Repellent Transcranial Magnetic Stimulation for Treating Medication-resistant Depression in Taiwan: A Preliminary Study

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Background: We conducted an open trial to evaluate the efficacy of repetitive transcranial magnetic stimulation (rTMS) in medication-resistant depression. This is the first study in Taiwan of rTMS for the treatment of depression.

Methods: A 2-week regimen of rTMS (100% of motor threshold, 5 Hz, 8 sec, 40 trains/20 min/day, 10 weekdays) applied to the left dorsolateral prefrontal cortex was administered to 11 patients with medication-resistant depression.

Results: Ten subjects completed 2 weeks’ treatment with rTMS. Scores on the 21-item Hamilton Depression Rating Scale (HAM-D21) and Beck Depression Inventory decreased by 48% and 28%, respectively. Five patients were clinical responders (≥ 50% reduction in HAM-D21 score): 2 of these were in complete remission (HAM-D21 score ≤ 7). Five patients were less responsive: 2 of these were partial responders (20–49% reduction in HAM-D21 score), whereas 3 did not improve. Younger versus older age was identified as a potential predictor of response to rTMS used as add-on therapy.

Conclusion: Our preliminary results indicate that rTMS can improve mood in patients with medication-resistant depression, and can also potentially replace electroconvulsive therapy for certain types of medication-resistant depression. Future double-blind, placebo-controlled trials of rTMS are warranted. [J Chin Med Assoc 2005;68(5):210–215]

Key Words: left dorsolateral prefrontal cortex, major depression, transcranial magnetic stimulation

Introduction

In the United States, the widespread prevalence of depression was determined in a large national survey by Kessler et al.1 The lifetime risk of major depression was estimated to be as high as 34%, and this estimate rose to 50% when bipolar and chronic minor depressions were included.1 While most depressive symptoms are eliminated by current pharmacologic treatments, as many as 50–60% of patients have incomplete recovery or significant adverse effects.2 Nonpharmacologic methods for alleviating depression have recently received renewed attention. Electroconvulsive therapy (ECT) is the most effective nonpharmacologic treatment, particularly for refractory depression.3 Although the antidepressant mechanisms of ECT are unknown, recent data indicate that production of a generalized convulsion is not sufficient for treating depression.4–7 However, the effect of the ECT seizure on regional brain function is important in determining the therapeutic benefit.4,5 These data are consistent with evidence from functional neuroimaging studies that have implicated prefrontal, temporal, and limbic structures in depression.6
Recently, transcranial magnetic stimulation (TMS) has been developed as a novel tool for potential antidepressant treatment that, unlike ECT, does not cause a seizure or require anesthesia.\textsuperscript{7} TMS is a non-invasive method of influencing regional electrical activity in the brain with safe, subconvulsive stimulation, and with little or no pain. A powerful but local magnetic field is generated by passing brief, powerful electrical current through a conducting coil placed on the scalp. The rapidly alternating magnetic field passes unhindered through the skull and produces weaker, focal electrical currents, thereby activating neurons in the brain.\textsuperscript{8} Subjects usually notice no adverse effects, except for occasional mild headache and discomfort at the site of stimulation. Recent technologic advances led to the development of magnetic stimulators that can repeatedly stimulate faster than 1 cycle of frequency per second. Repeated magnetic stimulation at ≥ 1 Hz is, by convention, called “repetitive transcranial magnetic stimulation” (rTMS). The results of some positron emission tomography (PET) studies suggested that stimulation at different frequencies may have divergent and even opposite effects on neuronal activity.\textsuperscript{9,10} High frequency rTMS may enhance, while low frequency rTMS may inhibit, cortical excitability.

George and Wassermann\textsuperscript{11} hypothesized, based on the following evidence, that selective subconvulsive rTMS over key brain regions might have an antidepressant effect: abnormalities of the left prefrontal cortex were found in functional neuroimaging studies of depression; changes in prefrontal cortex activity predicted response to ECT; and patients with left prefrontal strokes had an increased risk of depression.\textsuperscript{4,12} In subsequent studies, George et al\textsuperscript{13–15} found a striking antidepressant effect for rTMS over the left prefrontal cortex in an open trial,\textsuperscript{11} a double-blind crossover trial,\textsuperscript{14} and a placebo-controlled study.\textsuperscript{15} All these experimental results indicated that the use of high-frequency stimuli over the left dorsal prefrontal cortex had a significant antidepressant effect.

The current study was designed as a 2-week, open trial to confirm the significant antidepressant efficacy of rTMS in Chinese patients with refractory depression. Additionally, some reports\textsuperscript{16,17} showed that older depressed patients may respond less well to rTMS. In 1 of our previous studies,\textsuperscript{18} the percentage shortening of choice reaction time induced by rTMS was negatively correlated with age in healthy individuals; in the current trial, we therefore examined whether age differences might influence the antidepressant efficacy of rTMS.

### Methods

#### Study participants

Eleven patients with a major or bipolar depressive episode diagnosed by Mini International Neuropsychiatric Interview\textsuperscript{19} and meeting DSM-IV criteria\textsuperscript{20} were enrolled in a 2-week, open trial of rTMS. After receiving a full explanation of the procedure, all subjects signed a consent form. The study protocol was approved by the Institutional Review Board of Taipei Veterans General Hospital and the National Health Department of Taiwan.

All study participants had medication-resistant depression, and had failed to respond to at least 2 trials of antidepressant drugs over a 3-month period before rTMS. The severity of depression at entry was above moderate (i.e. 21-item Hamilton Depression Rating Scale\textsuperscript{21} [HAM-D\textsubscript{21}] score > 18). Four subjects (numbers 2, 4, 7 and 9) were inpatients during the trial. For ethical reasons, all patients were allowed to continue their unsuccessful antidepressant medications during the 2-week course of rTMS: serotonin-noradrenaline reuptake inhibitors (venlafaxine \{n = 4\}, mirtazapine \{1\}); or selective serotonin reuptake inhibitors (paroxetine \{2\}, fluoxetine \{1\}, citalopram \{1\}, sertraline \{1\}, fluvoxamine \{1\}). One patient (number 8) took antidepressant medication in combination with an antipsychotic (olanzapine; Table 1). No medication changes were allowed for 2 weeks before, or during, rTMS.

Patients were excluded from the study for the following reasons: physical and neurologic abnormalities; implanted pacemakers; a substantial risk of suicide during the trial; a history of seizures, major head trauma or psychotic symptoms. No patients had a history of ECT. Ten patients completed the rTMS regimen, and 1 dropped out because of intolerable headache induced by rTMS.

#### TMS procedure

A trained psychiatrist (CCH) performed rTMS using a Magstim® super-rapid magnetic stimulator (Magstim Co Ltd, Whitland, Wales, UK), with 4 booster modules equipped with a 70-mm, air-cooled, figure-of-8-shaped coil. The coil was held with the handle posterior and oriented sagittally. Subjects were seated upright in a comfortable chair with eyes open, and foam earplugs were used during rTMS to diminish noise from the discharging coil.

At the initial treatment visit, patients had their motor threshold (MT) determined at rest in the contralateral (right) abductor pollicis brevis (APB) muscle, as described previously.\textsuperscript{22} The stimulation site...
on the left dorsolateral prefrontal cortex was defined as the region 5 cm rostral and in a parasagittal plane from the site of maximal APB stimulation. This method of locating the stimulation site has been used in other rTMS studies of depression.15,23 Each day, subjects were asked about events that could have changed the MT (medications, sleep deprivation, etc.), the MT was quickly rechecked, and the daily dose was adjusted accordingly. The re-calculated MT never changed more than 5% from baseline.

Subjects received 20 minutes of rTMS each weekday for 10 sessions during a 2-week period. They were given 40 trains in each session, with each train of 5 Hz (8 seconds on and 22 seconds off) at 100% of MT. In other words, 1,600 pulses per session and a total of 16,000 pulses were delivered throughout the 10-session treatment schedule.

Ratings and response classification
The severity of depression at baseline and at the end of each week was rated by a psychiatrist (TPS) using the HAM-D21, and by patients using the Beck Depression Inventory (BDI).24 Clinical response to rTMS was evaluated by calculating the percentage improvement in HAM-D21 scores from baseline to the end of treatment: responders had a reduction of ≥ 50%; partial responders a reduction of 20–49%; and non-responders a reduction of < 20%.

Statistical analysis
HAM-D21 and BDI score differences between study entry and the end of treatment were compared by the Wilcoxon matched-pairs signed-ranks test, and the relationship between age and rTMS-induced changes in HAM-D21 scores was obtained by Pearson’s product-moment correlation test. In seeking predictors of clinical responsiveness to rTMS, characteristics such as demographic variables and clinical features at study entry were compared between responders and non-responders using the non-parametric Wilcoxon test, or the non-parametric Chi-squared test. All statistical tests were 2-sided, and used the 5% level of significance.

Results
Demographic data and depression scores over time are shown in Table 1. The rTMS regimen was generally well tolerated by all except 1 patient (number 6) who dropped out in the third rTMS session because of intolerable headache; this patient required acetaminophen to reduce her headache. Three patients (numbers 2, 4 and 9) reported mild headache on a few occasions immediately after rTMS; these headaches were relieved by a short period of rest. No patients reported problems with memory or attention, and there were no seizures (a possible adverse effect of rTMS).

Significant decreases in HAM-D21 score (Z = –2.666, Nties = 9, p = 0.008) and BDI score (Z = –2.807, Nties = 10, p = 0.005) were observed with rTMS. The 2-week treatment schedule produced overall decreases

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (yr)</th>
<th>Diagnosis</th>
<th>Antidepressant therapy and daily dose</th>
<th>Score on HAM-D21 Score on BDI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>1</td>
<td>F</td>
<td>32</td>
<td>MDD</td>
<td>Fluvoxamine 150 mg</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>31</td>
<td>MDD</td>
<td>Venlafaxine 300 mg</td>
<td>38</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>50</td>
<td>MDD</td>
<td>Venlafaxine 300 mg</td>
<td>30</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>47</td>
<td>MDD</td>
<td>Venlafaxine 300 mg</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>39</td>
<td>MDD</td>
<td>Sertraline 100 mg</td>
<td>22</td>
</tr>
<tr>
<td>6*</td>
<td>F</td>
<td>46</td>
<td>MDD</td>
<td>Paroxetine 20 mg</td>
<td>23</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>33</td>
<td>MDD</td>
<td>Paroxetine 40 mg</td>
<td>31</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>21</td>
<td>MDD</td>
<td>Fluoxetine 20 mg, olanzapine 10 mg</td>
<td>24</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>42</td>
<td>MDD</td>
<td>Mirtazapine 30 mg</td>
<td>34</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>65</td>
<td>MDD</td>
<td>Citalopram 40 mg</td>
<td>19</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>40</td>
<td>BD2</td>
<td>Venlafaxine 150 mg</td>
<td>23</td>
</tr>
<tr>
<td>Mean</td>
<td>–</td>
<td>40.6 ± 11.7</td>
<td></td>
<td>–</td>
<td>26.9 ± 6.0</td>
</tr>
<tr>
<td>± SD</td>
<td></td>
<td>11.7</td>
<td></td>
<td></td>
<td>16.2</td>
</tr>
</tbody>
</table>

* Dropped out because of headache. BD2 = bipolar disorder type II; BDI = Beck Depression Inventory; HAM-D21 = 21-item Hamilton Depression Rating Scale; MDD = major depressive disorder; SD = standard deviation.
rTMS for treating depression

In HAM-D21 score of 48% and in BDI score of 28%. Five patients (numbers 1, 2, 4, 7 and 8) were clinical responders, and 2 of these (numbers 4 and 7) were in complete remission (HAM-D21 score ≤ 7). Another 5 patients were less responsive: 2 of these (numbers 5 and 9) were partial responders, whereas 3 (numbers 3, 10, and 11) were non-responders. In total, 7 of 10 patients (70%) experienced symptom amelioration after 2 weeks of rTMS treatment. Nevertheless, a trend was observed towards a negative association between percentage decrease in HAM-D21 score and increase in patient age in individuals subjected to rTMS (n = 10, r = –0.59, p = 0.072).

In the search for predictors of clinical outcome, a significant age difference was noted between responders and non-responders (Z = –1.984, p = 0.047), i.e. responders were significantly younger than non-responders (mean age 32.8 vs 47.2 years). However, there were no significant differences in terms of age at disease onset, gender, types of depression (unipolar vs bipolar), number of previous depressive episodes, duration of current episode, and depression and anxiety scores at study entry. Conversely, changes in HAM-D21 scores from baseline to weeks 1 and 2 were significant in responders (Z = –2.417, p = 0.016; and Z = –2.611, p = 0.008, respectively), but not in non-responders (Figure 1).

Discussion

rTMS for the treatment of medication-resistant depression is one of the major advances in modern psychiatry, and this is the first study examining the efficacy of rTMS over the left prefrontal cortex in Chinese patients with such depression. The results are comparable with previous reports from Western countries, but demonstrate a robust effect for rTMS in ameliorating depression in Chinese patients with medication-resistant depression.

Table 2 shows a comparison of stimulation parameters, patient diagnoses, concomitant anti-depressant therapy, and response rates, between our study and 3 others. The same parameters and total pulses were used in our study and 2 others: our response rate was identical to that in 1 trial (48%), but markedly greater than that in the other (48% vs 25%), despite the latter trial27 using a higher intensity of rTMS (MT 110% vs 100%). Shajahan et al26 used only about 1-third of the total number of pulses (5,000 vs 16,000 pulses) and a lower MT (80% vs 100%) than in our study, but reported the same clinical response rate (48%) as in our trial and in that conducted by George et al.15 Clearly, the applied stimulus does not

Table 2. Comparison of repetitive transcranial magnetic stimulation parameters, patient diagnoses, medication status and response rates in 4 studies

<table>
<thead>
<tr>
<th>Present study (Huang et al)</th>
<th>George et al15</th>
<th>Shajahan et al26</th>
<th>Nahas et al27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (Hz)</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Train duration (sec)</td>
<td>8</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Trains per session</td>
<td>40</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Total number of pulses</td>
<td>16,000</td>
<td>16,000</td>
<td>5,000</td>
</tr>
<tr>
<td>Intensity (% of MT)</td>
<td>100</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>Site of stimulation</td>
<td>LDPF</td>
<td>LDPF</td>
<td>LDPF</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Unipolar depression (most)</td>
<td>Unipolar depression (most)</td>
<td>Unipolar depression</td>
</tr>
<tr>
<td>Medication resistant</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Concomitant antidepressant therapy</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Clinical improvement (% decrease in HAM-D21 score from baseline)</td>
<td>48</td>
<td>48</td>
<td>48</td>
</tr>
</tbody>
</table>

HAM-D21 = 21-item Hamilton Depression Rating Scale; LDPF = left dorsolateral prefrontal cortex; MT = motor threshold.
correlate absolutely with clinical efficacy. On the other hand, depressed patients in Shajahan et al’s study, unlike the treatment-resistant patients in George et al’s and our studies, might be more responsive to less intensive treatment. The lower clinical response rate in the study conducted by Nahas et al than in our study and the other 2 trials, despite the greater intensity of treatment, may have resulted from the diagnosis of bipolar rather than unipolar depression. In our study, rTMS patients received concomitant antidepressant medication, whereas patients in the study conducted by George et al did not. Whether such concomitant therapy confounds the clinical outcome of rTMS remains unclear. Indeed, rTMS plus antidepressant therapy may provide a greater benefit than rTMS alone, or the heterogeneity of antidepressant medication may interact negatively with rTMS. These potential confounding factors may explain the discrepant results for rTMS in the abovementioned studies.

Corresponding with previous reports, we observed a trend towards a negative correlation between age and decrease in HAM-D21 score, indicating that younger depressed patients respond better to brain stimulation than their older counterparts. Imaging studies have shown prefrontal cortex atrophy in older depressed patients. The degree of brain atrophy, particularly in the prefrontal lobe, might explain the relatively reduced antidepressant response to rTMS in older depressed patients. However, our elderly patients were aged 50–65 years, and not > 65 years as usually defined. Therefore, further investigations using larger sample sizes will help to determine whether reduced responses to rTMS are associated directly with patient age (i.e. > 50 or > 65 years), or with the degree of brain atrophy regardless of patient age.

In this study, we also observed a significant reduction in HAM-D21 scores from the first week of treatment and into the second week of the trial. This finding is supported by the report of Grunhaus et al, in which a positive response to rTMS was evident by day 3 of treatment. Since the sample size was small in these 2 studies, further investigation of these findings is needed.

There were several methodologic limitations in our study. First, the sample size was too small to validate the general application of rTMS in depressed patients. Second, our study was an open trial; therefore, a placebo response, resulting from factors such as daily contact, support for rTMS, and popular beliefs concerning the effects of magnetism, cannot be ruled out, even though, as George et al mentioned, placebo responses would be unexpected in patients with medication-resistant depression. The psychiatrist who rated responses (TPS) was totally blinded to the performance of rTMS throughout the treatment sessions. This, together with the unlikelihood of a marked placebo response, may have reduced some of the potential study bias. Third, our study had an add-on design, such that concomitant antidepressant medication may have confounded the results of rTMS treatment. To resolve the above issues, a double-blind study with medication-free patients, either refractory or non-refractory to pharmacologic treatment, is recommended.

Grunhaus et al reported that the efficacy of rTMS is comparable to that of ECT in non-delusional major depression, but with fewer and/or less intense adverse effects, e.g. no pain, no requirement for anesthesia, no need for coupled seizure induction, and fewer risks and cognitive impairments. Although the antidepressant mechanisms of rTMS action remain unclear, the need to induce generalized convulsion (as is thought to be critical for ECT efficacy) can be questioned. Also relevant is whether subconvulsive rTMS can replace ECT for difficult-to-treat depression, and whether it may be more beneficial than ECT. Some major discrepancies among rTMS studies indicate that treatment parameters (intensity, duration, pulses, and frequency) have not been optimized. The use of optimal treatment parameters may increase and sustain the response to rTMS.

In conclusion, our preliminary findings support the notion that rTMS may improve mood in patients with medication-resistant depression in Taiwan. However, these findings require confirmation in a double-blind, placebo-controlled study. How to optimize rTMS treatment, with appropriate changes in parameters, particularly in the Chinese population, also needs to be explored.

Acknowledgments

This work was supported by a grant (VGH-91-237) from Taipei Veterans General Hospital. The authors would like to thank Dr. Shih-Jen Tsai for patient referral.

References


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J Chin Med Assoc • May 2005 • Vol 68 • No 5

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