Utility of repetitive transcranial magnetic stimulation as an augmenting treatment method in treatment-resistant depression

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ABSTRACT

Background: About 30–46% of patients with major depressive disorder (MDD) fail to fully respond to initial antidepressants. Treatment-resistant depression is a severely disabling disorder with no proven treatment options; novel treatment methods, such as repetitive transcranial magnetic stimulation (rTMS) can be used as augmentation to ongoing pharmacotherapy or as a solitary method of treatment.

Aim: To evaluate the utility of rTMS as an augmenting method in treatment-resistant depression.

Materials and Methods: In an open-label study, 21 patients with DSM-IV MDD without psychotic features who had failed to respond to an adequate trial of at least 2 antidepressants were given rTMS therapy for 4 weeks keeping the dose of pre-existing antidepressants unchanged. High-frequency (10 Hz) stimulations were delivered over left dorsolateral prefrontal cortex at an intensity of 110% of the patient’s motor threshold. Treatment response was defined as a reduction in score on the Hamilton Rating Scale for Depression (HAM-D) from baseline to end of treatment. Secondary efficacy measures included scores on the Clinical Global Impressions-Change and -Severity scales.

Results: At the end of 4 weeks, 19 patients completed the 4 weeks study and were assessed. In ITT analysis the mean HAM-D17 scores were reduced from 30.80±5.00 to 19.00±6.37 (t=8.27, P<0.001). Only 4 patients reported headache but there was no discontinuation due to adverse effects.

Conclusions: The study indicates the potential utility of rTMS as an augmenting agent in treatment-resistant depression. Adequately powered, randomized controlled trials are necessary to evaluate the role of rTMS in treatment-resistant depression.

Key words: Transcranial magnetic stimulation, treatment-resistant depression
about 15% of the general population and accounting for approximately 10% of consultations in primary care. The World Health Organization (WHO) has ranked MDD as the fourth most disabling disorder. Despite pharmacologic advances in the treatment of MDD, 30%–46% of patients fail to respond adequately to their initial antidepressants and only 25%–35% achieve symptom remission. Patients with MDD who show partial or no response to an adequate trial of 1 or more antidepressants are considered to have treatment-resistant depression (TRD). Between 10% and 30% of depressed patients taking an antidepressant are partially or totally resistant to the treatment. Comorbid psychiatric and medical disorders, poor compliance, and adverse effects of pharmacotherapy are few causes of partial or nonresponse. The primary aim of the present study was to assess whether augmentation with rTMS would benefit patients with MDD who did not demonstrate significant clinical improvement with adequate trial of a standard antidepressant. The secondary aim was to assess the tolerability and adverse effect profile of this novel treatment method.

Technical parameters
Most of the studies have evidence in support of high-frequency pulsed application over left prefrontal cortex. High-frequency (more than 3 Hz) rTMS, when applied to the motor cortex, generates motor-evoked potentials of progressively increasing amplitude leading to cortical excitability correlated with increased regional cerebral blood flow. With the rTMS use in depression, different hypotheses about pathophysiology of depression have been suggested by researchers. Patients with global cerebral hypometabolism responded better to excitatory treatment, while hypermetabolism was associated with response to inhibitory TMS. Another is that TMS affects a lateralized element of mood control. Observations of decreased glucose metabolism and excitability and localized areas of reduced volume in the left cortex as well as data from stroke victims have suggested a relative hypofunctioning of the left frontal lobe in depression. The longer course duration was consistent with better results in depressed patients. Similarly, previous studies have suggested that more intense magnetic pulses (100–110% of motor threshold) and higher number of pulses per day (about 1200–1600) result in better outcome. Most researchers have used the dorsolateral prefrontal cortex as a site for application of magnetic pulses. Methods to accurately target TMS on the basis of mapping of brain anatomy by MRI have been described. It will be useful to test whether anatomical accuracy enhances clinical efficacy.

MATERIALS AND METHODS
Design
This was a prospective, 4-week, open-label, study to assess the clinical utility and safety of the repetitive transcranial stimulation as an augmenting treatment method to antidepressant therapy in treatment-resistant depression. The study was conducted between February and June 2009.

Subjects
The subjects were recruited from out-patient psychiatric department of Deva Mental Health Care, Deva Institute of Health Care and Research, Varanasi. Inclusion criteria were patients with diagnosis of MDD without psychotic features (defined by DSM-IV criteria); a 17-item Hamilton Depression Score (HAM-D17) more than 20 at screening; at least two adequate trials of antidepressant medications. Exclusions were DSM-IV criteria for organic mood disorder, substance use disorder, neurologic disorders, pregnancy; cardiac pacemakers, any metallic implant; psychiatric symptoms of significant severity that patients could not tolerate a 4-week trial of rTMS or would require psychiatric hospitalization; acute, unstable medical conditions. No change of medication was acceptable after inclusion into the study. A written informed consent was obtained by all participants prior to participation.

Stimulation in our study
Stimulation was applied to the left dorsolateral prefrontal cortex by holding the coil flat on the scalp with the intersection of the two wings centered over the stimulation position. Stimulation of the left prefrontal cortex refers to rTMS with the coil centered along the lateral convexity 5 cm rostral to the optimal position for induction of motor-evoked potentials in the abductor pollicis brevis muscle in the contralateral hand. Wassermann et al have shown that the optimal scalp position for induction of motor-evoked potentials in hand muscles using TMS corresponds to activation of the hand area representation of the anterior bank of the central sulcus, that is, primary motor cortex. Stimulation was applied at 110% of the subject’s motor threshold, was determined by the method of limits, and was defined as the lowest stimulation intensity capable of inducing motor-evoked potentials in the right abductor pollicis brevis muscle with the coil centered over the optimal scalp position.

In our study, the rTMS therapy was given on 5 consecutive days every week and thus a total of 20 therapy sessions over 4 weeks. Stimulation was delivered in trains of 5-s duration and 10-Hz stimulation frequency. In each stimulation session, each subject received 25 trains of stimulation separated by 25-s pauses. Each stimulation session, therefore, lasted nearly 10 min, and each subject received a total of 625 stimuli per session.

Outcome measures and assessment
The MINI was used to diagnose MDD and exclude other diagnoses. The HAM-D17 and the Clinical Global Impressions-Severity (CGI-S) and Clinical Global
Impressions-Change (CGI-C) scales were used to assess the response to the treatment method. The primary efficacy measure was defined as a reduction in HAM-D17 score from baseline to end of treatment. The HAM-D (also known as the HDRS) is the most widely used clinician-administered depression assessment scale. The original version contains 17 items (HAM-D17) pertaining to symptoms of depression experienced over the past week. Secondary efficacy measures were defined as a CGI-I score of 1 or 2 at end of treatment and a 1-point reduction in CGI-S score from baseline to end of treatment. The CGI score reflects the rater’s impression of participant’s illness severity at a given point of time. Tolerability was assessed by recording of adverse effects, which were reported by patients.

Scores on depression rating scales administered to study subjects before, during, and after the treatment sessions were completed at 4 weeks.

Data analysis

Data analysis was done using the Statistical Package for the Social Sciences (SPSS 17.0; SPSS, Inc., Chicago, IL, USA). Paired t tests were employed to compare changes in HAM-D17 (primary outcome), CGI-I, and CGI-S scores from beginning to end of treatment. An intent-to-treat analysis with last observation carried forward (ITT with LOCF) examining all patients enrolled in the trial and a complete analysis for all subjects who completed the 4-week study were performed.

RESULTS

Subjects

Total 23 patients were screened for the study and 21 were found eligible for the study. Two patients were screen failed; both of them had suicide ideations at screening and needed hospitalization. The mean SD age for the sample size was 38±8.35 years. Thirteen were males and 8 were females. The sample was homogenous since all subjects were from the same sociocultural background. The mean duration of current episode of illness was 36.57 months with SD of ±16.41. All the patients were on combination of either two or more than two antidepressants or antidepresants and augmenting agents. All the subjects have failed at least one trial of antidepressant or combinations during the current episode of illness. Nineteen patients (90.47%) completed the study; one patient withdrew the consent and one was lost to follow-up. None of the patients was discontinued due to adverse effects. All subjects completing the study received a total of 20 treatment sessions.

Efficacy measures

In ITT analysis, the mean±SD HAM-D17 score at baseline was 30.80±5.00 and at the end of 4 weeks was 19.00±6.37 and the reduction proves to be significant (t=8.27, P<0.001).

The change in CGI-S score showed evidence of significance determined by paired t test (t=7.071, df=20, P<0.001).

At the end of 2 weeks, all the 21 patients were assessed; 2 patients had slight increase in total HAM-D score and one had no change. On clinical global impression of change (CGI-C) 11 of 21 patient had scores of either 2 (very improved) or 3 (minimally improved).

At the end of 4 weeks, 19 patients completed the 4 weeks study and were assessed. All of them had reduction in total scores on HAM-D. On CGI-C scale, 12 patients were either very improved or very much improved. Only 2 patients did not show significant change over 4 weeks treatment. Two patients discontinued after 2 weeks assessments and before 4 weeks assessments.

Safety measures

Only 4 patients reported headache and pain over left scalp area during treatment period and in all cases the pain stopped immediately with cessation of the rTMS treatment. Two patients required analgesic for treatment of headache. There was no discontinuation due to headache or any other adverse effect. No patient developed a new onset of seizures during the course of rTMS treatments. No patients complained of any memory or cognitive side effects during rTMS. rTMS had no effect on any patient’s blood pressure or heart rate during the treatments.

DISCUSSION

The most important finding of this study is that rTMS may be used safely and effectively as an augmenting treatment method in patients with treatment refractory depression.

In a similar study in past, 21 of 50 patients with depression (42%) responded to rTMS.[17-18] In a significant study by Pascual-Leone et al., 11 of 17 depressed patients (65%) responded to rTMS. Consistent with the studies by Pascual-Leone et al. and Figiel et al., all the subjects in our study were medication resistant and were receiving combination of antidepressants. The rTMS protocol used in our study was similar to that of Pascual-Leone et al. In our study the therapeutic benefits of rTMS were observed after 10 rTMS treatments by stimulating the left prefrontal cortex. We used higher magnetic field intensity (110% motor threshold) than was used in the Pascual-Leone et al. study (90% motor threshold) and a shorter stimulus train with far fewer total pulses per session (500 vs 2000 pulses, 5 vs 20 min). Clearly, additional placebo-controlled rTMS depression studies are required that examine the potential effects of different protocols on the therapeutic response from rTMS.[19]

Although the antidepressant mechanisms of action for ECT and rTMS remain unknown, recent works are beginning to examine the neurochemical basis for rTMS and its effects on several animal behavioral models.[20] Similar to ECT
and antidepressants, rTMS may alter brain monoamines. Regional alterations in dopamine, serotonin, and 5-hydroxyindoleacetic acid levels have been reported with rTMS. A recent SPECT study in healthy adults that used left prefrontal rTMS demonstrated that compared to baseline, there was reduced blood flow at the coil site and in the anterior cingulate during stimulation, with increases in brainstem activity.\(^{[21]}\) Previous studies have demonstrated that rTMS at similar parameters over the prefrontal cortex results in increases in serum thyroid-stimulating hormone, which suggests the possibility of increases in thyrotropin-releasing hormone and an indirect effect of rTMS on hypothalamo-pituitary structures.\(^{[12,22,23]}\) Finally, like antidepressants and ECT, rTMS can significantly decrease the number of beta-adrenergic receptors in certain parts of the rat’s brain.\(^{[24]}\) On the basis of these works, it is not unreasonable to expect that further rTMS studies will enhance our understanding of the pathophysiology of depression and may ultimately lead to the development of safer, more effective treatments for depression.

In our study, not a single patient reported seizures during rTMS treatments like in the study by Pascual-Leone et al. Headaches were the most common complaint; however, these were minor in most patients and none of them needed to discontinue from study. There were no observed cardiovascular or neurologic complications in any patients. This is of potential significance given the high incidence of co-morbid depression in many of our elderly patients. None of our patients complained of memory impairment or cognitive side effects from rTMS. These observations are consistent with previous safety reports on rTMS.

In summary, rTMS appears to be safe and effective in treating some medication-resistant depressed patients. However, the therapeutic benefits of rTMS appear to be greater in younger patients. More research is needed to identify the ways to sustain the therapeutic benefits of rTMS and to identify the optimum techniques for its administration. The potential neurobiological and clinical predictors of response to rTMS will also need further study.

**LIMITATIONS**

The principal limitations of this study were the small sample size, an open-label design, and lack of a placebo arm. Additional limitations of the study include the retrospective definition of treatment resistance and a relatively short duration of study. All these limitations did not permit us to study whether the antidepressant efficacy of augmentation with rTMS is maintained following the initial improvement.

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Source of Support: Nil. Conflict of Interest: None declared.