REVIEW ARTICLE

Transcranial magnetic stimulation for depression and other psychiatric disorders

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ABSTRACT

Introduction. Repetitive transcranial magnetic stimulation (rTMS) has been proposed as a possible alternative to electroconvulsive therapy for the treatment of selected patients with depression, bipolar affective disorder and schizophrenia. The aim of this study was to evaluate the evidence for the effectiveness of rTMS in mood disorders and schizophrenia.

Methods. Studies were identified using MEDLINE (1966 to January 2000), EMBASE/Excerpta Medica (1980 to January 2000), Biological Abstracts and Index to Scientific and Technical Proceedings. A number of biomedical and TMS related websites were also searched. We estimated the number needed to treat to show beneficial effect of rTMS when compared with the placebo controlled group.

Results. Seven controlled trials of rTMS depression were identified. Five of these were suitable for meta-analysis and show a beneficial effect of rTMS compared to placebo, with a number needed to treat of 2.3 with a 95% confidence interval 1.6 to 4.0, total; 81 patients. A single trial of rTMS has also been performed in mania, which shows a beneficial effect of right hemisphere stimulation when compared with left hemisphere stimulation. A controlled trial in schizophrenia failed to show any benefit of rTMS.

Discussion. rTMS has demonstrable beneficial effects in depression. The extent and the duration of the anti-depressant effect of rTMS has yet to be defined. There now needs to be randomized controlled trials to compare rTMS directly with standardized electroconvulsive therapy in order to take this subject forward. With regard to the treatment of other mood disorders and schizophrenia, we are at an early stage in the assessment of further studies that are needed to examine any potential role for rTMS.

INTRODUCTION

Transcranial magnetic stimulation (TMS) involves placing a high intensity magnetic field of brief duration at the scalp surface. This induces an electrical field at the cortical surface that can alter neuronal function. Repetitive TMS (rTMS) involves applying trains of these magnetic pulses. In animal models, rTMS or electrical stimulation have been shown to enhance forebrain serotonin output (Juckel et al. 1999) and to modulate 5-HT receptor function (Ben-Schachar et al. 1999; Kole et al. 1999). rTMS has also been shown to produce behavioural biochemical changes similar to that produced by electroconvulsive therapy (ECT) (Zyss et al. 1997). In humans, rTMS has been shown to produce changes...
frontal lobe blood flow (Tenebak et al. 1999) and to normalize the response to dexamethasone in depression (Pridmore, 1999; Reid & Pridmore, 1999). rTMS has also been shown to produce changes in mood in normal volunteers (George et al. 1996).

Since trials in the late 1990s, rTMS has been proposed as a treatment for drug resistant depression, schizophrenia and mania (Reid et al. 1998; Pridmore & Belmaker, 1999). In particular, it has been suggested that rTMS has a role in those patients with drug resistant depression who are unable to have treatment with electroconvulsive therapy (ECT) (Reid et al. 1998). The aim of this study, therefore was to evaluate the collective evidence for the effectiveness of rTMS in mood disorders and schizophrenia by a systematic review of the published data.

METHOD

Search criteria

Studies were identified using MEDLINE (1966 to January 2000), EMBASE/Excerpta Medica (1980 to January 2000), Biological Abstracts and Index of Scientific and Technical Proceedings. We searched the Meta-register of Controlled trials (www.controlled-trials.com), the national register (www.doh.gov.uk/research/ntr), the Cochrane Library (www.update-software.com/clibhome/clib.htm) and the worldwide web using the Omni biomedical search tool (www.omni.ac.uk). The following TMS related world wide web sites were also searched: the ‘TMS Resources and Published Articles’ (www.musc.edu/tmsmirror/TMSresrc), ‘Avery-George Index’ of depression trials site (www.ists.unibe.ch/ists/TMSAvery), the International Society of Transcranial Magnetic Stimulation (www.ists.unibe.ch/), ‘TMS and Depression’ (www.psycnet.nim.nih.gov/pubs/depression.html) and the ‘Helsinki TMS’ site (www.biomag.helsinki.fi/tms/).

Inclusion criteria

Only randomized controlled trials were included in this study. Placebo treatment can have a significant anti-depressant effect (Bialik et al. 1995), consequently we included only the placebo controlled trials.

Statistical methods

We examined the studies included for meta-analysis with a test of heterogeneity as outlined by DerSimonian & Laird (1986). We used absolute benefit increase (rate of improvement in the treated group—rate of improvement in the control group) and its reciprocal, number needed to treated (NNT) to estimate treatment effect. These were estimated using a random effects model (DerSimonian & Laird, 1986). To test for significance we constructed fourfold tables and calculated a Mantel-Haenszel statistic (Fleiss, 1981).

RESULTS

Depression

Sixteen published clinical trials of rTMS for depression were identified (George et al. 1995, 1997; Conca et al. 1996; Pascual-Leone et al. 1996; Geller et al. 1997; Feinsod et al. 1998; Figiel et al. 1998; Avery et al. 1999; Klein et al. 1999; Loo et al. 1999; Menkes et al. 1999; Padberg et al. 1999; Tenebak et al. 1999; Triggs et al. 1999; Berman et al. 2000; Grunhaus et al. 2000). Eight of these studies were excluded because there was no randomized control group (George et al. 1995; Geller et al. 1997; Feinsod et al. 1998; Figiel et al. 1998; Avery et al. 1999; Menkes et al. 1999; Tenebak et al. 1999; Triggs et al. 1999). One study was excluded because the control group was treated with ECT (Grunhaus et al. 2000). The remaining studies were randomized-controlled trials. In five of these rTMS was applied at 10 Hz or 20 Hz to the left frontal region (Conca et al. 1996; Pascual-Leone et al. 1996; George et al. 1997; Loo et al. 1999; Bergman et al. 2000). In one study it was applied at 1 Hz to the right hemisphere (Klein et al. 1999 a) and in another both techniques were applied (Padberg et al. 1999). We needed to exclude one controlled trial (Conca et al. 1995) as there was no placebo TMS treatment included as part of the trial protocol. Finally, there was one study, which included 18 patients, that failed to show any significant benefit of rTMS (Loo et al. 1999), however the individual responses in the TMS group and the control groups were not available. In the five remaining studies the standardized placebo treatment was
Transcranial magnetic stimulation for depression

Table 1. Characteristics of the trials included in this study

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnostic criteria</th>
<th>Medication withdrawn</th>
<th>Rating</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pascual-Leone et al. 1996</td>
<td>DSM-III-R</td>
<td>No</td>
<td>HDRS (21) BQ</td>
<td>Blind</td>
</tr>
<tr>
<td>George et al. 1997</td>
<td>DSM-IV</td>
<td>No</td>
<td>HDRS (21) MADRS</td>
<td>Blind</td>
</tr>
<tr>
<td>Padberg et al. 1999</td>
<td>DSM-IV</td>
<td>No</td>
<td>HDRS (21)</td>
<td>Blind</td>
</tr>
<tr>
<td>Berman et al. 2000</td>
<td>DSM-IV</td>
<td>Yes</td>
<td>HDRS (21) BQ</td>
<td>Blind</td>
</tr>
<tr>
<td>Klein et al. 1999a</td>
<td>DSM-IV</td>
<td>No</td>
<td>HDRS MADRS</td>
<td>Blind</td>
</tr>
</tbody>
</table>

HDRS, Hamilton Depression Rating Scale; MADRS, Montgomery–Åsberg Depression Rating Scale; BQ, Beck Questionnaire; EEG, electronencephalography; NPT, neuropsychological testing.

Table 2. Results of the trials included in this meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients treated (NT)</th>
<th>Number of patients that improved following treatment (RT)</th>
<th>Number of patients in the control group (NC)</th>
<th>Number of patients that improved following placebo treatment (RC)</th>
<th>ABI (%)</th>
<th>95% CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pascual-Leone</td>
<td>17</td>
<td>11</td>
<td>17</td>
<td>6</td>
<td>28</td>
<td>6–50</td>
</tr>
<tr>
<td>George</td>
<td>7</td>
<td>7</td>
<td>5</td>
<td>1</td>
<td>86</td>
<td>42–100</td>
</tr>
<tr>
<td>Padberg</td>
<td>12</td>
<td>8</td>
<td>6</td>
<td>2</td>
<td>33</td>
<td>0–84</td>
</tr>
<tr>
<td>Berman</td>
<td>10</td>
<td>4</td>
<td>10</td>
<td>0</td>
<td>40</td>
<td>10–70</td>
</tr>
<tr>
<td>Klein</td>
<td>35</td>
<td>17</td>
<td>32</td>
<td>8</td>
<td>48</td>
<td>38–58</td>
</tr>
</tbody>
</table>

NT, Number of patients treated in the trial; RT, number of patients that improved following treatment; NC, number of patients in the control group; RC, number of patients that improved following placebo treatment; ABI, difference between the rate of improvement in the treatment groups and the rate of improvement in the control group.

Characteristics of the trials

All of the trials included only patients who met DSM criteria for a major depressive episode (DSM-III-R or DSM-IV Table 1). One study included only those patients who had at least three episodes of depression that had been resistant to medication. In four of the five studies reviewed here the patients remained on antidepressant medication, in the other study (Berman et al. 2000) medication had been withdrawn for at least 1 week prior to commencing the trial (Table 1). In all of the studies it is clearly stated that the patients were randomly assigned to the treatment and control groups, however, the method of randomization is clearly described in only one of the trials (Klein et al. 1999a). Two of the trials had a crossover design, in one of these (George et al. 1997) there was two treatment periods, patients were randomly assigned to have placebo treatment or rTMS in the first treatment period, we included data from the first treatment period only. In the other study with a crossover design (Pascual-Leone et al. 1996), patients were studied in five treatment periods, rTMS was applied to the left dorso-lateral pre-frontal cortex in one of those periods, sham stimulation was applied in the other four treatment periods. The trialists found that treatment effect was independent of when the real rTMS treatment was applied, consequently, we have included data from all patients in the meta-analysis. All of the studies employed either a 17-, 21- or 25-point Hamilton Depression Rating Scale to assess outcome, some of the studies also added the Montgomery–Åsberg Depression Rating Scale or the Beck Questionnaire (Table 1). In all of the trials the rating scales were implemented by blinded raters. Some of the studies did not specifically assess for adverse outcomes and report only those side-effects that were mentioned by the patients. In others, patients were assessed either by electronencephalography (EEG) or by formal neuropsychological assessment (Table 1).

Outcomes

The results of the trials included in the meta-analysis are summarized in Table 2. The overall chi-squared test of association was 13.3 (df = 1), implying a statistically significant benefit of rTMS ($P < 0.001$). The weighted statistic in the difference scale ($Q_w$) was 5.3 ($P > 0.1$, df = 4), implying no significant heterogeneity in the studies included in our meta-analysis. The difference between rate of improvement in the treated group and that in the control group was 43% (95% CI 25% to 61%). The estimated number needed to treat was 2.3 (95% CI 1.6 to 6.0).
4-0). The duration of the therapeutic response was not defined in any of these studies.

**Adverse effects**

There were no withdrawals from treatment because of the side effects. The main side effects reported in other studies of transcranial magnetic stimulation are seizures, there were no seizures reported in the studies examined here. All the studies report transient headache occurring after the TMS treatment sessions. This occurred in 19 of the patients who received rTMS. However, in all cases it is reported that the headache resolved spontaneously or responded to treatment with paracetemol or aspirin. The only other side effect recorded was local scalp discomfort at the site of treatment during the rTMS session. There was no alteration in the EEG or in performance on neuropsychological testing.

**rTMS and other disorders**

We identified one controlled trial of rTMS in mania (Grisaru *et al.* 1998). This study compared right hemisphere stimulation with left hemisphere stimulation. Stimulation of the right prefrontal cortex produced a greater improvement than left hemisphere stimulation. However, there was no sham-treated control group and the possibility that the difference in the effect between the two hemispheres was due to a harmful effect of right hemisphere stimulation was not excluded.

We identified one published controlled trial in schizophrenia (Klein *et al.* 1999b). This double-blinded sham controlled trial included 16 patients in the treated group. It included patients who met DSM-IV criteria for schizophrenia. Patients remained on medication for the duration of the study. Patients were blindly assessed using the Positive and Negative Symptom Scale and the Brief Psychiatric Rating Scale. This study did not show any significant beneficial effects of rTMS.

**DISCUSSION**

The aim of this review was to examine the published evidence in order to determine the effectiveness of magnetic stimulation in psychiatric disorders. Sever small randomized controlled trials have now been published. A meta-analysis of five of these six studies demonstrates beneficial effects of rTMS in depression. There is insufficient published evidence to evaluate the benefit of rTMS in mania and schizophrenia.

The trials that show beneficial effects of rTMS in depression need to be examined quite closely, however. First, the sham condition in these trials was to alter the orientation of the coil with respect to the scalp, which is a standard manoeuvre. There is some concern that patients may not be effectively blinded by this sham condition. A more effective way to deal with this problem in the future might be to use a sham coil (sham coils look and sound similar to the usual TMS coils however, the magnetic pulse that they deliver is too small to alter neuronal function). Secondly, the duration of the antidepressant effect has not been defined in any of these studies and neither has the effect of multiple treatment regimes. Finally, because of the small size of these trials it has not yet been determined if there are subgroups of patients who would particularly benefit from rTMS.

There is little evidence on how rTMS compares with other treatments for depression. There has been one open randomized trial comparing rTMS to ECT (Grunhaus *et al.* 2000): 40 patients were included in the study, 20 of these were treated with rTMS and 20 with ECT. This study included patients who fulfilled DSM-IV criteria for depression. Patients were assessed with a 17-item Hamilton Depression Rating Scale, the Global Depression Rating Scale and the Global Assessment of Function Scale, the raters were not blind to the method of treatment. Overall, the patients who received ECT did significantly better than those who received rTMS (28% more patients responded to ECT, 95% CI 7% to 63%). Interestingly, this difference was most striking in those patients who had psychotic symptoms (88% more patients responded to rTMS, CI 66% to 100%). In contrast, in patients with no psychotic symptoms there was a similar response rate to ECT and to rTMS (60% of patients responded to ECT, CI 32% to 88%, 63% of patients responded to rTMS, 95% CI 31% to 91%). There are, however, a number of methodological concerns about this study. Patients were not blindly rated. The rTMS treatment regime was altered after treating the first eight patients. Patients in the ECT group
were allowed to remain on psychotropic medication while the rTMS group were treated with clonazepam only. Any differences in outcome could therefore be attributable to differences in pharmacotherapy or an interaction between rTMS or ECT and the medication. This study does, as its authors suggest, illustrate the need for further direct comparison between rTMS and ECT.

These important initial studies support the use of rTMS in depression. However, further large trials will be needed if rTMS is to be considered as an alternative to ECT in treating selected patients with depression and other psychiatric disorders. In particular, we feel that these trials should address some of the following questions: is rTMS as effective as ECT in depression? What is the most effective treatment regimen for rTMS? Are there any subgroups of patients who do particularly well with rTMS? A large multi-centre trial comparing rTMS and ECT has been commissioned by the Health Technology Assessment Programme (HTA) to take place in the UK.

REFERENCES


