Single I.V.-ketamine Augmentation of Newly Initiated Venlafaxine Hydrocortisone for Treatment-resistant Depression: Randomized, Double-blind Controlled Study Protocol

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Study Protocol

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Abstract

Background: The critical issue of treating Treatment-Resistant Depression (TRD) is to improve antidepressant effect rapid onset and the recovery rates. Significant antidepressant effects of ketamine onset rapidly, but decay rapidly and repeated dosing increases the risks. This study aimed to explore the efficacy and safety of single intravenous ketamine, combined with venlafaxines hydrochloride for TRD.

Methods: 32 patients with treatment-resistant depression will be randomly selected to undergo a four weeks double-blind treatment with single-dose ketamine (0.5 mg/kg over 40 min) and venlafaxine hydrochloride (4 weeks) or midazolam maleate (0.045 mg/kg over 40 min) and venlafaxine hydrochloride (4 weeks). Depressive symptoms will be measured by the Montgomery–Asberg Depression Rating Scale (MADRS) and the 16-item Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR_{16}). Adverse effects will be measured by the Brief Psychiatric Rating Scale-4 (BPRS-4), Young Manic Rating Scale (YMRS), the Clinician-Administered Dissociative States Scale (CADSS), Frequency and Intensity of Side Effects Rating/Global Rating of Side Effects Burden (FISER/GRSEB and Patient Rated Inventory of Side Effects (PRISE). Patients will be assessed at baseline, after intervention 1, 2, 4, 24, 48, 72 hours and 7, 14, 21 and 28 days.

Discussion: This study will provide important information on whether this new combined intervention can rapidly relieve the symptoms of depression and improve the remission rates of treatment-resistant depression.

Background

Major Depressive Disorder (MDD) affects more than 300 million people worldwide and has an increased risk of suicide and mortality [1, 2].12%-30% of patients with MDD are Treatment-Resistant Depression (TRD) which have a failed response to antidepressant therapies [3–5].The patients with TRD have a higher risk of suicide [6, 7]. Although electroconvulsive therapy (ECT) is the most reliably effective therapy for TRD [8, 9]; some patients forgo ECT due to adverse effects [10, 11]. Moreover, oral antidepressants onset at least two weeks, and about two-thirds of patients have an insufficient response [12–14]. Important issues in the treatment of TRD is antidepressant effect rapid onset and improve the recovery rates of TRD.

The rapid antidepressant actions of ketamine have been proven in many clinical studies [15–18]. Ketamine was approved to be effective by the U.S. Food & Drug Administration (FDA) for the use of anaesthetic in 1970. It has become a revolutionary discovery in the last few decades, and researchers have developed a keen interest in its use since the onset of rapid antidepressant effects of ketamine was discovered [19, 20]. Ketamine improves depressive symptoms rapidly by blocking the N-methyl-D-aspartat receptor's (NMDAR) dependent bursting activity of the lateral habenula (LHb) neurons to disinhibit reward centres [21] Ketamine onset within hours after injection significantly relieves the symptoms of depression, and reduces the risk of acute suicide with a maximum efficacy at 24 hours after injection, with the effects

of ketamine lasting seven days [22, 23]. Moreover, when other traditional treatments have failed, ketamine improves depressive symptoms [24].

On March 5, 2019, the U.S. FDA approved intranasal es-ketamine for TRD [25]. Previous studies have assessed the efficacy and safety between es-ketamine and ketamine in patients with TRD, and it shows that both medicines are effective, relatively safe and well-tolerated [26, 27]. Compared with nasal spray, intravenous ketamine is preferred for greater dosing accuracy and ease of administration.[28].

The antidepressant effect of single dose ketamine is maintained for about seven days [29–31], to maintain the antidepressant effect have to use multiple doses ketamine. The researchers have limited longer-term studies 0.5mg/kg ketamine on safety[13, 24, 32, 33],and the potential neurocognitive impairment and urinary difficulties by chronic and repeated use of ketamine are the main safety concerns [34, 35]. To that end, the purpose of our study is to prolong the antidepressant effect of ketamine, and avoid to intravenous multiple doses ketamine.

Previous studies attempted to use ketamine with other antidepressants or treatments [16, 36–39] to find a therapeutic dose which can balance safety and effectiveness. Intravenous ketamine has been used in combination with various antidepressants, such as escitalopram, sertraline duloxetine or venlafaxine extended-release [40, 41]to enhance the antidepressant effect. In these studies, on the variety of oral antidepressants, venlafaxine, a serotoninergic and noradrenergic reuptake inhibitor (SRNI) has had an increased efficacy on treatment than selective serotonin reuptake inhibitors (SSRIs). It has been well-tolerated in patients with TRD [42, 43].

Previous studies are shown that patients responded to an antidepressant with a placebo [44, 45], using an active placebo in the control group is essential to improve the reliability of research. Midazolam maleate is a psychoactive anaesthetic agent, the half-life and partial clinical response for ketamine and midazolam maleate are similar, and it is not proven to have an antidepressant effect [46, 47]. In previous studies about the effectiveness of ketamine, midazolam was used as an active placebo control for nasal spray esketamine and infusion of ketamine [48–52]. Therefore, we use midazolam as active placebo insides of saline.

Objectives

In the study we use single I.V.-ketamine augmentation of newly initiated venlafaxine hydrocortisone for TRD to improve the recovery rate of TRD, prolong the antidepressant effect of ketamine, and avoid the side effects of intravenous multiple doses ketamine.

Methods

Study design

This study is a randomized, double-blind parallel controlled and clinical experiment. The control group will have an active medical control in the form of a single I.V. injection of midazolam maleate.

Participants

The samples will consist of 32 outpatients with TRD recruited from the Department of Clinical Psychology, Beijing Chaoyang Hospital, Capital Medical University. Participants will be randomly divided into a study group and a control group, with 20 in each group.

Inclusion criteria

1. Patients who meet the diagnostic criteria for depression in the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) without psychotic symptoms diagnosed by a psychiatrist;
2. Meet the criteria for TRD. The treatment was ineffective after a sufficient and complete course of treatment with at least two antidepressants (over six weeks);
3. The total score is great than or equal to 17 on the 17-item Hamilton Rating Scale for Depression (HAMD);
4. 25-64 years old, both genders;
5. No antidepressants, antipsychotics, mood stabilizers, electrical shock treatments in the last two weeks;
6. Have the ability to understand the content of the scale and cooperate with the assessment;
7. Sign research informed consent and be able to follow up.

Exclusion criteria

1. Patients with a previous history of substance use disorders or acute poisoning; patients with psychotic disorder, bipolar disorder, obsessive-compulsive disorder;
2. The primary diagnosis is not depression;
3. History of inefficacy or intolerance to Venlafaxine;
4. Women who are pregnant or breastfeeding;
5. Patients who are at high risk of suicide: suicide attempts, recent suicide attempts; no family caregivers;
6. Patients who are contraindicated in using ketamine, or midazolam maleate, or venlafaxine hydrochloride;
7. Patients who have used ECT or NMDA receptor antagonists within the past six months;
8. There are currently patients with respiratory disease, hypertension, or other physical severe diseases, such as patients with severe cardiovascular disease and hyperthyroidism, patients with intracranial hypertension or cerebral haemorrhage and glaucoma.

Participant withdrawal and termination criteria

1. The patient has a concomitant physical illness or serious adverse effect and others, who are unable or unwilling to continue to complete the study protocol;

2. The patient of lost follow-up;
3. The patient switch to mania, hypomania during the study;
4. The patient suicide or attempted suicide occurred during the study;
5. The patient no longer wishes to be part of the trial.

Safety considerations

The anesthesiologist and nurse will give the injection treatment in the operating room. During the injection process, the blood pressure, oxyhemoglobin saturation and other significant physiological indicators will be monitored in real-time. The psychiatrist will evaluate and record the side effects throughout the injection treatment. Any discomfort of the patient during the whole treatment process will be reported to the psychiatrist and anesthesiologist, who will act to alleviate this and record the side effects. Four hours after the injection treatment, the patient can be discharged from the hospital, only if they do not have discomfort and have been safely evaluated without side effects.

Randomization and allocation concealment

Block randomization will be used, the length of the block is four, which means there are 4 study subjects in each block. SAS software will be used to generate a random allocation list. Based on the random allocation list, the research subjects in the block group will be randomly allocated to the experimental group and the control group at a ratio of 1: 1. The random allocation is sealed with an opaque random concealed letter printed by a pinhole and given to a designated person (not involved in clinical observation assigned by the project center for keeping).

Blind

The double-blind method will be used in this study，neither the experimenter nor the participants know which treatment is received. We chose midazolam maleate instead of the placebo used in previous experiments-0.5% saline, because ketamine can cause some unique drug interactions within patients. Participants are randomly assigned to a single intravenous infusion of I.V.-ketamine 0.5mg/kg or midazolam maleate 0.045mg/kg. Questionnaires will be scored by professional raters who do not know which kind of drugs participants have been administered.

Primary outcome measures

The time required to reach the clinical effective standard and clinical cure standard will be measured. The effective standard is the remission rates of the total Montgomery–Asberg Depression Rating Scale (MADRS) score ≥50% compared with the baseline, and the clinical cure standard is defined as the total MADRS score ≤10.

Secondary outcome

16-item Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR_{16}). Patients will be assessed at baseline, after I.V.-ketamine at 1, 2, 4, 24, 48, 72 hours, 7, 14, 21 and 28 days.

Side Effects and Safety

Record vital signs (blood pressure, heart rate, and oxygen saturation) every 5 minutes in the duration I.V.-ketamine.

Adverse psychopathological effects will be measured by/with the Brief Psychiatric Rating Scale-4 (BPRS-4), Young Manic Rating Scale (YMRS), the Clinician Administered Dissociative States Scale (CADSS), Frequency and Intensity of Side Effects Rating/Global Rating of Side Effects Burden (FISER/GRSEB), and Patient Rated Inventory of Side Effects (PRISE). Patients will be assessed at baseline, after I.V.-ketamine at 1, 2, 4, 24, 48, 72 hours, 7, 14, 21 and 28 days. The schedule of assessments and procedures is summarized in Table 1.

Table 1. Study procedures and schedule of assessments

	Study period											
	Screening(Visit 0)	Baseline (Visit 1)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
			After infusion									
Timepoint	Day -7~-1	Day 0	1 hours	2 hours	4 hours	Day 1	Day 2	Day 3	Day 7	Day 14	Day 21	Day 28
Informed consent	×											
Demographic and clinical characteristics	×											
Physical examination	×	×	×	×	×	×	×	×	×	×	×	×
Major depression disorder(DSM-V)	×											
Treatment-resistant depression	×											
Clinical examination		×										×
HAMD-17	×											
Vital signs	×	×	×	×	×	×	×	×	×	×	×	×
MADRS		×	×	×	×	×	×	×	×	×	×	×
BPRS-4		×	×	×	×	×	×	×	×	×	×	×
CADSS		×	×	×	×	×	×	×	×	×	×	×
YMRS		×	×	×	×	×	×	×	×	×	×	×
QIDS-SR16		×	×	×	×	×	×	×	×	×	×	×
PRISE		×	×	×	×	×	×	×	×	×	×	×
FISER/GRSEB		×	×	×	×	×	×	×	×	×	×	×

Intervention

Participants will meet the criteria and sign informed consent. Participants will undergo a psychotropic medications washout period of two weeks (fluoxetine hydrochloride for four weeks).

The injection treatment is performed on the first day of the intervention. Preparation before treatment: The patient fasts for 12 hours and drinks water for 4 hours. Control Groups: establish an intravenous infusion channel in the operating room, and inject physiological saline at a rate of 20-30 drops/min. Connect a physiological monitor to monitor BP, SpO2, ECG. Ketamine Group: 0.5mg / kg ketamine hydrochloride injection, diluted with a physiological saline injection to 50ml intravenous for 40 minutes. Control group: midazolam maleate injection, a dose of 0.045mg / kg, diluted with a saline injection to 50ml intravenous injection for 40 minutes. Both groups: Blood pressure, heart rate, and oxygen saturation will be recorded every 5 minutes during drug injection. Observe the patient's consciousness and mental state for 4 hours during and after administration.

Both groups are treated with venlafaxine hydrochloride 150 mg/day (the initial dose was 75 mg / d and increased to 150 mg/d one week later) from the first day of the intervention for four weeks.

In the study, if the subject has severe insomnia (cannot fall asleep half an hour after going to bed), zolpidem tartrate can be temporarily administered 5-10 mg, ≤ 3 times a week. Do not use systemic psychotherapy, electroconvulsive therapy, antidepressants, and antipsychotics other than research medications.

Sample size

Sample size calculation: using the superiority hypothesis test, setting unilateral = 0.05, β = 0.2.With reference to the previous study setting [53], the treatment time of the control group that reached the clinical cure standard was set to 28.0 ± 0.0 days, and the mean treatment standard deviation of the experimental group was 15.8 ± 13.0 days. Based on previous literature and the time required for clinical cure [4-6], the optimal effect cut-off value △ = -5 days was calculated using PASS14.0 software. 13 samples were required for each group. Considering the 15% missed follow-up rate and random block capacity, the number of expanded samples is 16 in each group, and 32 samples are required for the two combinations.

statistical analytical plan

Primary outcome analysis

Kaplan-Meier survival analysis will be used as the time required to reach the effective standard and clinical cure standard. Cox proportional-hazards regression models are to be used to compare the estimated time to respond and to remission between the two groups, controlling the baseline effects.

Secondary outcome analysis

Baseline demographics, clinical feature analysis, effectiveness, and clinical cure rate between the two groups will be measured using two independent samples' t-test or Mann-Whitney U test or $\chi 2$ test or Fisher's exact test. The significance level will be set at 0.05(in a two-tailed test).

Data management and monitoring strategies

Researchers fill in the data on the case report form in time after each visit, and this is to be consistent with the original record. The data will be collected on Epidata to build the database. Special management and double verification are adopted to ensure the accuracy of data entry. According to the Intention to Treat (ITT), an intent analysis data set (subjects who took at least one drug after enrollment) will be established to analyze the research data statistically.

For subjects who did not observe the full effect evaluation, a mixed model will be used for data processing.

Discussion

In recent years, although oral antidepressants have improved in terms of side effects and effectiveness [54], patients still face the dilemma of the long onset of antidepressants and limited treatment effect [55]. Since the discovery of rapid antidepressant effect, ketamine has been the focus of treatment research. However, there are always some problems that need to be solved within clinical applications. The antidepressant effects of ketamine decay rapidly after a single dose [56, 57], while repeated dosing increases the risks includes physical injury and substance use disorders.

In order to avoid the risks of repeated dosing, the current study only uses a single injection of I.V. ketamine at the beginning of treatment. Initiated at the beginning of oral antidepressants solves the dilemma in efficacy decreasing after a single injection of ketamine. This combination therapy reduces patients suicide risk during these weeks before oral antidepressants onset. In our study, it is first important to select venlafaxine,a SNRI, as an oral antidepressant in combination with I.V. ketamine. We will set follow-up after injection I.V. ketamine at 1, 2, 4, 24, 48, 72 hours and 7, 14, 21 and 28 days. Follow-up at multiple time points can indicate the law of ketamine decay,to accurate evalution the time of ketamine onset and recover. From compared ketamine and control in this study, we explore more precisely enhancement of venlafaxine to ketamine for accelerating the reduction of symptom.

The study is the first to verify the effectiveness and safety of ketamine with TRD in Chinese. In the past studies, there are few RCT studies use ketamine in Chinese with TRD, who are needs more effective and safer treatment options due to the higher risk of suicide and mortality within this group.

The clinically meaningful treatment effect of therapy will be evidenced by the reduction of MADRS and QIDS-SR_{16} total score, the most commonly and valid standard clinician rating scale for depression [58.59]. In previous studies, either the MADRS or QIDS-SR_{16} have been used alone. Because there are individual differences in emphases and evaluation methods between these scales, we will use both scales in our trial to more accurately assess depressive symptoms. Both scales will be used to examined depressive symptoms comprehensively due to their different characteristics in evaluations. Previous research has shown that minor side effects briefly experienced by patients include symptoms like dissociation and elevated blood pressure after using ketamine, but these side effects usually happened during the initial dosing and the first few hours [60.61]. BPRS-4,YMRS, CADSS, FISER/GRSEB, PRISE total score and the physical sign during injection will be monitored for side effects. This data can then provide information on the safety of ketamine combined with venlafaxine.

In conclusion, this clinical trial is intended to study the efficacy and safety of I.V.ketamine initiated venlafaxine for TRD and our findings will provide valuable information for clinical applications, which may assist psychiatrist to use treatments more effectively in the future in China.

Declarations

Availability of data and materials

All the data and materials are availability.

Competing interests

The authors declare they have no competing interests.

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Authors' contributions

Y Du as the first author designed the whole study and wrote this manuscript. R-B Feng and W-L Zhang helped with the statistical analysis and language modification. J-X Fang, K Ma and E-C Wang went through and revised the manuscript. Y-D Hu supervised the design of the study through the writing of the manuscript.

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Ethics approval and consent to participate

The Human Ethics Committee of Beijing Chaoyang Hospital, Capital Medical University provided approval for the conduct of the study (2018-6-11-1). All participants gave written informed consent for participating in the study. Registered 11 June 2018.

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