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ORIGINAL RESEARCH

Superior antidepressant effect occurring 1 month after rTMS: add-on rTMS for subjects with medication-resistant depression

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Abstract: Depression is a major psychiatric disorder. The standard treatment for depression is antidepressant medication, but the responses to antidepressant treatment are only partial, even poor, among 30%–45% of patients. Refractory depression is defined as depression that does not respond to antidepressant therapy after 4 weeks of use. There is evidence that repetitive transcranial magnetic stimulation (rTMS) may exert effects in treating psychiatric disorder through moderating focal neuronal functions. High-frequency rTMS on the left prefrontal area and low-frequency rTMS on the right prefrontal area were shown to be effective in alleviating depressive symptoms. Given the statistically significant antidepressant effectiveness noted, the clinical application of rTMS as a depression treatment warrants further studies. Application of rTMS as an add-on therapy would be a practical research model. High-frequency (5–20 Hz) rTMS over the left dorsolateral prefrontal cortex was found to have a significant effect on medication-resistant depression. In the present study, we not only measured the acute antidepressant effect of rTMS during treatment and immediately after its completion but also evaluated participants 1 month after completion of the treatment protocol. Study participants were divided into two groups: an active rTMS group (n = 10) and a sham group (n = 10). The active rTMS group was defined as participants who received the rTMS protocol, and the sham group was defined as participants who received a sham rTMS procedure. A significant Hamilton Depression Rating Scale score reduction was observed in both groups after the fifth and tenth treatments. However, those in the active rTMS group maintained their improvement as measured one month after completion of the rTMS protocol. Participants who received active rTMS were more likely to have persistent improvement in depression scores than participants who received sham rTMS.

Keywords: major depressive disorder, repetitive transcranial magnetic stimulation, treatment-resistant depression, efficacy, adverse effect

Introduction

Major depressive disorder (MDD) is not a rare disorder in the general population. In the 21st century, it has become one of the most prevalent disorders in the world, with a gradually increasing disease burden.[1] Standard medical treatment includes many different psychotherapy and antidepressant medications.[2] However, more than 30% of patients receiving antidepressants do not respond well to these drugs.[3,4]

Repetitive transcranial magnetic stimulation (rTMS) is a new technique that is increasingly popular for the treatment of neurologic and psychiatric diseases.[5,6] Because antidepressants cannot help all depressed people, the use of rTMS to treat MDD is reported with increasing frequency around the world.[7] High-frequency (5–20 Hz) rTMS over the left dorsolateral prefrontal cortex (DLPFC) was found to

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have a significant effect on medication-resistant depression in meta-analyses.[7–11] However, few studies with good sham-controlled designs have been performed in East Asia in order to investigate subacute effects of high-frequency rTMS.[12,13]

Given the dearth of studies of rTMS for MDD in East Asia, we sought to evaluate the efficacy of rTMS in treating depressed Chinese patients. In addition, previous studies of the efficacy of rTMS in treating MDD have focused on the acute antidepressant effect during treatment. In the present study, we not only measured the acute antidepressant effect of rTMS during treatment and immediately after its completion but also evaluated participants 1 month after completion of the treatment protocol. The study protocol was approved by the institutional review board of the Department of Health of the Republic of China (Taiwan).

Methods

Participants

The participants in this study were recruited from our hospital from January 1, 2008, to October 31, 2008. Patients who had received a diagnosis of MDD according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. criteria were evaluated using the Mini-International Neuropsychiatric Interview. Participants were also required to have treatment-resistant depression that had not responded to two different antidepressants administered for 6 weeks each. Patients were excluded from the study if they were considered to have a high risk of suicide. Patients were also excluded if they had any physical abnormality such as a head injury or epilepsy or if they had an implanted pacemaker.

In the screening phase, if a patient had a score of over 24 on the Beck Depression Inventory, version 2 (BDI-II), he or she was invited to complete a subsequent interview. Those with scores of over 18 on the 17-item Hamilton Depression Rating Scale (HAM-D) were entered into the trial. Initially, 60 inpatients were selected and asked to visit our clinics for the study. A total of 34 patients completed the screening process and met the inclusion criteria.

Study participants were randomized into two groups: an active rTMS group and a sham group. They received the same antidepressant and keep unchanged dosage during the rTMS protocol. The active rTMS group was defined as participants who received the rTMS protocol, and the sham group was defined as participants who received a sham rTMS procedure. A total of 13 patients were unable to be hospitalized during the rTMS protocol, so they were not included in this study. The final study sample consisted of 21 people because people who met the criteria were able to receive the protocol in our hospital. The clinical trial was performed using a double blind and randomized design. All subjects joining the trial gave informed consent before they entered the protocol.

rTMS protocol

A well-trained psychiatrist (CHC) performed rTMS using a magnetic stimulator (Magstim Company Ltd, Whitland, UK) with four booster modules with a figure-eight-shaped coil. Participants were seated upright in a comfortable chair during the procedure. Before the first treatment, we determined the motor threshold at rest for the right abductor pollicis muscle, as in previous studies.[14,15] The DLPFC stimulation was defined as 5 cm in front of the site of the right abductor pollicis muscle in the parasagittal plane (the thumb), as described previously.[16]

None of the patients had received rTMS prior to this study. Each patient underwent 10 sessions of rTMS over the left DLPFC within 4 weeks, at 90% motor threshold. Sham stimulation occurred in exactly the same manner as active rTMS, except that the angle of the coil, rather than being tangential to the skull, was at 90 degrees to the skull. This created a similar sensation in the patient but appeared not to actually stimulate the motor cortex as in the active condition. Other parameters of stimulation characteristics were as follows: 20 Hz, 20 trains of 2 seconds duration, 12 minutes per session, 10 sessions of stimulation over a 2-week period (10 weekdays).

Psychiatric assessment

Two scales were used to evaluate the efficacy of rTMS in medication-resistant depression: the BDI-II and the 17-item HAM-D. In addition, the Young Mania Rating Scale (YMRS) was used because of a previous report of rTMS-induced mania.[17] The Brief Psychotic Rating Scale (BPRS) was used if the participant suffered from depression with psychotic features. Thus, assessments using the BDI-II, HAM-D, YMRS, and BPRS were performed before the start of the treatment protocol, after the fifth treatment session, after the tenth treatment session, and 1 month after completion of ten treatment sessions. The raters who evaluated the patients did not know whether a participant had been assigned to the rTMS or sham group.

Statistical analysis

The sex and age of study participants were recorded. The effects of rTMS on BDI-II and HAM-D scores were analyzed. Analysis was performed using SPSS software

(v 13.0; IBM Corporation, Armonk, NY, USA), and the level of statistical significance was set at $P < 0.05$.

Results

A total of 21 participants (9 males and 12 females) entered the trial. The baseline YMRS and BPRS scores were less than 4 in both groups, and they remained stable during and after the trial. One patient in the sham group withdrew from the study because of unspecified somatic complaints. Thus, 20 patients completed the trial and 1 month follow-up. Of these 20 patients, 10 were in the active rTMS group and 10 were in the sham group. The patients' ages ranged from 20 to 62 years, and the mean (SD) age was 44.1 (4.4) years in the active rTMS group and 47.3 (3.5) years in the sham group, as shown in Table 1.

The baseline mean (SD) BDI-II scores were 32.1 (4.5) in the active rTMS group and 37.8 (2.4) in the sham group. The BDI-II scores after the fifth treatment were 26.5 (3.8) in the active rTMS group and 29.2 (3.4) in the sham group. The BDI-II scores after the tenth treatment were 24.2 (4.4) in the active rTMS group and 26.0 (4.9) in the sham group. The BDI-II scores 1 month after the completion of treatment were 25.9 (8.4) in the active rTMS group and 21.8 (2.7) in the sham group. No significant difference was found in the change in BDI-II scores between the two groups (Table 1).

The baseline mean (SD) HAM-D scores were 23.5 (1.9) in the active rTMS group and 24.9 (1.9) in the sham group. The HAM-D scores after the fifth treatment were 16.1 (2.8) in the active rTMS group and 17.5 (1.6) in the sham group. The HAM-D scores after the tenth treatment were 9.6 (1.5) in the active rTMS group and 12.3 (1.4) in the sham group. A significant change was observed in both groups after the fifth and tenth treatments. However, those in the active rTMS group maintained their improvement as measured by the HAM-D 1 month after the completion of treatment. The HAM-D scores 1 month after the completion of treatment were 9.8 (1.6) in the active rTMS group and 16.4 (1.5) in the sham group with the difference being statistically significant. If we used a 50% decrease in the HAM-D scores as the cut-off point of a responder, there were no significant differences between two groups after the tenth treatment but the active rTMS group was significantly superior than the sham group 1 month after the protocol (Table 1).

The YMRS and BPRS scores were less than 4 at baseline in both groups. These scores remained stable during the trial and 1 month after the completion of treatment.

Discussion

The change in HAM-D scores indicates that participants in both study groups improved after the completion of treatment (Table 1). There were similar responders in the two groups after the tenth treatment. This result differs from previous reports of a significant difference between active and sham rTMS groups immediately after the completion of treatment.[12,15,18] However, in the present study, participants in the active rTMS group retained their improvement after 1 month, with a significant difference observed between the two groups. Thus, participants receiving active rTMS had a longer antidepressant-like response than did participants receiving sham treatment. Percentage of responders in the active rTMS group was also significantly higher in comparision to the sham group. The longer-term effect of rTMS is not well understood, and studies with longer follow-up are needed to evaluate the duration of its effectiveness.

No significant difference was observed between the two groups in change in BDI-II scores. This result differs

Table 1 BDI-II and HAM-D scores of active rTMS and sham groups

Variable	Active rTMS (n = 10)	Sham (n = 10)
Male, n (%)	3 (30.0)	6 (60.0)
Age, years	44.1 (4.4)	47.3 (3.5)
Baseline BDI-II score	31.4 (4.5)	37.8 (2.4)
After 5th treatment BDI-II score	26.5 (3.8)	29.2 (3.4)
After 10th treatment BDI-II score	24.2 (4.4)	26.0 (4.9)
1 month after treatment BDI-II score	25.9 (8.4)	21.8 (2.7)
Baseline HAM-D score	23.5 (1.9)	24.9 (1.9)
After 5th treatment HAM-D score	16.1 (2.8)	17.5 (1.6)
After 10th treatment HAM-D score	9.6 (1.5)	12.3 (1.4)
Percentage of responder after 10th treatment HAM-D score	7 (70%)	8 (80%)
1 month after treatment HAM-D score	9.8 (1.6)*	16.4 (1.5)
Responder 1 month after treatment HAM-D score	7 (70%)*	2 (20%)

Notes: Unless otherwise indicated, data are given as mean (SD). *$P < 0.05$ for comparison between the two groups (*t* test).
Abbreviations: BDI-II, Beck Depression Inventory, version 2; HAM-D, Hamilton Depression Rating Scale; rTMS, repetitive transcranial magnetic stimulation.

from those of previous reports.[12,19] It is important to evaluate the difference between raters' reports and self-report measurements such as the BDI-II in order to better evaluate the antidepressant effect of active rTMS. The discrepant antidepressant effects evaluated by HAM-D and BDI have at least four possible explanations: First, they are evaluated in different ways.[20] HAM-D is an observer rating and BDI is a self-report. Second, they measure different depression symptoms.[21,22] The HAM-D accentuates somatic and behavioral symptoms of depression, whereas the BDI emphasizes the subjective experience of depression. Third, they have different sensitivity and effect sizes. In the course of antidepressant treatment, a more pronounced decline in HAMD than in BDI scores has often been reported.[21,22] Fourth, the discrepancy between HAM-D and BDI is not a unique phenomenon. It was also reported in a previous rTMS study.[23]

Although the discrepant change in HAM-D and BDI scores existed, our study still demonstrated the antidepressant effect of rTMS. However, the effect was "modest," just as Garcia-Toro et al claimed.[23] The effects might be more related to somatic and behavioral symptoms than subjective experiences. Therefore, the antidepressant effect of rTMS could be noticed more easily by the observer rather than the patients themselves.

Some limitations of this study may affect interpretation of its results. First, the sex distribution was not the same in the two groups; thus, the effect of rTMS may differ between female and male populations. Another limitation is that all the data were collected while the patients were also using antidepressant medication. The possibility that the difference in change in HAM-D scores between the two groups was influenced by the combined effect of antidepressants and rTMS cannot be excluded.

Conclusion

In summary, this study revealed an effect of rTMS that remained 1 month after the completion of treatment. Participants who received active rTMS were more likely to have persistent improvement in depression scores than were participants who received sham rTMS. This information may be useful in future planning of rTMS treatment for MDD or other psychiatric diseases. Further studies of the duration of effectiveness of rTMS are warranted.

Disclosure

HCT received a grant from Tzu-Chi General Hospital. CCHL worked as a fulltime psychiatrist at Tzu-Chi General Hospital and as an assistant professor at Tzu-Chi University when he joined this study. CCHL currently works as a medical director at Eli Lilly and Company (Taiwan/Hong Kong/Macau), as a consultant psychiatrist at Tzu-Chi General Hospital, and as an adjunct assistant professor at Tzu-Chi University. STC received a grant from Tzu-Chi General Hospital, Tzu-Chi University, and the National Science Council (Taiwan, Republic of China). The authors report no other conflicts of interest in this work.

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