Therapeutic Efficacy of Right Prefrontal Slow Repetitive Transcranial Magnetic Stimulation in Major Depression

A Double-blind Controlled Study

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Background: Transcranial magnetic stimulation (TMS), a noninvasive technique for stimulation of the brain, has recently been suggested to be effective for the treatment of major depression. We conducted a double-blind, placebo-controlled study to assess the efficacy of slow repetitive TMS (rTMS) in patients with major depression.

Methods: Seventy patients with major depression (53 women, 17 men; mean age, 58.7 years; SD, 17.2 years) were randomly assigned to receive rTMS or sham rTMS in a double-blind design. Treatment was administered in 10 daily sessions during a 2-week period. Severity of depression was blindly assessed before, during, and after completion of the treatment protocol.

Results: All patients completed the first week of treat-

ment and 67 completed the entire protocol. Patients who received rTMS had a significantly greater improvement in depression scores compared with those who received sham treatment. At the end of 2 weeks, 17 of 35 patients in the rTMS group, but only 8 of 32 in the sham-treated group, had an improvement of greater than 50% in their depression ratings.

Conclusions: This controlled study provides evidence for the short-term efficacy of slow rTMS in patients with recurrent major depression. Additional studies will be necessary to assess the efficacy of rTMS as compared with electroconvulsive therapy as well as the long-term outcome of this treatment in major depression and possibly other psychiatric disorders.

Arch Gen Psychiatry. 1999;56:315-320

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TRANSCRANIAL magnetic stimulation (TMS) has been used, since its introduction in 1985,[1] as a means for noninvasive and safe stimulation of the cerebral cortex. When applied over the motor cortex, a single magnetic stimulus can induce motor evoked responses in the contralateral limb muscles.[2] As such, TMS was found to be a valuable tool for cortical mapping and assessment of the functional integrity of the motor system.[2] The development of stimulators capable of discharging at high frequencies (up to 60 Hz) has expanded the application of TMS into the areas of assessment of cognitive and behavioral functions.[3] Depending on stimulation parameters (frequency, rate, and duration), repetitive stimuli to specific cortical regions can either decrease or enhance the excitability of the affected brain structures.[4] Repetitive stimulation of the pre-

frontal regions in normal volunteers has been shown to have a lateralized effect on mood,[5-7] with increased sadness following left prefrontal stimulation and increased happiness following right prefrontal stimulation. These findings are consistent with imaging studies that link depression with lateralized prefrontal dysfunction.[8]

See also page 300

Based on the assumed role of these regions in depressive illness, and the observed effects in normal volunteers,[5] TMS was tried in depressed patients. Grisaru et al[9] reported some improve-

SUBJECTS AND METHODS

SUBJECTS

Seventy-nine inpatients meeting *DSM-IV* criteria for major depression were invited to participate in the study, which was approved by the institutional review board. Seventy patients (53 women and 17 men; mean age, 58.7 years; SD, 17.2 years; age range, 27-88 years) provided written informed consent. **Table 1** summarizes demographic and clinical characteristics of the 2 treatment groups. The 2 groups were matched for age and sex and did not differ significantly on most of the clinical variables, with the exception of melancholic features, which were more prevalent in the TMS group.

Diagnosis was established by 2 senior psychiatrists (I.K. and L.M. or S.M.) following an extended clinical interview and review of past data. All patients scored 15 or above on the Hamilton Depression Rating Scale (HDRS),[17] and none were treatment-resistant (as defined by failing to respond to at least 2 medication trials). All patients were right-handed, based on their self-report, and none had a history of major brain trauma or seizure disorder. None of the patients had a history of substance abuse and all had normal neurological and general physical examination results. Patients were assigned to treatment condition using a computer-generated random number list.

Because at this point we could not ethically justify discontinuation of potentially helpful pharmacotherapy, patients were maintained with their previous medication regimen throughout the course of the study. The groups were matched on frequency and type of adjunctive pharmacotherapy. In addition, none of the patients were receiving psychotherapy during the study.

TREATMENT

A magnetic stimulator (Cadwell Inc, Kennewick, Wash) with a 9-cm external diameter circular coil was used in this study. Initially, motor threshold was determined in both groups over the right motor cortex, by finding the minimal intensity that produced a motor response in the left distal wrist muscles. During the treatment, the coil was placed over the right prefrontal area (without crossing the midline) at a point 6 cm anterior to the scalp position at which the motor threshold was determined. In accordance with Chiappa et al,[17] current flow through the coil, during all phases, was in the clockwise direction.

Stimulation parameters were frequency of 1 Hz, 0.1-millisecond pulse duration, and field intensity of 10% above motor threshold (mean intensity, 1 T; SD, 0.1 T). The treatment protocol consisted of 10 daily sessions during a 2-week period. At each session a train of 60 stimuli was delivered for 1 minute followed by a 3-minute interval and another train of 60 stimuli.

For the sham treatment group, stimulation parameters were the same; however, the stimulation coil was placed perpendicular to the scalp surface without direct contact, thereby minimizing the flow of energy into the skull. The coil position was fixed throughout the TMS sessions and stimulation at this site evoked none or only minimal motor activity in the vicinity of the coil.

CLINICAL RATINGS

Clinical ratings were assessed at baseline (before treatment), after 5 treatment sessions (1 week), and 24 hours after the last rTMS treatment. The HDRS (17-item version)[18] and the Montgomery-Asberg Depression Rating Scale (MADRS)[19] were used to assess depressive symptoms and a 7-point clinical global impression scale was used as a global outcome measure. The rater was a senior psychiatrist (I.K.) who was involved in the diagnostic evaluation but was blind to the nature of treatment, which was delivered outside the department. In addition, the rater avoided asking questions that could disclose the nature of the treatment.

DATA ANALYSIS

To examine the relationship between demographic and clinical characteristics as related to the 2 treatment groups, a set of Student t tests and χ^2 tests were used for continuous and categorical variables, respectively.

To compare the overall effect of treatment over time in the 2 groups, a set of repeated-measures multivariate analyses of variance (MANOVAs [GLM procedure]),[20] one for each dependent variable, was used with treatment as the between-group factor and time as the within-subject factor. Comparisons between the first 2 time points and the last (end of treatment) time point were done using the contrast transformation. Owing to technical reasons, 15 patients (6%) were not administered the MADRS at either the second or third time points. To apply multivariate techniques, without affecting the representativeness of the analyzed sample (multivariate procedures delete cases with any missing values), we imputed those missing data using the minimum generalized variance method (PRINQUAL procedure).[20]

Differences in dichotomous outcome measures (eg, ≥50% reduction in depression ratings) were assessed using χ^2 tests (FREQ procedure).[20]

ment in depressed patients following a single TMS session and Kolbinger et al[10] demonstrated a measurable antidepressant effect of repetitive TMS (rTMS) in 15 depressed patients. George et al,[11] employing rTMS at a high frequency (25 Hz), showed a marked beneficial effect in 4 of 6 patients with medication-resistant depression. Pascual-Leone at al[12] and George et al[13] found, in 2 sham-controlled crossover studies, that rTMS administered to the left dorsolateral prefrontal cortex resulted in a significant decrease in depression scores in patients with major depression. In a recent uncontrolled study[14] we showed that slow rTMS (1 Hz) given to the right prefrontal region produced a significant improvement of depressive symptoms in 7 of 14 patients with major depression, and a modest improvement in 4 of 10 patients with schizophrenia. Lastly, it has recently been shown that target symptoms in patients with obsessive-compulsive disorder

Table 1. Demographic and Clinical Characteristics of the 2 Study Groups*

	TMS (n = 36)	Sham TMS (n = 34)	Significance Test
Demographics			
Mean (SD) age, y	60.5 (15.1)	58.9 (18.3)	−0.5, $df = 68$, NS
Sex, F/M	29/7	24/10	0.9, $df = 1$, NS
Clinical characteristics			
Unipolar/bipolar depression	29/7	28/6	0.0, $df = 1$, NS
Melancholic depression, yes/no	27/9	18/16	3.7, $df = 1$, $P = .05$
Psychotic depression, yes/no	9/27	7/27	0.2, $df = 1$, NS
Clinical history			
Past major depressive episode, yes/no	29/7	20/14	3.9, $df = 1$, $P < .05$
Mean (SD) No. of hospitalizations	3.4 (2.2)	2.5 (2.0)	−1.6, $df = 68$, $P < .10$
Suicide attempts, yes/no	9/27	13/21	1.4, $df = 1$, NS
Previous ECT, yes/no	10/26	8/26	0.2, $df = 1$, NS
Adjunctive treatment			
SSRI	13	14	0.2, $df = 1$, NS
TCA	4	5	0.2, $df = 1$, NS
Other antidepressants	5	4	0.1, $df = 1$, NS
Lithium	4 (concomitant) 1 (monotherapy)	3 (concomitant)	0.4, $df = 1$, NS
Carbamazepine	1 (concomitant)		0.0, $df = 1$, NS
No medications	13	11	0.1, $df = 1$, NS

*Data are presented as number of patients unless otherwise indicated. TMS indicates transcranial magnetic stimulation; ECT, electroconvulsive therapy; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; and NS, not significant.

were partially ameliorated after a single session of rTMS.[15]

The role of various stimulation parameters has not yet been assessed but seems important for the clinical outcome of TMS. The current convention, as adopted in the last international rTMS safety conference (Bethesda, Md, June 1996), is to distinguish TMS from rTMS at a cutoff point of 1 Hz.

The use of rTMS in the high-frequency range (>20 Hz) has been associated in some cases with the induction of seizures.[16] Therefore, lower frequency rates of rTMS are potentially advantageous if clinical efficacy can be demonstrated.

The present study was designed to extend previous studies, including our own preliminary observations, and further assess the efficacy of rTMS in a cohort of patients with major depression under double-blind conditions.

RESULTS

Sixty-seven of the 70 patients who initially started the study completed the entire treatment protocol. The other 3 patients (1 in the TMS group and 2 in the sham group) withdrew after 5 sessions for clinical reasons.

ADVERSE EFFECTS

Generally the treatment was well tolerated and no serious adverse effects were reported by any of the patients. Five patients (14%) in the rTMS group reported a slight discomfort due to facial muscle twitches, which required lowering of the stimulus intensity by 10% during subsequent treatment ses-

sions. Three rTMS patients (9%) reported a mild to moderate headache that lasted a few hours after treatment and responded favorably to paracetamol. None of the patients complained about memory, concentration, or other cognitive difficulties. No adverse effects were reported by subjects in the placebo group.

TREATMENT EFFICACY

Table 2 presents the scores on the clinical rating scales over time in the 2 groups. Baseline ratings were similar in the 2 groups. A clear difference between the 2 groups was noted after the first week, and became robust after the second week, with the rTMS group showing a greater reduction in depression scores. The overall MANOVA revealed a significant group × time interaction for HDRS (Wilks λ $F_{2,64} = 3.29$, $P < .03$) and for MADRS (Wilks λ $F_{2,64} = 3.2$, $P < .05$). The MANOVA for the clinical global impression ratings showed the same trend with borderline significance (Wilks λ $F_{2,64} = 2.4$, $P = .09$). Contrast transformation showed a significant group × time interaction for the interval between baseline and week 2 for HDRS ($F_{1,65} = 7.9$, $P < .01$) and MADRS ($F_{1,65} = 5.7$, $P < .02$).

Even though the groups were matched for medication status, we repeated the same MANOVAs adding adjunctive treatment as a covariate to further rule out this factor as a possible explanation for the difference between the groups. This did not change the pattern of results, as previously mentioned.

We also analyzed our data in a dichotomous fashion using a criterion of 50% or more reduction in HDRS or MADRS scores following treatment, as compared with baseline. In the TMS group, 17 patients (49%) had a reduction of 50% or more on at least 1 of

Table 2. Scores on the Clinical Rating Scales of the 2 Groups Over Time*

	Baseline		Week 1		End of Treatment		ANOVA (Group × Time)	
	TMS (n = 35)	Placebo (n = 32)	TMS (n = 35)	Placebo (n = 32)	TMS (n = 35)	Placebo (n = 32)	$F_{2,64}$	*P*
HDRS	25.8 (5.6)	25.3 (6.4)	16.6 (7.8)	20.8 (9.7)	13.7 (9.2)	19.7 (10.3)	3.3	.03
MADRS	34.5 (5.4)	34.0 (7.6)	21.8 (10.3)	28.8 (11.4)	19.5 (12.2)	27.3 (11.5)	3.2	.05
CGI	4.9 (0.8)	4.9 (0.8)	3.9 (1.1)	4.4 (1.4)	3.5 (1.4)	4.2 (1.5)	2.4	.09

Data are presented as mean (SD) unless otherwise indicated. Only subjects who completed the entire study are included. HDRS indicates Hamilton Depression Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; CGI, clinical global impression;TMS, transcranial magnetic stimulation; and ANOVA, analysis of variance.

their depression scales, while only 8 patients (25%) met this criterion in the sham TMS group. This difference was statistically significant ($\chi^2 = 4.0$, $df = 1$, $P<.05$). Similarly, when using a final HDRS score of 10 or less as improvement criterion, 16 subjects (46%) in the rTMS group, but only 6 (19%) in the placebo group met this criterion. This difference was significant ($\chi^2 = 5.5$, $df = 1$, $P<.02$). Eleven of the 16 rTMS subjects and 4 of the 6 placebo subjects reached this criterion after the first week ($\chi^2 = 3.4$, $df = 1$, $P = .06$). Improvement in the rTMS group was not related to clinical characteristics, such as melancholia, psychotic features, or bipolar illness (Fisher exact test, $P=.75$, .38, and .14, respectively).

Furthermore, 15 patients in the rTMS group and 13 in the placebo group were initially (ie, before participation in the study) considered for electroconvulsive therapy (ECT). Eventually only 7 patients (47%) in the rTMS group but all 13 subjects in the placebo group went on to receive ECT. This difference was significant (Fisher exact test, $P = .002$); however, the proportion of patients who responded to ECT in each group was not significantly different (Fisher exact test, $P = .27$). The decision to administer ECT after the rTMS trial was made blindly with regard to the rTMS treatment status.

COMMENT

The results of this placebo-controlled study show that right prefrontal rTMS in the low-frequency range of 1 Hz has beneficial effects in patients with major depression. These results support and expand results from previous studies, including our own preliminary report.[11-14]

Furthermore, we believe that these results are not only statistically significant but also clinically meaningful. This was evidenced by the fact that rTMS prevented the need for ECT in more than 50% of the patients for whom it was initially planned, but not for any of the subjects in the placebo group. Moreover, while 46% of the rTMS patients reached subclinical scores on the HDRS (<10) at the end of the study, only 19% in the placebo group met this criterion.

Our results suggest that the therapeutic effect of rTMS may be comparable to that of ECT, at least in the short term. However, this beneficial effect was obtained without producing a seizure, which is necessary for the clinical efficacy of ECT.[21,22] When used in the high-frequency range, rTMS delivers more energy within a given time unit as compared with rTMS in lower frequencies. This might account for the seizure-producing potential of high-frequency rTMS. Our results show that low-frequency rTMS, which seems to be safer owing to its lack of proconvulsant effects, is therapeutically efficacious. Clearly, comparative data on the efficacy of rTMS and ECT, which are not available, are needed.

The published studies on the efficacy of rTMS in depressed patients differ substantially in their design and stimulus parameters. Kolbinger et al[10] reported improvement in 15 patients with major depression who received low-frequency TMS (0.25-0.5 Hz) over the vertex on 5 consecutive days. Grisaru et al,[9] also using low-frequency rTMS (1 Hz) to the vertex of 10 depressed patients, found mild improvement in 5 subjects 1 hour after a single treatment session. George et al, using left prefrontal, focal rTMS at a high frequency, reported in an open study,[11] and later in a placebo-controlled crossover study,[13] beneficial effects in patients with medication-resistant major depression. Finally, Pascual-Leone et al[12] studied the effects of focal rTMS (10 Hz) in 17 medication-resistant patients with psychotic major depression in a sham-controlled crossover design. All patients were treated with nimodipine, and 76% received concomitant antidepressant medications. Their results showed that left dorsolateral prefrontal rTMS, but not of other cortical regions, resulted in a significant reduction in depression scores in 11 of 17 patients after 5 treatment sessions. These effects lasted for about 2 weeks.

Our study, which used the same protocol as in our earlier uncontrolled study,[14] differs from previously published studies in several aspects. First, the treatment protocol was longer than in most other studies and resembles the duration and number of treatments of a typical ECT course. Second, we found our effect with right prefrontal stimulation, while Pascual-Leone[12] and George et al[8,13] reported improvement following left prefrontal stimulation. The other 2 studies[9,10] used the vertex as the stimulation site. The decision to use right prefrontal stimulation in our study was based on studies with normal volunteers,[5-7] which found mood eleva-

tion following right prefrontal stimulation, as well as on the assumption that adverse effects associated with stimulation of the nondominant prefrontal region might be less pronounced.

Third, we used a circular coil, while the other 3 studies[11-13] that examined lateralized stimulation used a figure-8 coil. The 2 types of coils differ substantially, since a figure-8 coil produces focal stimulation under the center of the coil while a circular coil causes diffuse stimulation of the cortical area under the coil. Thus, it is likely that a larger cortical area was stimulated in our study. In addition, the human cortex is sensitive to the direction of current flow in the coil, and with circular coils this effect is more pronounced. This results in a lower threshold in the right motor cortex for a current flow in the clockwise direction (in the coil), and in the left motor cortex for a current flow in counterclockwise direction.[23] Since right cortical stimulation was used in this study, the coil was positioned with the current flow in the clockwise direction. It is noteworthy that this physiological direction specificity is seen mostly with stimulators that have a predominantly monophasic pulse, while we used a polyphasic pulse stimulator.

Fourth, we used a slow stimulation rate of 1 Hz, while the other studies with lateralized stimulation used higher frequencies ($\geq$10 Hz).[11-13] From an electrophysiological perspective, this difference might be important since stimulation at lower frequencies seems to induce a poststimulation inhibition of the underlying cortex, whereas higher-frequency stimulation increases the excitability of the underlying cortex.[12] It is therefore possible that inhibition of the right prefrontal structures, which might have been the result of our treatment protocol, and excitation of left prefrontal areas, as in the other studies,[11-13] might achieve the same end result as far as antidepressant action is concerned. This explanation is at this point speculative, and determination of the relationship between laterality of stimulation and relief of depression requires further study.

Some further comments regarding our results are noteworthy. Most of our patients received concomitant antidepressant medications during the study. This could account for at least some of the improvement seen in both study groups. However, the preferential improvement noticed in the rTMS group is most likely not the result of medications, since the proportion of patients receiving them was similar in both groups and our statistical analysis failed to show any significant treatment $\times$ drug interaction effect.

The fact that rTMS, despite being generally well tolerated, did induce some mild adverse effects in a small proportion of patients could produce a placebo effect in the rTMS group, or bias the rater. These possibilities are not likely given the small number of patients reporting adverse effects. However, these potential confounds should be directly assessed in future studies. In this regard, adverse effects of rTMS did not seem to be affected by concomitant antidepressant medications, as patients in the rTMS group reported similar frequencies of adverse effects whether or not they were receiving medication. The lack of complaints about cognitive difficulties following rTMS is encouraging but does not preclude more subtle cognitive adverse effects. Thus, neuropsychological assessment, which was not done in this study, should be added to future studies.

Longer and preferably medication-free follow-up studies of TMS outcome are essential in the future. This was not possible in this study; given the ethical limitations mentioned earlier, all patients, responders and nonresponders, were prescribed or continued receiving antidepressant medications immediately after the study. Similarly, patients in the Pascual-Leone et al[12] study, which showed relatively transient effects ($\leq$2 weeks), were not medication free. Since the therapeutic effect of ECT is also transient when not followed by medications, combining rTMS with medications might be required to ensure a long-lasting effect.

In conclusion, our results support the therapeutic potential of rTMS in the low-frequency range of 1 Hz for major depression. Further evaluation of the therapeutic efficacy of rTMS should assess the importance of various treatment parameters such as frequency, intensity, pulse duration, and stimulation site for its optimal outcome. The suggestion that rTMS may become, in some cases, an alternative treatment to ECT seems promising but still needs further investigation.

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