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Study Protocol

Repetitive Transcranial Magnetic Stimulation (rTMS) with Traditional Chinese Medicine for Depression: Study Protocol for a Pragmatic Randomized Controlled Trial

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Abstract

Background and objectives: Previous studies have shown that a traditional Chinese herbal medicine, Yinyangdayu decoction, and repetitive transcranial magnetic stimulation (rTMS) are both effects treatment methods for depression. This study is designed to observe the combined clinical efficacy of Yinyangdayu decoction and rTMS with magnetic stimulation at the taichong point (LR03) in the treatment of depression.

Methods: Based on the real-world study, 204 patients with depressive disorder will be recruited and randomized into 3 groups (control group, treatment group 1, and treatment group 2). The control group will receive rTMS only (1 HZ, 1,800 pulses, 100% threshold). Treatment group 1 will receive rTMS + magnetic stimulation at LR03 (the left side, 1 HZ, 1,800 pulses, 100% threshold), and treatment group 2 will be given rTMS + Yinyangdayu decoction (200 mL, 2 times/day). The treatment course will last for 8 weeks, and relevant rating scales will be assessed at baseline, week 4, and week 8 to evaluate the efficacy.

Conclusions: This study might optimize the TCM comprehensive treatment scheme of depression, integrated with Western and traditional Chinese medicine.

Trial Registration: Chinese Clinical Trial Registry, ChiCTR1900027443. Registered on 13 November 2019, www.chictr.org.cn

Keywords: Depression; Repetitive transcranial magnetic stimulation; Taichong point (LR03); Yinyangdayu decoction; Study protocol.

Abbreviations: HIS, Hospital information system; rTMS, Repetitive transcranial magnetic stimulation; TCM, traditional Chinese medicine; HAMD, Hamilton's Depression Scale; SCL, Symptom check list; PHQ, Patient Health Questionnaire; SSRIs, selective serotonin reuptake inhibitors; pRCT, pragmatic randomized controlled trial; MV, mean value; SD, standard deviation; rMT, resting motor threshold; PSQI, Pittsburgh Sleep Quality Index; FAS, full analysis set; PPS, per protocol set; M, mean; ANOVA, analysis of variance; LR03, taichong point.

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Introduction

Depressive disorder is a common mood disorder caused by various reasons and accompanied by feelings of hopelessness or sadness, loss of interest or pleasure, etc. This disease can lead to a series of physical, psychological, and social dysfunctions, especially insomnia and cognitive impairment, as well as a potential high risk of suicide, which increases the burden of patients, their families, and society.[1,2] Studies have revealed the pathophysiological characteristics of depressive disorders, particularly that cerebral cortex hyperexcitement is closely related to emotional regulation.[3] There-

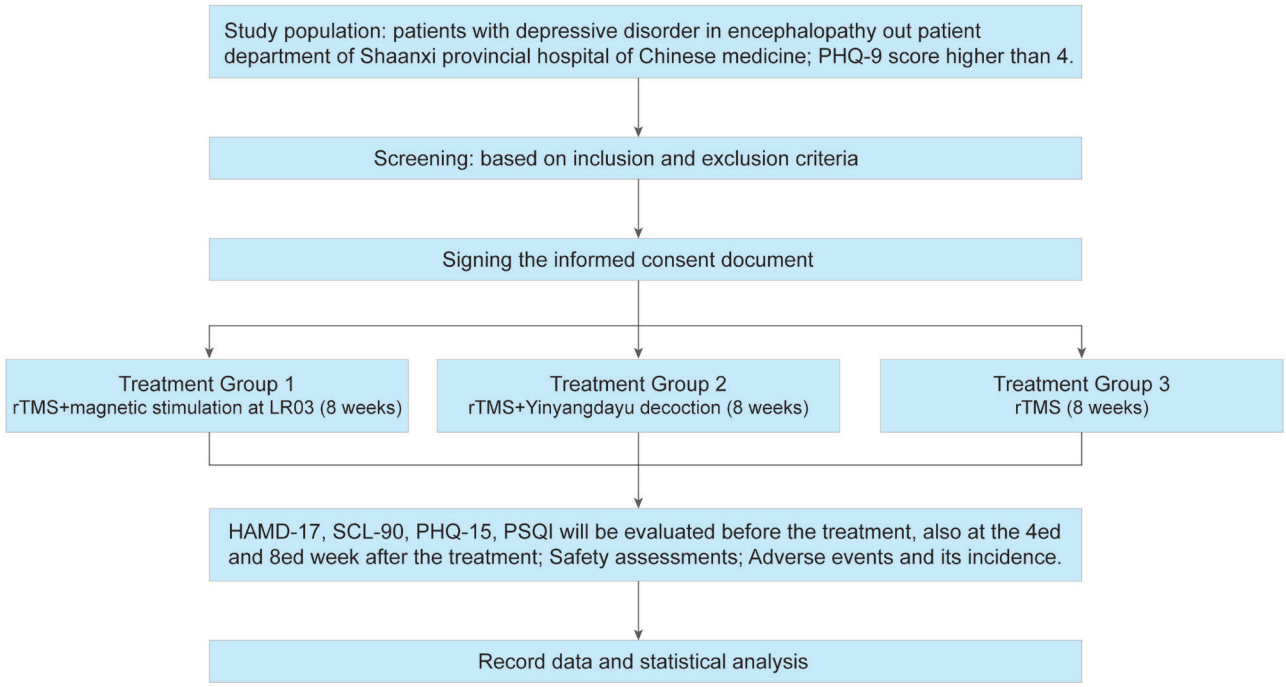

Fig. 1. The flow diagram of this trial. HAMD, Hamilton's Depression Scale; LR03, taichong point; PHQ, Patient Health Questionnaire; PSQI, Pittsburgh Sleep Quality Index; rTMS, repetitive transcranial magnetic stimulation; SCL, Symptom check list.

fore, measurement of cortical excitability may help uncover the physiological mechanism of depression.

Specifically, repetitive transcranial magnetic stimulation (rTMS) therapy alone or in combination with selective serotonin reuptake inhibitors (SSRIs) can effectively treat depression (category I evidence/strength A recommendation)[1,4] with no cumulative toxicity and adverse reactions following long-term application. Acupuncture is another TCM option for depression, whereby LR03, the Yuan-primary point of liver meridian, is one of the most commonly used acupoints.[5] Compared with traditional acupuncture points, magnetic stimulation at peripheral acupoints has the advantages of safety, non-invasive, painless and repeatable. In addition, Yinyangdayu decoction is a self-designed TCM that is prescribed in Shaanxi Provincial Hospital of Chinese Medicine, which has demonstrated a good clinical for improving depressive symptoms.

To establish new treatment ideas, we intend to conduct a trial to observe the effect of rTMS with magnetic stimulation at LR03 and rTMS with Yinyangdayu decoction on depressive mood, sleep quality, and cortical excitability of patients with mild and moderate depressive disorder.

Methods and materials

Design

This pRCT trial is a prospective, randomized, controlled study. Figure 1 illustrates the design process, including enrollment, interventions, and assessment. The study was performed in accordance with the Declaration of Helsinki, and was approved by Institutional Review Board of Shaanxi Provincial Hospital of Chinese Medicine; the trial registration number in the Chinese clinical trial registry is ChiCTR1900027443 (www.chictr.org.cn). Informed consent was obtained before the patients' enrollment. The protocol is formulated in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement (Supplementary File 1).

Participants

204 patients with depressive disorder in Encephalopathy Outpatient Department of Shaanxi Provincial Hospital of Chinese Medicine will be enrolled. Patients will be preliminary enrolled if they score higher than 4 points in PHQ-9. Then, HAMD-17 will be used for further evaluation, and those who score 8–24 points, indicating severity mild-moderate, will be included. In addition, diagnostic criteria contain typical symptoms of depressive mood and at least four accompanied following symptoms, including loss of interest or pleasure, loss of energy or feeling fatigue, mental movement hysteresis or agitation, low self-evaluation or feeling of guilt, tendency of suicide or suicidal behavior, sleep disorders, loss of appetite or obvious weight loss, and sexual dysfunction. TCM diagnostic criteria include symptoms, such as being depressive or agitated, chest distress or pain, hiccough, loss of appetite, irregular bowel movement, and insomnia. Table 1 illustrates the detailed inclusion criteria and exclusion criteria.

Randomization

Eligible participants will be randomly assigned into 3 groups at a ratio of 1:1:1. The random seed number will be generated by SPSS statistical analysis software (version 19.0), and accordingly, 204 patients will be assigned to the control group (rTMS), treatment group 1 (rTMS + magnetic stimulation at LR03), and treatment group 2 (rTMS + Yinyangdayu decoction), with the flow number 001-204 listed.

Table 1. Inclusion and exclusion criteria

Inclusion criteria
1. Voluntary to sign informed consent.
2. Aged 18–65.
3. Score of 8-24 in HAMD-17 (mild-moderate).
4. Consistent with the diagnostic criteria of both western medicine and TCM.

Exclusion criteria
1. Diagnosis of other mental disorders, such as panic disorder, obsessive-compulsive disorder, schizophrenia and hypochondria.
2. Patient who had been treated with anti-anxiety, anti-depression, anti-psychotic medicine or similar traditional Chinese medicine within 4 weeks before inclusion.
3. Patient who is taking antidepressants or antidepressant pharmacological action hasn't been washout.
4. A woman who is pregnant or preparing to be pregnant, or she is a lactational mother.
5. Combined with hyperthyroidism, coronary heart disease, hypertension, irritable bowel syndrome and other endocrine, cardiovascular and digestive diseases.
6. Organic mental disorders, postpartum depression and depression caused by psychoactive substances and non-addictive substances.
7. Patients with a history of suicide, a tendency of suicide, or a score ≥ 1 in the suicide scale of HAMD-17.
8. Patient who had participated in any other clinical trial within 1 month or is participating in.
9. Magnetic metal objects implanted near the head or in the brain, such as intracranial stents, cochlear implants.
10. Patient who is unsupervised or unable to complete the clinical trial.

HAMD, Hamilton's Depression Scale.

Sample Size Calculation

The sample size was calculated according to the sample size calculation formula of the pros and cons clinical trials, $N = 2\delta^2 \times f(\alpha, \beta)/(\mu_1-\mu_2)^2$. Based on a previous study,[6] after a 6-week rTMS treatment, the HAMD scores' mean value (MV) = 6.53, standard deviation (SD) = 2.11. According to the results of pre-experiment, it was estimated that the experimental group 1 (acupoint magnetic stimulation group) and group 2 (traditional Chinese medicine group) could make a 20% reduction in scale, we obtained u1 = 6.53, u2 = 5.224. We valued $\alpha = 0.05$, $\beta = 0.1$, and got $f(\alpha, \beta) = 10.5$ in the look-up table, and then obtained the results of N1=N2=N3=57 cases. With an estimated loss rate of 20%, we calculated a total sample size of 204 cases, 68 cases for each group.

Interventions and procedures

All patients will receive an 8-week course of treatment. All groups will be administered rTMS (r-DLPFC) therapy with 1 HZ, 1800 pulses, 100% threshold, once a day, 5 days per week during weeks 1–4, which will be changed to one treatment per week during weeks 5–8, for a total of 24 treatments. The control group will receive rTMS alone. Treatment group 1 will receive rTMS and magnetic stimulation at LR03 on the left side, with the same usage and course. Treatment group 2 will receive rTMS and Yinyangdayu decoction, 200 mL for 2 times/day and 10 days/week for weeks 1–4 weeks, then 5–7 times for the remaining 4 weeks.

Yinyangdayu decoction is comprised of Radix Angelicae Sinensis (10 g), Radix Paeoniae Alba (20 g), Radix Bupleuri (10 g), Fructus Gardeniae (10 g), Semen Sojae Preparatum (10 g), Fructus Schisandrae Chinensis (15 g), Radix Ophiopogonis (15 g), Bulbus Lilii (10 g), Os Draconis (30 g), Semen Ziziphi Spinosae (20 g), Tuber Fleeceflower Stem (20 g), Triticum Aestivum (30 g), Fructus Jujubae (6 g), and Radix Glycyrrhizae (6 g). Yinyangdayu decoction is prepared by the hospital's pharmacy following the specific TCM decoction method: (1) soak the decoction in cold water for 30 min; (2) boil each dose twice, and simmer for 30 min; (3) add the residue in cold water for a second time, and mix it with the first medicine after 30 min; (4) consume half the dose in the morning and evening separately; (5) if loose stool and diarrhea occur, add 2–3 pieces of ginger when each dose boiled.

Outcome measures and safety assessments

Both primary and secondary endpoints will be respectively evaluated before the treatment, and then 4 and 8 weeks after the treatment. The effective rate will be calculated by the nimodipine method.

Primary endpoints are evaluated by questionnaires, including HAMD-17, SCL-90 and PHQ-15. HAMD-17 evaluates the depression state with a score of 5 levels from 0 to 4. SCL-90 contains 90 items to evaluate a broad range of psychological problems and symptoms. PHQ-15 is a 15-item self-administered somatic symptom scale, which is a validated measurement.

Secondary endpoints include measuring the resting motor threshold (rMT) of the cerebral cortex and Pittsburgh Sleep Quality Index (PSQI). When performing measurement of rMT of cerebral cortex, patients will be asked to relax in a seated position, while the motor induction is produced by stimulating the M1 region. The recording electrode is placed on the contralateral abductor brevis muscle belly of the stimulated side. The stimulus intensity will start at 30% and gradually increase at a rate of 2.5%. In 5 out of 10 consecutive stimuli, the minimum stimulus intensity with the induced amplitude greater than 50-uV motor evoked potential is rMT. PSQI differentiates sleep quality from poor to good by 7 aspects (including subjective sleep quality, sleep latency, sleep du-

ration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction) in the last month, with a score range from 0 to 21; the higher the score, the worse the quality of sleep.

Safety assessments contain physical examination and laboratory examination of liver and kidney function. Adverse events will be recorded, and their incidence in each group will be compared.

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 19.0 by IBM (SPSS Inc, Chicago, Illinois, USA) is used for demographic and other baseline characteristics analysis, efficacy analysis, side effects analysis, and compliance analysis. The full analysis set (FAS) and per protocol set (PPS) will be used for the efficacy analysis. If the data are normally distributed, the results can be described with mean (M) and standard deviation (SD). If the variances are homogeneous, the comparison of effect indicators can be made by using a completely randomly designed analysis of variance (ANOVA). If the variances are not homogeneous, the rank-sum test (Kruskal-Wallis test) of a completely random design can be used for multi-group comparison. Two-sided hypothesis tests will be used, and the p value less than 0.05 is statistically significant.

Quality assurance

To manage patient compliance problems and control of cases shedding, it is suggested to strengthen interaction with patients and inform patients of the precautions of TCM decoction in detail to improve compliance with clinical treatment. At the same time, it is pertinent to record the contact information of the patient or family members to facilitate timely feedback of observation information and improve the cooperation of patients.

For clinical cases observation standardization, the use of TMS is performed by the physician. A training course on case observation and use of scales shall be held in advance. The patient scale assessment will be performed in a quiet environment to ensure that patients could clearly understand the meaning of scales. The question is asked by one expert and two experts will score the patient at the same time, then average score from the two appraisers will be taken to reduce human errors. The whole process of observation will be under quality control and monitoring by the hospital's ethics committee. All observation data and case report forms shall be recorded correctly and completely, and the consistency with the original data will be ensured.

Discussion

More than 300 million people of all ages suffer from depression worldwide. It is estimated that the overall global burden of depression will soon become the second most predominant disease following cardiovascular disease. The current treatments for depression mainly include SSRIs, SNRIs, NaSSA, SARIs, NDRIs and other drugs; however, there are obvious adverse drug reactions, drug dependence, and limited application in the elderly, children, pregnant women, and people with abnormal liver and kidney function.

rTMS is based on the principle of electromagnetic induction and conversion in which an inductive current is produced by a magnetic field generated by the transient current of the stimulation coil. The current penetrates the skull current to stimulate neurons and subsequently to trigger a series of physiological and biochemical reactions. It is considered a safe, well-tolerated method for the treatment of depression. High-frequency stimulation on the left dorsolateral prefrontal cortex or low frequency stimulation on the right dorsolateral prefrontal cortex has been approved for the treatment of depression in the acute phase. It has also been reported as an effective therapy for recurrent depression following previous rTMS treatment, acute depression, and medication-resistant major depression in adults. Continuous treatment for 4–6 weeks is recommended, and the treatment course can be extended if necessary (category I evidence).[7–10]

Acupuncture at LR03 can cause activation of the frontal lobe in brain regions related to emotional regulation of depression disorders.[11–13] Our experience and literature review suggest that repeated magnetic stimulation of acupoints can cause changes in human brain electrical signals and brain function networks.[14–25] Different acupoints activated functional brain regions are consistent with the efficacy of acupoints themselves. Low-frequency stimulation of acupoints can inhibit the brain regions, while high-frequency stimulation can activate the brain regions.

By data mining of the TCM prescription for depression, we found that the main pathogenesis is depressive liver generating fire and the heart losing nourishment.[26] Based on the theory of TCM, obstruction of the heart qi and liver qi leads to depression, where the heart belongs to yang and liver belongs to yin. Therefore, we prescribed Yinyangdayu decoction and conducted a pilot trial, which demonstrated satisfactory treatment results. In the proposed trial study, we will administer the questionnaire to obtain scores before treatment, 4 and 8 weeks after to compare and evaluate the treatment efficacy. The primary endpoints include HAMD-17, SCL-90 and PHQ-15 questionnaires, while secondary endpoints are rMT of cerebral cortex and PSQI. Safety assessments will include a physical examination and laboratory examination of liver and kidney function. Adverse events in each group will be recorded and compared. This study's scales can generally infer the severity and actual changes during the treatment process of insomnia, anxiety, and depression before treatment then 4 and 8 weeks after treatment. This evaluation method can be used to the screening of inclusion and exclusion criteria and clinical efficacy observation. Besides, calculating the HAMD-17 score by dimension or classification can accurately reflect the specific disease aspects of patients, which is conducive to the accuracy and purpose of treatment. In future studies, the two scoring methods should be combined to explain the disease characteristics and treatment comprehensively.

In recent years, there has been an increasing demand for real-world evidence in clinical practice. To deepen the understanding of how intervention works, a pragmatic randomized controlled trial (pRCT) is regarded as an important component of real-world research and has become a focus in the field of healthcare.[27]

Based on the real-world research methods, this trial aims to observe the efficacy of rTMS combined with acupoints magnetic stimulation and traditional Chinese medicine on depression. We expect to acquire valid evidence for the further promotion and application of a comprehensive treatment program to treat depression.

Supporting information

Supplementary material for this article is available at https://doi.org/10.14218/ERHM.2021.00067.

Supplemental File 1. SPIRIT checklist.

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Conflict of interest

The authors have no conflicts of interest to declare.

Author contributions

Conception and design (QL), administrative support (YL), provision of study materials or patients (YL, JY), collection and assembly of data (WL, HL, PW, LZ), data analysis and interpretation (YL, RY, FC). All authors participated in writing the manuscript and final approval of submission.

Ethical statement

The study was approved by Institutional Review Board of Shaanxi Provincial Hospital of Chinese Medicine. The trial registration number of Chinese clinical trial registry is ChiCTR1900027443. Informed consent was obtained before the patients' enrollment.

Data sharing statement

Following the study's completion and publication of results, the individual participant data after deidentification (text, tables, figures, and appendices), study protocol, and statistical plan are available from the corresponding author upon request.

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