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STUDY PROTOCOL

Effects of Binaural Beat Music and Esketamine for ECT in the Treatment of Major Depressive Disorder: A Randomized Controlled Trial Protocol

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Purpose: Major depressive disorder (MDD) has a high incidence and high risk of suicide. Electroconvulsive therapy (ECT) is a highly effective and rapid physical therapy for MDD but limited by adverse effects. Ketamine/esketamine are new emerging rapid antidepressants, which can synergize the efficacy and safety of ECT but come with other side effects. Binaural beat music (BBM) is a non-invasive somatopsychic therapy with the potential to improve mood and assist the efficacy of (es)ketamine. Purpose of this study is to investigate the modification of BBM on effects of (esketamine combined with) ECT for MDD, and the probable interaction between BBM and esketamine, aiming to provide insights for optimizing ECT and improving outcomes of patients with MDD.

Patients and Methods: This study is a 2×2 factorial, prospective, randomized, controlled, blinded clinical trial that recruiting 476 patients with MDD who require ECT treatments. These participants are randomly 1:1:1:1 allocated to the following groups (119 in each group): ① Group B0E0 (blank sound and normal saline); ② Group B0E1 (blank sound and esketamine); ③ Group B1E0 (BBM and normal saline); ④ group B1E1 (BBM and esketamine). The primary outcome is the response rate of patients to ECT treatment, assessed using the Hamilton depression scale (HAMD). Secondary outcomes include remission rate of depression and remission of suicidal ideation (assessed using HAMD), accompanied psychotic symptoms assessed using the Brief Psychiatric Rating Scale, cognitive function assessed using the Montreal Cognitive Assessment Scale, parameters of ECT, perianesthesia vital signs and anesthesia-related indices, blood biomarkers, and side effects.

Discussion: This study provides the first clinical evidence of the effects of BBM alone or interacted with esketamine in patients with MDD undergoing ECT. Our data are expected to suggest BBM's potential for developing better ECT therapeutic strategies, optimizing treatments for MDD and promoting prognosis.

Keywords: ketamine, music therapy, depression, electroconvulsive therapy, adverse effect, efficacy

Introduction

According to update of the World Health Organization, approximately 280 million people in the world have depression, which has become a leading cause of morbidity and disability.[1,2] Major depressive disorder (MDD) is extremely harmful for leading to suicide, which causes the death of more than 700000 people every year.[1] The conventional antidepressants for depression have a slow onset (a few weeks or more) and exert inefficacy in up to one-half of patients with MDD.[3] Rapid and efficient treatment for MDD is of great significance for reducing the disease burden and suicide-related mortality.

Electroconvulsive therapy (ECT), which is recognized as an effective physical therapy for depression, particularly MDD (with suicidal ideation), has the distinct advantage of being fast and robust, and relieving suicidal ideation rapidly.[4] ECT has also been considered as the gold standard treatment of treatment-resistant depression (TRD).[5] However, the side effects of ECT, including impaired learning and memory, cognitive deficits, and muscle pain, are still not negligible,

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limiting its clinical application.[6] Since the exact mechanism of ECT is still unclear, based on a variety of biological and molecular studies, the oxidative, immune-inflammatory, and neurotrophic responses to ECT may provide some insights for improving its efficacy and/or reducing its side effects.[7,8] Moreover, there are ongoing explorations for better practical strategies for ECT, which are associated with less side effects such as mild cognitive impairment, including modifying the parameters of ECT (eg, the usage of nonconvulsive electrotherapy, NET), improving auxiliary techniques during the peri-anesthesia period for ECT (eg, the usage of transnasal humidified rapid-insufflation ventilatory exchange, THRIVE), and optimizing anesthesia plans (eg, the usage of novel or specific anesthetics).[5,9–13] As compared with the standard ECT, NET is similar but without inducing convulsions using subthreshold stimulation, which remains the antidepressant effects and reduces the side effects of ECT.[9–11] By supplying constant temperature and humidified high-flow oxygen, THRIVE, as a novel technique that is currently being used in ECT, effectively benefits the safe implementation of ECT and prevents the patients from peri-anesthetic hypoxia and related function impairment.[12] Anesthetic factors for improvement in ECT have been attracted more attentions as well.[13]

Recently, ketamine, traditionally used for anesthesia and analgesia, has been considered as "a major breakthrough" in the treatment of depression over the last decades due to its rapid antidepressant effect at subanesthetic doses.[3,14,15] In current clinical practice, intravenous ketamine can be used at an anesthetic dose for the general anesthesia required for ECT, and used at a subanesthetic dose to assist with ECT treatment.[5,13] As the S-enantiomer of (R, S)-ketamine, esketamine (S-ketamine) offers advantages in terms of performance.[16,17] Although both being irreplaceable, compared with ECT, (es)ketamine has its own advantages and disadvantages for the treatment of depression, and it is still difficult to distinguish between the two, which are not interchangeable at present.[18–20] In fact, the combination of (es)ketamine can enhance or accelerate the antidepressant efficacy of ECT and alleviate its adverse effects, such as cognitive dysfunction, etc.[21–24] However, (es)ketamine brings side effects and potential risks as well, especially in the neuropsychiatric and cardiovascular systems, including psychosis, dissociation, addiction, hypertension, and so on, which cause intolerance and limit the application.[25] The search for methods that assist the benefits of (es)ketamine, ECT, and their combination for MDD will contribute to the optimization of clinical practice.

In addition to physical therapies and pharmacotherapies, as a non-invasive somatopsychic therapy, binaural beat music (BBM) therapy may provide a more appropriate option. Music therapy has been shown to have positive effects on mood and alleviate depressive symptoms in different populations.[26–29] Moreover, music added to ketamine or esketamine can improve the patients' response to the agents with enhancing not only their antidepressant effects but also the patients' tolerance and reducing the side effects.[30–34] A preference survey of patients found that up to 80% preferred to listen to music prior to ECT.[35] Binaural beats or BBM can exert relaxing, anxiolytic, sedative, analgesic, and antidepressant effects in different populations and/or disease states, possibly by directing the main frequencies of electroencephalogram to accompany external stimuli.[36–42] BBM is the combination of an additional binaural beat with different frequencies and background music for better comfort, which can better play a positive role in improving mood and other outcomes, especially in terms of anxiety and depression.[39–42]

However, there are currently no reported clinical studies of the effects of music or BBM and (es)ketamine for ECT in the treatment of depression. Therefore, the purpose of this study is to investigate the modulation of BBM on effects of (esketamine combined with) ECT for MDD, and the probable interaction between BBM and esketamine, aiming to provide new insights for optimizing ECT and improving outcomes. BBM's potential benefits can support its use in combination with the rapid and potent therapies as optimization strategies for treating MDD.

Materials and Methods

Study Design

The protocol of this study has received ethical approval from the Institutional Review Board of the First Affiliated Hospital of Chongqing Medical University (ethics approval number: 2024-358-02) and been registered in the Chinese Clinical Trial Registry (number: ChiCTR2400094873). The present protocol has been developed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (from: www.spirit-statement.org) and the trial will comply with the Declaration of Helsinki. This study is designed as a prospective randomized controlled blinded and factorial design clinical trial. It is designed to investigate the effects of BBM, esketamine, and their

combination in patients with MDD undergoing ECT, as well as the possible interaction between BBM and esketamine. Therefore, according to the 2×2 factorial design at each level of the two factors, the participants will be randomly divided into four groups, group B0K0, group B1K0, group B0K1, and group B1K1. The flowchart of design is shown in Figure 1.

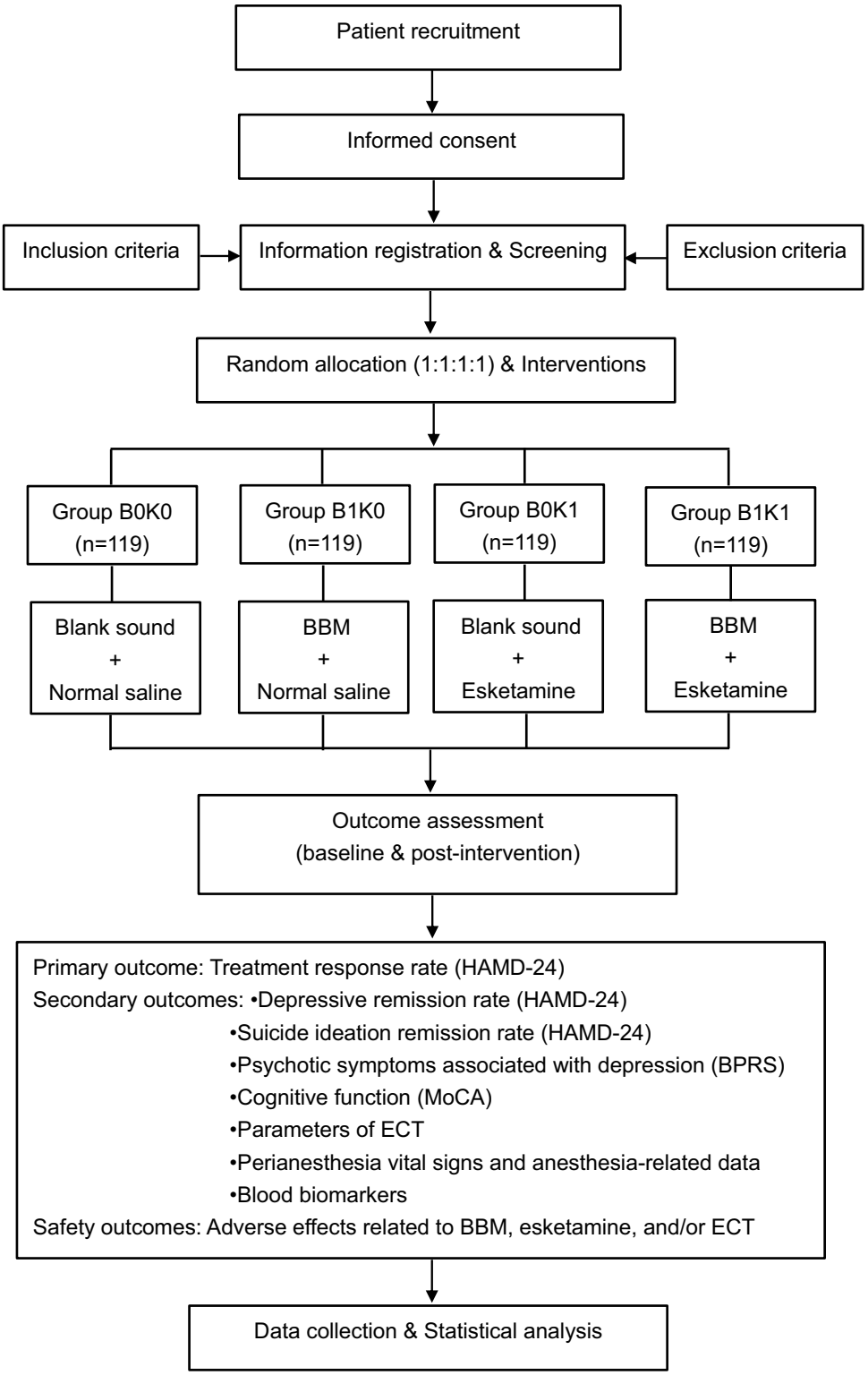

Figure 1 Study design and flow chart.
Abbreviations: BBM, binaural beat music; BPRS, Brief Psychiatric Rating Scale; HAMD-24, 24-item Hamilton Rating Scale for Depression; ECT, electroconvulsive therapy; MoCA, Montreal Cognitive Assessment.

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Participant Recruitment

Eligibility Criteria

Inclusion criteria: (1) patients with a diagnosis of MDD who need to be hospitalized for ECT therapy; (2) age 19–59 years; (3) with no previous serious comorbidities; (4) American Society of Anesthesiologists grade I to II; (5) with body mass index being 18.5–30 kg/m^2; (6) the patient and/or his/her guardian understand and agree and sign the informed consent.

Exclusion Criteria: (1) concomitant serious diseases, such as presence of intracranial electrode clips or cardiac pacemakers; (2) combined with other psychiatric diseases, such as schizophrenia, etc; (3) suffering from diseases or conditions that result in inability to complete or affect the efficacy assessment, such as cognitive dysfunction, illiteracy, intellectual disability, etc; (4) with contraindications to anesthesia or ECT; (5) hypertension, risk of intracranial hypertension, hyperthyroidism, severe heart disease or any contraindication to the use of (es)ketamine; (6) allergy to (es) ketamine; (7) (es) ketamine, or other drug or alcohol dependence; (8) no response to (es)ketamine or serious adverse effects of it in previous administration; (9) hearing loss or impairment; (10) inefficacy or serious adverse effects of previous ECT therapy; (11) pregnant women; (12) participated in other clinical trials within the past 1 year.

Discontinuation Criteria

If one of the conditions occurs as following, the follow-up will be discontinued: (1) serious adverse reactions during the trial need to be terminated; (2) the patient and/or his/her family members request to terminate or withdrawal; (3) the patient's condition changes, and the psychiatric physician in charge judges that ECT should be terminated; (4) loss of contact or out-of-contact; (5) violation of legitimacy of the trial.

Randomization, Allocation Concealment and Blinding

A total of 476 participants are planned to be included in the study, randomly divided into four groups in equal proportions, ie, 119 patients in each group, by investigator A. Each participant will be assigned to each group with a serial number randomly generated by the computer. Investigator B prepares the interventions for each group, investigator C conducts the implementation of the interventions, and investigator D collects and manages the data. In this study, investigators A, C, and D are unaware of the specific content of the intervention. Esketamine used in this study is a colorless transparent liquid, which can be modified to be consistent with the appearance of the normal saline as control and can be blinded to both the investigators and the participants. BBM and blank sound cannot be blinded to the participants, but the investigators can be blinded. During the whole process of the trial, the participants are required to keep the content listening to through the headphones confidential and not to disclose them to the investigators.

Intervention

BBM and esketamine are the two interventions in this study. BBM is the combination of the beats with a carrier frequency of 400 Hz and the beat frequency of 4 Hz and light music as the background. Blank sound content is the control for BBM. Binaural noise-cancelling headphones will be distributed, and patients will be assisted in adjusting the appropriate volume. According to different groups, the patients will listen to two sessions of one-hour BBM interventions or blank sound content, the first session starts one hour before bedtime on the night before each ECT and the second session starts one hour before the beginning of the anesthetic induction of ECT procedure. Esketamine (50 mg/2 mL, Hengrui Pharmaceutical Co., Ltd., Lianyungang, Jiangsu, China) is used with a dose of 0.125 mg/kg, and slowly injected intravenously after the general anesthetic propofol and muscle relaxant succinylcholine having been given for anesthetic induction. The control of esketamine is a slow intravenous bolus of normal saline with the same appearance. In general, each ECT procedure will be preceded by the two 2-hour sessions of BBM or its control intervention and the administration of esketamine or its control intervention, with the total times of intervention depending on the total number of ECT procedures performed. According to the design, the four groups of participants will receive the following interventions: (1) group B0K0, blank sound and equal volume normal saline; (2) group B1K0, BBM and equal volume normal saline; (3) group B0K1, blank sound and esketamine; (4) group B1K1, BBM and esketamine.

Electroconvulsive Therapy (ECT) Procedure

The ECT procedure is conducted between 08:00 a.m. and 16:00 p.m. Qualified psychiatrists perform ECT using Thymatron IV (Somatics LLC, Lake Bluff, IL, USA) equipment. The electrode locations of ECT are bilateral temporal, and the specific parameters are set as follows: bidirectional square wave, bidirectional pulse 125 / sec, short pulse width 1.5 ms, and constant stimulating current 0.9 A.[43,44] The initial charge dose of ECT is standardized according to the age, set to 50% of the age, and the subsequent charge dose will be adjusted individually according to the patient's seizure status and clinical response.[45] When ECT is first administered, the patient's seizure threshold (defined as the minimum charge dose to induce a seizure for at least 25 seconds) needs to be determined.[46] If the initial dose of ECT does not induce seizures, electrical stimulation will be repeated by increasing the charge dose by 5% each time according to the age-adjusted titration method, with an interval of at least 30 seconds, and the first ECT procedure cannot exceed 3 electrical stimuli. If the first ECT fails to induce a successful seizure, the charge dose of the second ECT will be twice that of the first ECT. If the seizure threshold of ECT is successfully determined, the charge dose of subsequent ECT will be set to 1.5 to 2 times the seizure threshold.[47] The overall duration of ECT will be evaluated according to the clinical response of the patient to ECT as assessed by the psychiatrists. ECT is performed once daily for the first 3 days, and then once every 2 days, with 2 days off on weekends. The total number of ECT will be no more than 12.[48] Before ECT, general anesthetic propofol (1.5–2 mg/kg) and muscle relaxant succinylcholine (0.5–1 mg/kg) are intravenously injected by qualified anesthesiologists.[49]

Outcomes

The outcomes of this study include the primary outcome, secondary outcomes and safety outcomes, and Table 1 shows the classification and evaluation timing of each outcome, which will be collected using a series of questionnaires or scales, objective indicators, and blood biochemical measurements by other independent investigators.

Primary Outcome

The response rate of patients to the treatments is the primary outcome. Depressive symptoms are assessed by the investigators using the 24-item Hamilton Depression Scale (HAMD-24), which is evaluated by a qualified psychiatrist and consists of a total of 24 tests, each with a score of 0 to 4. A score of 0 is none, 1 is mild, 2 is moderate, 3 is severe, and 4 is very severe. The total score of a patient is the sum of the scores of each individual item, with higher scores indicating more severe depressive symptoms. The post-treatment response of depression is defined as a 50% or greater reduction in HAMD scores. The response rate is calculated as a percentage (%) of patients treated who have achieved a response in the total number.[50]

Secondary Outcomes

Rate of Remission of Depression

The HAMD-24 scale is used to assess the rate of remission of depression after ECT treatment. HAMD-24 scale scores being less than 10 after two consecutive ECT treatments is defined as a clinical remission, and the remission rate is calculated as a percentage (%) of the number of patients with remission in the total number.

Rate of Remission of Suicidal Ideation

Suicidal ideation (SI) is defined in terms of a score of item 3 in the HAMD-24 scale≥2. Each score represents as following: 0 represents absent; 1 represents a feeling that life is not worth living; 2 represents the wish that he/she is dead or that there is any possible thought of self-death; 3 represents suicidal thoughts or gestures; 4 represents a suicide attempt. SI remission rate is calculated as a percentage (%) of the patients with SI remission after ECT in those with SI.[51]

Psychotic Symptoms Accompanied with Depression

The Brief Psychiatric Scale (BPRS) is used to assess the change in psychotic symptoms accompanied with depression. The BPRS is evaluated by a qualified psychiatrist and consists of 18 items with a total score of 18 to 126, with each individual score ranging from 1 to 7. A score of 1 is asymptomatic, 2 is very mild, 3 is mild, 4 is moderate, 5 is relatively severe, 6 is severe, and 7 is very severe. The final score is the sum of each item, and those get larger scores are with greater severity of psychotic symptoms.[52]

Table 1 Outcomes Assessment

Outcomes	Measurements	Assessment Time			
		The First Day After Admission	Each ECT		The Day Before Discharge
			During	After	
Primary outcome:					
• Treatment response rate	• HAMD-24 scale	√	×	×	√
Secondary outcomes:					
• Depression remission rate	• HAMD-24 scale	√	×	×	√
• Suicide ideation remission rate	• HAMD-24 scale (item 3)	√	×	×	√
• Psychotic symptoms associated with depression	• BPRS scale	√	×	×	√
• Cognitive function	• MoCA scale	√	×	×	√
• Parameters of ECT (Electroconvulsive seizures, etc)	• Electroconvulsive device recording data and field recording data	×	√	×	×
• Perianesthesia vital signs and anesthesia related data (Heart rate, blood oxygen saturation, blood pressure, etc; duration of anesthesia, dosage of anesthetics, etc)	• Monitor recording data and field recording data	×	√	×	×
• Blood biomarkers (CRP, IL-1β, IL-6, TNF-α, BDNF)	• Blood collection and detection	√	×	×	√
Safety outcomes:					
• Adverse effects of BBM (Not yet reported)	• Observation, inquiry or patient initiative to inform and record	×	×	√	√
• Adverse effects of esketamine (Hallucinations, dizziness, dreams, nightmares, etc)	• Observation, inquiry or patient initiative to inform and record	×	×	√	√
• Adverse effects of ECT (Cognition impairment, muscle aches, etc)	• Observation, inquiry or patient initiative to inform and record	×	×	√	√

Abbreviations: BBM, binaural beat music; BDNF, brain-derived neurotrophic factor; BPRS, Brief Psychiatric Rating Scale; CRP, C-reactive protein; ECT, electroconvulsive therapy; HAMD-24, 24-item Hamilton Rating Scale for Depression; IL-1β, interleukin-1beta; IL-6, Interleukin-6; MoCA, Montreal Cognitive Assessment; TNF-α, tumor necrosis factor alpha.

Cognitive Function

The Montreal Cognitive Assessment Scale (MoCA) is used to evaluate the cognitive function of patients. MoCA is a commonly used rapid screening tool to assess patients' cognitive function. The total score is 30, and the final score of each sub-score is summed together. Higher MoCA scores indicate better cognitive function.[53]

Parameters of ECT

After the discharge of electroconvulsive stimuli, parameters such as the characteristics of seizure of the brain will be recorded, which may reflect the patient's immediate physical response to ECT treatment. Seizure patterns including 3 Hz spike and wave activity, multiple spike activity, post-seizure suppression, and seizure duration will be observed. Furthermore, a seizure with a duration longer than 25 s indicates an effective ECT treatment. Seizure characteristics can be used to evaluate the quality of seizures, guide the timely adjustment of electrical stimulation and evaluate the clinical efficacy.[43,45]

Perianesthesia Vital Signs and Anesthesia-Related Data

Patient's vital signs during each ECT treatment will be recorded, including heart rate, oxygen saturation, blood pressure, etc. Anesthesia-related data will also be recorded, including anesthesia duration, dosages of anesthetics and so on.

Blood Biomarkers

The blood samples will be taken for assessing biomarkers related to depression, including C-reactive protein (CRP), interleukin-1beta (IL-1β), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and brain-derived neurotrophic factor (BDNF).

Safety Outcomes and Monitoring

Adverse events of the interventions will be focused on, including the side effects such as nausea, vomiting, dreaming, nightmares, dizziness, hallucinations that may be related to the usage of esketamine, and adverse events such as memory impairment, and muscle pain after ECT treatment. Although no adverse effects of BBM have been reported, if there are new side effects associated with BBM in this trial, they will be recorded. In the event of a serious adverse event, the study will be discontinued to break the blind, corresponding treatment measures will be taken to protect the safety of the patients, and the event will be reported to the Institutional Review Board.

Sample Size Estimation

The primary outcome is the response rate of patients after ECT treatment. As there have been no reported data on the effect of BBM on patients with MDD undergoing ECT, the sample size is estimated with the results of our pilot study. With the response rate of 50% in Group B0K0, 10% of increase in Group B1K0, 25% of increase in Group B1K1 and Group B0K1 being similar to that of Group B0K0, assuming a test level of α=0.05 (two-sided) and a power of (1-β)=0.9 and the allocation ratio was 1:1:1:1 in each group, the sample size is calculated using the Power Analysis and Sample Size software (PASS, version 2021; NCSS Statistical Software, Kaysville, UT, USA). Considering the 10% loss to follow-up, at least 119 participants in each group are finally required, and a total of 476 participants will be included.

Statistical Analysis

The statisticians responsible for data analysis are blinded to study design, grouping, and interventions. They will perform an intention-to-treat (ITT) analysis of the data. SPSS for Windows (version 26, IBM Corp., Armonk, NY, USA) will be used. Data will be presented according to their statistical features and distribution. All continuous variables are expressed as mean and standard deviation or median (interquartile range), and categorical variables are expressed as counts and percentages. Chi-square tests, Fisher's exact test, or nonparametric tests will be used for analyzing categorical data and analysis of variance or nonparametric tests will be used for analyzing continuous data. $P<0.05$ is statistically significant. We will perform additional multivariable regression analyses adjusting for potential confounders, including baseline severity, duration of disease and episode, etc. For secondary analyses, a Bonferroni correction will be applied to adjust for multiple comparisons with adjusted *P*-values.

Discussion

For a long time, the difficulties in the treatment of depression lie in the slow onset of conventional antidepressants, poor efficacy on MDD, and the existence of patients with refractory TRD. Many patients with depression, especially MDD, may commit suicide at any time during the onset "lag" between the initiation of treatment of conventional antidepressants and symptom remission, hence there is an urgent need for timely and effective treatment and rapid control of suicide attempts. With a relatively long history, ECT has been a rapid and powerful somatic physical therapy, especially for controlling MDD and suicidal ideation, but its side effects such as cognitive impairment are also the main shortcomings that affect patient compliance and limit its clinical application.[4,6] Ongoing research into ECT techniques have led to significant improvements in ECT practice over time. One important modification has been the addition of general anesthesia, and the other specific measures include the improvement of its internal parameters (stimulation current characteristics, placement of electrodes, etc.) and the usage of external auxiliary means (combination with drugs, other therapies, etc).[54–58] Among them, the addition of general anesthesia, which significantly prevents many adverse effects of ECT and improves the prognosis, has become a routine procedure. However, the mechanism of these commonly used general anesthetics for general anesthesia targets the γ-aminobutyric acid (GABA) system, which generally inhibits the delivery of convulsions required for ECT efficacy and interferes with its efficacy.[59] In contrast, the key mechanism of (es) ketamine is the blockade of glutamate receptors of the N-methyl-D-aspartate (NMDA) type, which avoids activating GABA system and impairing electroconvulsive seizure and efficacy.[60] There is currently clinical evidence to support the synergistic modification of the ECT effect from (es)ketamine with anesthetic doses and/or antidepressant doses (sub-anesthetic doses).[21–24] Meanwhile, animal studies have provided clues for the mechanism, including the inhibition of neuroinflammation, regulation of hippocampal glutamate receptor and GABA receptor balance, glutamatergic synaptic

plasticity, etc.[61–63] However, ketamine and esketamine are also accompanied by a higher incidence of adverse events, which affects their clinical promotion and application.[25,59]

Therefore, we aimed to find possible better modifications that would benefit the antidepressant effect without increasing or even reducing the side effects of esketamine and/or ECT. In view of these problems of esketamine, ECT and their combination, the addition of BBM may be a new alternative. Previously, some investigators observed the comfort of patients by playing ordinary music in the ECT treatment room, and someone else found that patients preferred to listen to music before ECT treatment, but these studies did not go further with the overall effects and prognosis.[35,64] To the best of our knowledge, this study will provide the first clinical RCT-based evidence of BBM's effects, alone or in combination with esketamine, on patients with MDD undergoing ECT and related potential biomarkers, as well as possible interactions between BBM and esketamine, compared with previous studies. Moreover, BBM has the advantages of non-invasive, safe, convenient, inexpensive with easy access, good patient tolerance and high compliance.

This study is a prospective randomized controlled blinded factorial design clinical trial with measures such as randomized group, control group, blind design and factorial analysis to reduce the possible influence from interference factors and ensure the scientific validity of analyzing, and the results will be reliability to achieve the expected objectives. In this study, ECT is the clinical treatments required for the participants, and general anesthesia and electroconvulsive therapy are implemented according to clinical routines.

As one of the interventions in this study, esketamine, the S-enantiomer of ketamine, has been approved for treating TRD since 2019 in nasal spray form.[65] Subsequently, the use of its intravenous dosage form has been found to be effective for treating depression, and its beneficial effects in ECT at anesthetic doses or subanesthetic doses have also been reported.[22,66–68] Because the potency of esketamine is twice that of ketamine, and based on the synergy of effect of music and (es)ketamine, the esketamine dose selected in this study is a subeffective dose corresponding to ketamine as an antidepressant referring to previous studies, and it is administered slowly by intravenous route after patients having received general anesthetics and muscle relaxants.[30,69,70] Therefore, reasonable and safe dosages, routes and methods of medication can be guaranteed.

As the other one of the interventions, the parameters of BBM in this study are selected and optimized for better efficacies. Binaural beat exerts effects on the brain mainly through a continuous entrainment on the electroencephalogram with leading cortical electrical activity to oscillate at the same frequency as that of an external stimulus, furtherly regulating neural communication and neuroplasticity, and improving mood and other higher brain functions.[71] It has been shown that binaural beats are more likely to be induced at a carrier frequency of 400 Hz, and preanesthetic BBM interventions appear to be more effective than interventions during or after anesthesia.[72–74]

Regarding the selection of outcomes, we adopt a comprehensive evaluation combining subjective scales and objective indicators. The assessments of treatment response, remission, and suicidal ideation alleviation are used to evaluate the severity and improvement of MDD, and the accompanying psychiatric symptoms and cognitive function are evaluated as well. The scales used are the current standard scales for relevant assessments. In the evaluation process, the interference of subjective bias on the data is minimized and the objectivity and credibility of the results are ensured through rigorous training of assessors, and independent scoring and cross-validation by multiple different assessors. During the treatment, electroconvulsive parameters, anesthesia-related data, and the patient's vital signs in the perianesthesia period are objectively recorded. Blood biomarkers closely associated with MDD, suicidal ideation, and their onset and treatments are selected to provide more objective assessment based on in vivo substances.[75–77]

The safety of this study has also been fully considered. Electrical stimulation delivery and general anesthesia in ECT treatment are current medical routines. The use of esketamine is also significantly lower than the conventional anesthetic dose, and the risk of serious adverse reactions is relatively very low; BBM is a non-invasive intervention, and no side effects have been reported. Nevertheless, we will still make detailed records and objective analyses of possible adverse effects.

This study also has the following limitations. First, it is a single-center study, and the final results may be biased regionally. Second, as BBM cannot be administered blindly in patients, it is not possible to be double blind regarding it as an intervention. Moreover, mental status scales are assessed mainly subjectively, although the quality of assessments has been controlled as possible and objective biomarkers will be measured as well.

Conclusion

In conclusion, this study's findings are expected to provide the first-hand clinical data for the efficacy and safety of BBM-esketamine-ECT triple therapy for MDD, the modulation of BBM on the effect of (esketamine-combined) ECT, and the interaction between BBM and esketamine. As an exploration for strategies that assist the benefits of (es)ketamine, ECT, or their combination for MDD, this study is expected to contribute to the optimization of relevant clinical practice and improvement of outcomes with providing new insights.

Abbreviations

BBM, binaural beat music; BDNF, brain-derived neurotrophic factor; BPRS, Brief Psychiatric Scale; CRP, C-reactive protein; ECT, electroconvulsive therapy; GABA, γ-aminobutyric acid; HAMD, Hamilton Depression Scale; HAMD-24, 24-item Hamilton Depression Scale; IL-1β, interleukin-1beta; IL-6, interleukin-6; ITT, intention-to-treat; MDD, major depressive disorder; MoCA, Montreal Cognitive Assessment Scale; NET, Nonconvulsive electrotherapy; NMDA, N-methyl-D-aspartate; SI, suicidal ideation; THRIVE, Transnasal humidified rapid-insufflation ventilatory exchange; TNF-α, tumor necrosis factor alpha; TRD, treatment-resistant depression.

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Disclosure

The authors report no conflicts of interest in this work.

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