readmission rate, hemodynamic status, recovery, and adverse events.

**Discussion:** This study aimed to compare the effects of propofol combined with different doses of esketamine for ECT. The results may provide a better choice for ECT anesthesia.

**Keywords:** esketamine, depressive disorder, electroconvulsive therapy, curative effect

## Introduction

Depressive disorder is a common mental disorder characterized by prolonged periods of low mood and loss of interest in social activities. The prevalence of depression is high; about 20% of people experience depression in their lifetime, and about 40% of patients have their first onset before the age of 20.<sup>1</sup> As early as 2008, the World Health Organization ranked it the third-largest disease burden.<sup>2</sup> Major depression causes significant impairment in social functioning, preventing people from working, performing daily activities, and school. At the same time, it is often closely related to suicidal tendencies and behaviors.

ECT is for the treatment of Treatment-Resistant Depression (TRD) and certain other psychiatric disorders.<sup>3</sup> TRD refers to depression that does not respond to at least two different types of antidepressants, typically showing no significant improvement in symptoms or minimal effect after a sufficient dosage and duration of antidepressant treatment has been attempted.<sup>4</sup> Patients are initially administered a general anesthetic during ECT administration to ensure their comfort throughout the procedure.<sup>3</sup> Subsequently, doctors administer a low-intensity electrical current through electrodes positioned on the scalp, inducing a transient seizure in the brain with the aim of modulating depressive symptoms by altering the brain's neurochemical environment.<sup>3,5</sup> In typical cases of depression, ECT has an effective rate of more than 50%, which is superior to psychotropic drug therapy alone, with adverse effects usually mild and transient, reduced rehospitalization rates, and high patient satisfaction.<sup>6,7</sup> However, it is crucial to highlight that the management of treatment-resistant depression typically necessitates multiple Electroconvulsive Therapy (ECT) sessions to achieve satisfactory outcomes.<sup>8,9</sup> Recent investigations have indicated that esketamine is advantageous in the therapy of depression. Esketamine, being the S-enantiomer of ketamine, demonstrates a high affinity towards the N-methyl-D-aspartate receptor (NMDAR), which enables it to effectively mitigate depressive symptoms and minimize suicidal ideation, accompanied by a low prevalence of adverse reactions.<sup>10,11</sup> As a frequently used anesthetic drug, Propofol demonstrates excellent soothing properties, characterized by its rapid onset and quick recovery, and can deliver a stable anesthetic effect.<sup>12,13</sup> Consequently, the combination of Propofol and esketamine could enhance the efficacy of ECT, decrease the frequency of ECT treatments, and open up a new avenue for improving the therapeutic outcomes of ECT and refining the anesthesia protocol.

Therefore, we designed this prospective, randomized, controlled, double-blind study to compare the effects of different combinations of esketamine and propofol for ECT.

## Materials and Methods

### Study Design

This was a prospective, randomized, controlled, double-masked study to investigate the effect of esketamine combined with propofol for ECT in the treatment of depression. Subjects were recruited at Deyang People's Hospital, Deyang City, Sichuan Province, China. The study shows the trial schedule by the SPIRIT statement (Table 1). The study shows the patient flow chart. All researchers will be trained to participate in the study according to a standard and uniform protocol (Figure 1).

### Registration and Ethics

This trial has been registered in the Chinese Clinical Trial Registry with the registration number ChiCTR2300074325. The Ethics Committee of Deyang People's Hospital, Deyang City, Sichuan Province, China (2023-04-032-H02) approved the study protocol. We adhered to the Declaration of Helsinki for the clinical trial.

**Table 1** Schedule of This Study

Time Point	Study Period									
	Enrollment	Allocation	Post Allocation		Follow-Up Visit					
	T	T0	T1	T2	T3	T4	T5	T6	T7	T8
<b>Enrollment</b>										
Eligibility screening	•									
Informed consent	•									
Allocation		•								
<b>Interventions</b>										
Propofol alone and ECT (P Group)		•								
Propofol, Esketamine and ECT (P+E Group)		•								
Propofol, Low-dose Esketamine and ECT (P+SE Group)		•								

(Continued)

**Table I** (Continued).

Time Point	Study Period									
	Enrollment	Allocation	Post Allocation		Follow-Up Visit					
	T	T0	T1	T2	T3	T4	T5	T6	T7	T8
<b>Assessments</b>										
Baseline variables										
Age	•									
Gender	•									
Height	•									
Weight	•									
Depression Diagnosis	•									
Depression Severity	•									
Depression onset time	•									
Recovery Time				•						
Hemodynamic										
Heart rate	•		•	•						
Pulse oxygen saturation	•		•	•						
Noninvasive blood pressure	•		•	•						
Respiratory rate	•		•	•						
Consciousness				•						
Orientation				•						
HAMD score	•			•	•	•	•	•	•	•
PHQ-9 score	•			•	•	•	•	•	•	•
C-SSRS score	•			•	•	•	•	•	•	•
DSST score	•					•	•	•	•	
Length of hospital stay					•					
Readmission Rate					•					
Satisfaction					•					
ECT times					•					
Adverse Reactions										
Bradycardia			•	•	•	•	•	•	•	•
Hypertension			•	•	•	•	•	•	•	•
Hypoxia			•	•	•	•	•	•	•	•
Nausea			•	•	•	•	•	•	•	•
Vomiting			•	•	•	•	•	•	•	•
Pruritus			•	•	•	•	•	•	•	•
Dizziness			•	•	•	•	•	•	•	•

**Notes:** T: before the study began, subjects were screened, collecting baseline data; T0: before the intervention, randomization was performed; T1: one minute after anesthesia induction; T2: at the end of treatment; T3: one week after ECT; T4: two weeks after ECT; T5: three weeks after ECT; T6: one month after ECT; T7: two months after ECT treatment; T8: three months after ECT treatment.

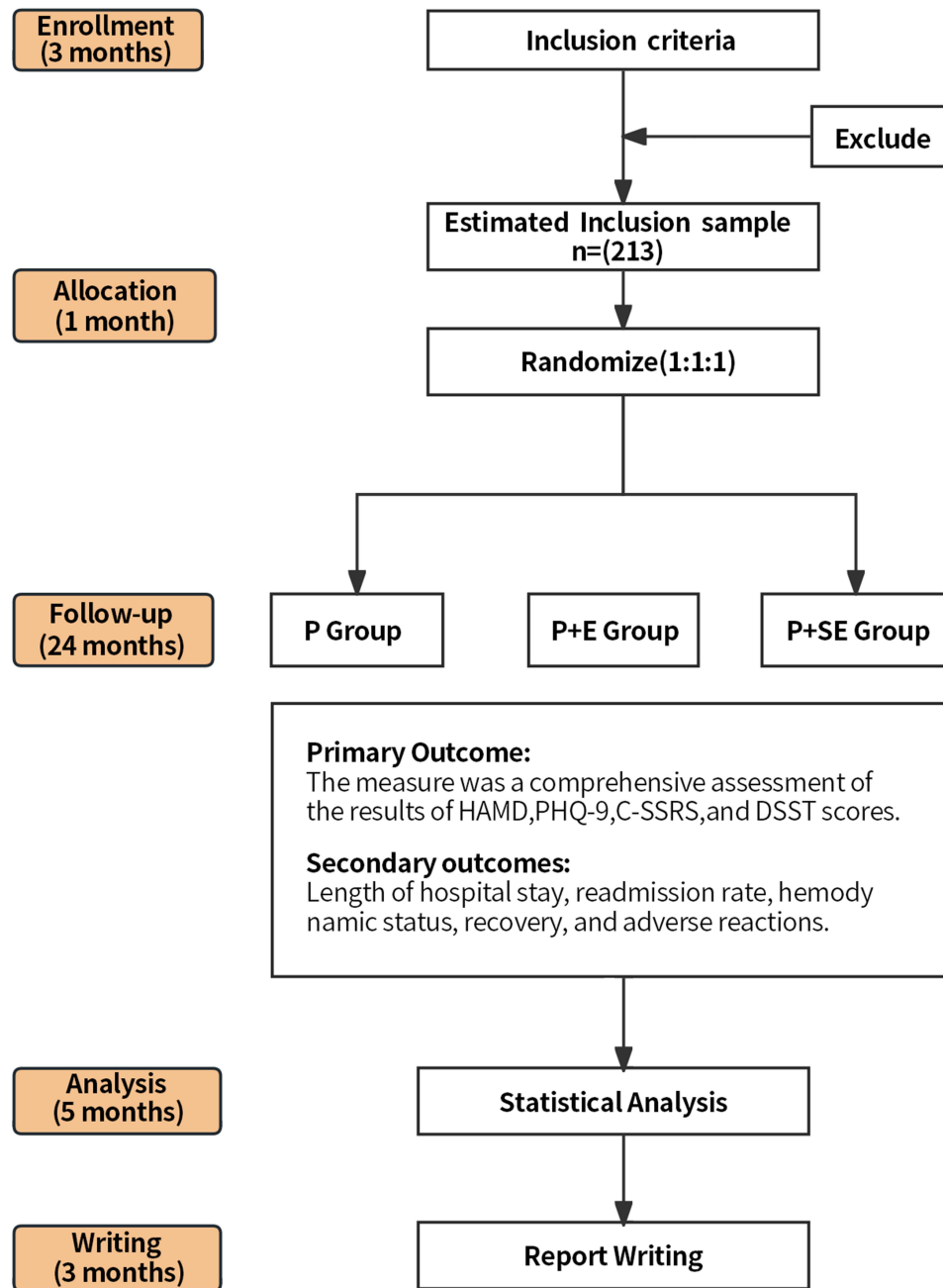
**Abbreviations:** HAMD, Hamilton Depression Scale; PHQ-9, Patient Health Questionnaire-9; C-SSRS, Columbia-Suicide Severity Rating Scale; DSST, Digit symbol substitution test.

The physicians responsible for conducting the study will thoroughly explain its details to eligible patients and request their signature on the informed consent form. After signing the relevant documents, the patient will be enrolled in the program and can withdraw anytime.

### Inclusion and Exclusion Criteria

Inclusion criteria: 1) Age  $\geq 18$  years old; 2) A definite diagnosis of depression was made and electroconvulsive therapy (ECT) was required; 3) Consent to participate in the study.

Exclusion criteria: 1) Use of esketamine within one month; 2) ASA grade  $> II$ ; 3) Severe cardiovascular disease (including poorly controlled hypertension), severe respiratory disease, cerebrovascular disease, intracranial hypertension



**Figure 1** Flowchart of this study.

(including glaucoma); 4) Epilepsy, schizophrenia; 5) Pregnant women; 6) Poorly controlled hyperthyroidism; 7) Allergic to related drugs.

## Dropout Criteria

If one of the following conditions occurs, the follow-up will be stopped: 1) Violation of legitimacy, that is, the patient selection violates the inclusion/exclusion criteria and does not meet the randomization; 2) Other drugs (Reserpine, Tricyclic Antidepressants, Monoamine Oxidase Inhibitors, Antiepileptic, Benzodiazepine Anti-anxiety) were not stopped or adjusted according to the regulations, which affected the observed indicators; 3) Patients have severe complications or withdrawal from the trial.

## Allocation and Blinding

NCSS software was used to randomly divide the subjects who met the inclusion and exclusion criteria into three groups at a ratio of 1:1:1. These groups included propofol alone (Group P), propofol combined with esketamine (Group P+E), and propofol combined with low-dose esketamine (Group P+SE). Specialized drug preparation personnel will select syringes of uniform specifications and prepare relevant drugs and will not participate in the subsequent experimental process. Allocation information will be concealed in opaque sealed envelopes. Once an application for ECT has been made, it is assessed. After enrollment, the investigator opened the envelope, selected the dosing regimen based on the information, and exited the room after induction of anesthesia. A second investigator responsible for follow-up visits entered the ward and participated in the subsequent anesthesia maintenance and recovery process. They will also be responsible for managing potential adverse effects. The researcher responsible for administering the drug will be barred from the follow-up process. Therefore, both patients and observers were double-blinded to group assignments.

## Intervention

Upon admission to the treatment room, patients are monitored for heart rate, pulse oxygen saturation, noninvasive blood pressure, and respiratory rate. Rescue medications, including atropine and dopamine, were prepared before treatment. Then, according to the group, the patients were given intravenous injections of propofol 1mg/kg (group P), propofol 0.5mg/kg+ esketamine 0.5mg/kg (group P+E), and propofol 0.75mg/kg+ esketamine 0.25mg/kg (group P+SE).<sup>8,14,15</sup> When the patient did not respond to the call, the eyelash reflex disappeared, succinylcholine 1mg/kg was administered, and ECT was started after the end of the myotremor. Ect-related parameters were set by psychosomatic physicians specializing in ECT treatment. The recovery time, hemodynamic changes, recovery of consciousness and orientation, and adverse reactions were observed after ECT. The same anesthesia protocol was used for the same patient until the end of the last treatment. The treatment plan after ECT was formulated and recorded by psychosomatic physicians. HAMD, PHQ-9, and C-SSRS scores were evaluated at one week, two weeks, three weeks, one month, two months, and three months after ECT treatment. DSST scores were evaluated at the end of ECT and one, two, and three months after ECT. The length of hospital stay, readmission rate, satisfaction, ECT times and adverse reactions were recorded in detail. Neither the researchers nor the patient was aware of the anesthesia assignments.

## Outcomes

### Baseline Data and Expected Parameters

Before ECT treatment, the researchers recorded demographic data such as age, gender, height, weight, blood pressure, heart rate, and SPO<sub>2</sub>. Meanwhile, the diagnosis, severity, onset time of depression, and baseline scores of HAMD, PHQ-9, C-SSRS, and DSST were recorded.

During ECT treatment, the researchers recorded the HAMD score, PHQ-9 score, C-SSRS score, DSST score, ECT times, bradycardia, hypertension, hypoxia, nausea, vomiting, pruritus, and dizziness.

### Primary Outcomes

The primary outcome measure was a comprehensive assessment of the results of HAMD, PHQ-9, C-SSRS, and DSST scores. HAMD, PHQ-9, Columbia-Suicide C-SSRS, DSST evaluation time: Before the first ECT and at one week, two weeks, three weeks, one month, two months, and three months after the first ECT treatment.

### Secondary Outcomes

The secondary outcomes included length of hospital stay, readmission rate, hemodynamic status, recovery, and adverse reactions. Adverse reactions included postoperative nausea and vomiting, somnolence, headache, postoperative agitation, postoperative delirium, and postoperative hallucination.

## Sample Size Determination

The sample size ratio of the three groups was 1:1:1 (the number of cases in the three groups was equal). The intervention groups were P+E and P+SE, and the control group was P. The remission rate of depression in the control group was estimated to be 50% based on previous literature reports.<sup>16</sup> After implementation of the intervention, depression remission rates were estimated to be 65% in the P+SE group and 80% in the P+E group.<sup>17</sup> Let  $\alpha=0.01$  (two-sided) and  $\beta=0.10$ . PASS 21 software was used to calculate 64 samples in each group. Assuming a dropout rate of 10%, we ultimately required 71 patients per group.

## Statistical Analysis

SPSS 26.0 (IBM, USA) will record data and perform statistical analysis. Variables such as demographics, main vital signs, HAMD score, PHQ-9 score, C-SSRS score, and DSST score will be validated using the Kolmogorov–Smirnov test to determine the normality of the data distribution. Data with normal distribution will be described as mean  $\pm$  SD, and data with abnormal distribution will be described as median (interquartile range). An independent *t*-test and Wilcoxon rank test were used to compare the differences between the two groups. Count data (adverse effects, length of hospital stay, readmission rate, recovery) will be described as percentages and analyzed by the chi-square test or Fisher's exact test. To control for multiple errors, we used Bonferroni's post hoc test. In addition, we analyzed the correlation between the variables using logistic regression. Finally, sensitivity tests were performed to ensure the reliability of the statistical analysis results.  $p < 0.05$  was considered statistically significant.

## Adverse Event Report

The patient's vital signs were monitored continuously after entering the room until he returned to the ward safely. Adverse events of induction of anesthesia, course of treatment, and postoperative resuscitation for ECT treatment will be evaluated periodically and recorded in case report forms. A senior anesthetist will be involved in the treatment. Adverse events were compared between groups using the chi-square or Fisher's exact tests.

## Arrangement

Subject recruitment phase: The duration was three months, from the study's start date to the completion date of sample recruitment.

Subject grouping phase: one month, when subjects are randomly assigned.

Clinical trial and data collection phase: The duration was twenty-four months, including the intervention implementation, clinical data collection, and post-treatment follow-up.

Statistical analysis phase: The duration was five months, including the time to collate the study results and analyze the report.

Manuscript writing phase: The duration was three months, including time to write, revise, and refine the report.

## Discussion

Depression is a common mental health problem of global concern that can lead to social isolation, lack of support, and even suicidal behavior.<sup>1</sup> Electroconvulsive therapy (ECT) has a significant effect on major depression, with a remission rate of 50%-60%, which can reduce the risk of suicide and improve the quality of life.<sup>18–24</sup> Currently, the anesthetic commonly used in ECT is propofol, which has an excellent soothing effect but may cause pain and low blood pressure during injection.<sup>12,13</sup> Esketamine, as the S(+) enantiomer of ketamine, is a more potent NMDA receptor antagonist, has good analgesia and sedation, and has a rapid antidepressant and anti-suicide effect.<sup>23–25</sup> Given the small number of studies on esketamine for ECT, we conducted this clinical trial.

The study is a single-center, double-blind, randomized controlled clinical trial. ECT was achieved by administering esketamine combined with propofol or propofol alone for anesthesia sedation with the exact dosage of the remaining drugs. At present, esketamine is usually used for the treatment of depression by nasal drops and is widely used in clinical practice.<sup>26–30</sup> Regarding the application of ECT treatment, studies have confirmed that the use of ketamine and propofol 1:1 is an effective ratio for the treatment of ECT considering that the potency of esketamine is twice that of ketamine,

equivalent to esketamine: propofol ratio of 0.5:1 or 1:2 can be used for ECT treatment.<sup>8,14,15</sup> However, there are few studies on using intravenous esketamine in ECT treatment. So, we chose esketamine doses of 0.5mg/kg and 0.25mg/kg, which are within the safety range and ensure adequate sedation depth during treatment. However, there is currently disagreement about the efficacy of ketamine in ECT. A study has shown that ECT with ketamine was not associated with greater improvements in depressive symptoms or higher rates of clinical response or remission, nor did it result in pro-cognitive effects.<sup>31</sup> This held true when limiting analysis to trials without barbiturate anaesthetic co-administration.<sup>31</sup> The other study has shown that the use of ketamine in electroconvulsive therapy is efficacious in improving the remission rate of depression.<sup>32</sup> Still, a higher incidence of adverse events accompanies it.<sup>32</sup> Therefore, this study chose propofol combined with esketamine for ECT. This choice was made to avoid the combination of barbiturates and consider that esketamine, a novel NMDA receptor antagonist, is associated with fewer adverse effects than ketamine.<sup>10,11</sup> We hope that by exploring the effectiveness of esketamine in electroconvulsive therapy for patients with depression, we can enrich relevant clinical evidence to improve the remission rate of depression and optimize the electroconvulsive therapy program.

In addition, for the selection of primary outcome measures, we needed to evaluate the benefits of esketamine in the treatment of ECT from the comprehensive aspects of psychology, severity, and cognitive function of patients with depression. Therefore, we selected the comprehensive evaluation of the results of HAMD, PHQ-9, C-SSRS, and DSST scales as the primary outcome measures.<sup>33–36</sup> However, it is worth noting that the scale evaluation has some subjectivity, which may be affected by the subjective report of patients and the subjective judgment of evaluators. In order to reduce the degree of data bias, we have taken a series of measures to ensure the objectivity and credibility of the evaluation. Firstly, we conducted rigorous training to ensure that the assessors were familiar with the methods and criteria of using the scale; in addition, we used multiple assessors to score independently to reduce subjective bias through cross-validation, and secondly, we focused on the combination of patients' self-assessment and professional assessment to comprehensively consider patients' subjective feelings and objective symptoms. Finally, in the study design, we introduced measures such as a control group, randomized group, and double-blind design to reduce the possible interference factors of the experimental results and ensure the scientific validity and reliability of the study.

Safety was an important part of our study. ECT treatment is usually simple and fast, and the anesthetic drugs used have been reviewed for drug safety, and the safety of the whole treatment process has been extensively tested. However, we may still observe related adverse reactions, such as hypertension, hypoxia, nausea and vomiting, pruritus, lethargy, dizziness, hallucination.<sup>28,37</sup> Therefore, the incidence and degree of related adverse effects were recorded in detail throughout the treatment process, and the data collected were analyzed objectively.

## Conclusion

This study aims to investigate the effect of esketamine combined with propofol electroconvulsive therapy on depression. If the P+SE and P+E groups have significant advantages in HAMD, PHQ-9, C-SSRS, and DSST scales, more information and evidence will be provided for the effect of ECT in treating depression. This study is expected to optimize the ECT treatment regimen and increase the remission rate of depression, thereby improving patient outcomes.

## Acquisition of Data

Relevant data may be obtained from the corresponding author more than six months after publication for a reasonable purpose.

## Trial Status

The trial was registered in the Chinese Clinical Trial Registry on August 3, 2023 (ChiCTR2300074325). The Ethics Committee of Deyang People's Hospital approved the study protocol on June 7, 2023 (2023-04-032-H02). The first subject was recruited on September 2, 2023, and the cutoff date was estimated to be February 2, 2025.

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## Disclosure

The authors report no conflicts of interest in this work.

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