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The Effect of Repetitive Transcranial Magnetic Stimulation on Functional Outcome in Acute Ischemic Stroke Patients

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Abstract

Background:Post-stroke depression (PSD) is a prevalent complication following a stroke, occurring at various stages with incidence rates around 33%. PSD significantly impacts patient outcomes, increasing the risk of cognitive impairment, disability, and mortality. While pharmacological treatments exist, they often have undesirable side effects, highlighting the need for safer alternatives. Repetitive transcranial magnetic stimulation (rTMS) has shown promise as a non-invasive treatment for alleviating depressive symptoms in stroke patients. However, its early application in preventing PSD after acute ischemic stroke remains underexplored.
Method:This randomized controlled trial involved patients aged 18 and older diagnosed with acute ischemic stroke, confirmed by MRI, and exhibiting persistent focal neurological deficits. A total of 66 participants were randomly assigned to either the rTMS group or the sham stimulation group between two to seven days post-stroke.The rTMS group received repetitive transcranial magnetic stimulation targeting the dorsolateral prefrontal cortex on the affected side at a frequency of 10 Hz, once daily for 5 days a week over a total duration of 4 weeks. The sham group underwent a similar procedure using an 8-shaped pseudo-stimulation coil. Outcomes were assessed using various scales, including the PHQ-9, HAMD, GAD-7, MMSE, and NIHSS.
Discussion: The aim of this intervention study is to explore an effective, safe, and reliable method for preventing post-stroke depression. The research findings will assist stroke patients with potential depression.

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The Chinese Clinical Trial Registry(ChiCTR) registration number for this trial is ChiCTR2400092636

Introduction

2 **1. Post-Stroke Depression—Increases Adverse Prognosis in Stroke Patients**
Post-stroke depression (PSD) refers to a syndrome that occurs after a stroke, characterized by a range of depressive symptoms and corresponding somatic symptoms. It is one of the common and treatable complications following a stroke. Epidemiological data show that PSD can occur during the acute phase (less than 1 month), the intermediate phase (1 to 6 months), and the recovery phase (more than 6 months), with incidence rates of 33%, 33%, and 34%, respectively[1]. PSD is one of the factors associated with poor prognosis in stroke patients, leading to an increased risk of cognitive impairment, disability, and death[2]

As a long-term mental disorder following a stroke, PSD severely affects the prognosis of stroke patients, prolonging hospitalization, reducing the quality of life, and being closely related to increased recurrence and mortality rates of strokes.

2. Repetitive Transcranial Magnetic Stimulation—An Effective Treatment for PSD

Repetitive transcranial magnetic stimulation (rTMS) refers to the repeated and systematic stimulation of a specific area by applying a series of pulses, thereby exciting or inhibiting the cortical excitability of the brain. rTMS has several advantages, including good efficacy, simplicity of operation, and non-invasiveness. In addition to producing immediate effects, its effects can persist for some time after the stimulation ends, providing possibilities for clinical treatment.

Hordacre et al. found that patients in the rTMS group experienced significant relief of depressive symptoms after treatment[3]. Kim et al. similarly divided patients into an rTMS group and a sham stimulation group, applying high-frequency rTMS to the affected dorsolateral prefrontal cortex (DLPFC) in the rTMS group. The results showed that patients with lesions on the left side had significantly lower Geriatric Depression Scale (GDS) scores compared to the sham stimulation group, while patients with right-sided lesions showed no significant difference in GDS scores from the sham stimulation group, indicating that high-frequency rTMS on the left (affected) DLPFC can improve depressive symptoms in subacute stroke patients[4].

Although rTMS helps improve depressive symptoms in stroke patients, there is currently no safe and precise diagnostic and treatment method for PSD[5]. Pharmacological treatment for PSD has a high relief rate but can easily lead to adverse effects related to the nervous system, cardiovascular system, and sexual function[6]. Therefore, there is still no particularly ideal treatment plan for PSD. Research by Paolucci et al. indicated that the incidence of depression is relatively high in stroke patients during the initial weeks to 4 months after treatment, despite significant improvements in physical disability due to systematic treatment; mental symptoms continue to persist[7].

3. rTMS in Preventing Post-Stroke Depression—Research Prospects

Risk factors for post-stroke depression can be divided into three categories: pre-stroke risk factors (genetic factors, gender, history of depression, etc.), stroke-related risk factors (cerebrovascular factors, stroke location, degree of neurological deficits, etc.), and post-stroke risk factors (social support, higher levels of disability, etc.)[8]. Some of these risk factors are not amenable to intervention, indicating that preventing the occurrence of post-stroke depression still requires efforts.

Currently, most rTMS treatments for post-stroke depression are initiated after the diagnosis of the condition, and there is a lack of studies on the early application of rTMS to prevent PSD in patients with acute ischemic stroke.

Research results show that rTMS can lower serum levels of MMP-9 and NSE in ischemic stroke patients while increasing Ang-I levels. It can effectively stimulate damaged neural protrusions, enhance neural plasticity, and repeatedly reduce the conduction threshold of these protrusions. This reactivates neurons in the affected hemisphere that are in a suppressed state, reconstructing synaptic connections in neural conduction pathways

and promoting recovery of neurological functions[9]. Some studies have shown that following rTMS combined with anticoagulant treatment, the NIHSS scores and levels of NSE and S100-β in the observation group were lower than those in the control group, suggesting that rTMS has advantages in repairing neurological injuries in patients with cerebral infarction[10]. Research by Sudan et al. indicated that rTMS could effectively improve neurological function in patients with cerebral infarction, with the NIHSS scores of the observation group being lower than those of the control group after rTMS combined with standard treatment[11].
Thus, it can be seen that rTMS aids in functional recovery for patients with ischemic stroke. The application of rTMS in patients with acute ischemic stroke may help reduce the incidence of post-stroke depression and alleviate the severity of post-stroke depression.

Equipment

3 **Tools and Equipment:**
1.Pulse magnetic field stimulator
2.8-shaped pseudo-stimulation coil

4 **Scale:**
1.PHQ-9
2.HAMD Scale
3.AIS Scale
4.GAD-7
5.MMSE
6.MoCA
7.IQCODE
8.NIHSS
9.ADL
10.Fugl-Meyer
11.water swallowing test

Procedure

5 **Inclusion and Exclusion Criteria:**
Inclusion Criteria:
1.The patient must be 18 years of age or older.
2.Clinical presentation includes focal neurological deficits. Hemorrhagic stroke has been excluded via head CT, and acute ischemic stroke has been confirmed through subsequent head MRI.
3.Patients were randomly assigned to two groups between two to seven days post-stroke, with persistent focal neurological deficits observed in the randomized group.

4.Participants must voluntarily provide signed informed consent.

Exclusion Criteria:
1.A history of cognitive impairment or depression.
2.A previous stroke.
3.Inability to complete follow-up assessments.
4.Presence of other life-threatening conditions, such as advanced cancer with a life expectancy of less than six months.
5.Contraindications for rTMS treatment.
6.Incapacity to cooperate with assessments due to consciousness disturbances or severe aphasia.
7.Presence of coronary stents, pacemakers, or other metallic implants in the body.
8.Current or recent (within the last month) receipt of rTMS treatment.

6 **Randomization:**
Use the Python code

```
random_numbers = random.sample(range(1, 67), 66)
```

to generate 66 random numbers. Based on the order in which the patients are enrolled, assign them sequentially: numbers 1-33 to the rTMS group and numbers 34-66 to the sham stimulation group.

7 **Group rTMS:**
Repetitive transcranial magnetic stimulation (rTMS) treatment:
Location: Dorsolateral prefrontal cortex on the affected side
Stimulation frequency: 10 Hz, once per day, 5 times per week, for a total duration of 4 weeks.

8 **Group sham stimulation:**
Sham or placebo stimulation :
Tool:.8-shaped pseudo-stimulation coil
Location: Dorsolateral prefrontal cortex on the affected side
Stimulation frequency: 10 Hz, once per day, 5 times per week, for a total duration of 4 weeks.

9 **Statistical Analysis:**
We will use the Python libraries statsmodels and scikit-learn for data analysis, and the Matplotlib library for visualization. Baseline data will be compared for differences using an independent samples t-test or chi-square analysis. Follow-up data will be analyzed using repeated measures ANOVA or generalized estimating equations (GEE) to assess the trend differences between the two groups over time. Outcome comparisons at different time points will be conducted using t-tests or linear regression models to compare the scores of the two groups. Differences in depression rates at different time

points will be compared using chi-square tests or logistic regression. Sensitivity analysis, handling of missing data, and covariate adjustments will be performed as needed.

Time Taken

10 After enrollment, the intervention began and lasted for 4 weeks. Follow-up was conducted at the time of enrollment, one month after enrollment, three months after enrollment, and six months after enrollment.

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