Utility of Repetitive Transcranial Stimulation as an Augmenting Treatment Method in Treatment-Resistant Depression

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ABSTRACT

About 30 to 46% of patients with major depressive disorder (MDD) fail to fully respond to initial antidepressants. Treatment-resistant depression (TRD) is a severely disabling disorder with no proven treatment options; novel treatment methods like rTMS can be used as augmentation to ongoing pharmacotherapy or as a solitary method of treatment. To evaluate the utility of repetitive transcranial magnetic stimulation as an augmenting method in TRD. 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 intensity of 110% of 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. At the end of 4 weeks, 19 patients completed the 4-week 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 four patients reported headache, but there was no discontinuation due to adverse effects. The study indicates the potential utility of rTMS as an augmenting agent in TRD. Adequately powered, randomized controlled trials are necessary to evaluate the role of rTMS in TRD.

Key words: *Transcranial magnetic stimulation, treatment-resistant depression, major depressive disorder*

INTRODUCTION

Transcranial magnetic stimulation (TMS) is a noninvasive application of pulsed magnetic field near an area of scalp, which causes depolarization of neurons in underlying part of cerebral cortex. At cellular level, mechanisms of electroconvulsive therapy (ECT) and TMS are the same.[1] In psychiatry, the application of rTMS was tested including major depressive disorder (MDD)[2,3] which was based on observation that a single pulse of magnetic stimulation elevated the mood for some period, though it was transient. Current challenges in the field include determining how to enhance the efficacy of rTMS in the psychiatric disorders and how to identify patients for whom rTMS can be a useful method of treatment.

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Depression is a common disorder with serious personal, interpersonal, and societal consequences, affecting about 15% of the general population and accounting for approximately 10% of consultations in primary care.[4] The World Health Organization has ranked MDD as the fourth most disabling disorder.[5] Despite

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pharmacologic advances in the treatment of MDD, 30 to 46% of patients fail to respond adequately to their initial antidepressants and only 25 to 35% achieve symptom remission.[6] Patients with MDD who show partial or no response to an adequate trial of one or more antidepressants are considered to have treatment-resistant depression (TRD).[7] Between 10 and 30% of depressed patients taking an antidepressant are partially or totally resistant to the treatment.[8] Comorbid psychiatric and medical disorders, poor compliance, and adverse effects of pharmacotherapy are few causes of partial or nonresponse.[9] 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 by increased regional cerebral blood flow.[10] With the rTMS use in depression, different hypothesis about pathophysiology of depression have been suggested by the researchers. Patients with global cerebral hypometabolism responded better to excitatory treatment, whereas hypermetabolism was associated with response to inhibitory TMS.[11] 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.[12,13] The longer course duration was consistent with better results in depressed patients.[14] Similarly, previous studies have suggested that more intense magnetic pulses (100-110% of motor threshold)[2] and higher number of pulses per day (about 1 200-1 600) 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.[15] 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 TRD. The study was conducted between February 2009 and June 2009.

Subjects

The subjects were recruited from outpatient 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 (HAMD17)[16] more than 20 at screening; and at least two adequate trials of antidepressant medications. Exclusions were DSM-IV criteria for organic mood disorder, substance use disorder, neurological 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; and 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, which 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 four weeks. Stimulation was delivered in trains of 5 seconds' duration and 10 Hz stimulation frequency. In each stimulation session, each subject received 25 trains of stimulation separated by 25-second pauses. Each stimulation session, therefore, lasted nearly 10 minutes, 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 the end of treatment and a 1-point reduction in CGI-S score from baseline to the 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). 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

A total of 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. Of the 21 patients, 13 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 antidepressants and augmenting agents. All the subjects have failed at least one trial of antidepressant or combinations during the current episode of illness. Of all, 19 patients (90.47%) completed the study, one patient withdrew the consent, and one was lost to follow-up. None of the patient 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 21 patients were assessed; 2 patients had slight increase in total HAM-D score and one had no change. On CGI-C, 11 of 21 patients had scores of either 2 (very improved) or 3 (minimally improved).

At the end of 4 weeks, 19 patients completed the 4-week 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-week treatment. Two patients disconinued before the assessment at 4th week.

Safety measures

Only four 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 patient 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] A significant study by Pascual-Leone *et al.* reported that 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 study (90% motor threshold) and

a shorter stimulus train with far fewer total pulses per session (500 *vs* 2 000 pulses, 5 *vs* 20 minutes). 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 repetitive TMS demonstrated that compared with 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 repetitive TMS 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 repetitive TMS on hypothalamo-pituitary structures.[3,22,23] 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 neurological complications in any patients. This is of potential significance given the high incidence of comorbid 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.

REFERENCES

1. Barker AT. An introduction to the basic principles of magnetic nerve stimulation. J Clin Neurophysio 1991;8:26-37.
2. George MS, Nahas Z, Molloy M, Speer AM, Oliver NC, Li X, *et al.* A controlled trial of daily left prefrontal cortex TMS for treating depression. Biol Psychiatry 2000;48:962-70.
3. George MS, Wassermann EM, Williams WA, Callahan A, Ketter TA, Basser P, *et al.* Daily repetitive transcranial stimulation (rTMS) improves mood in depression. Neuroreport 1995;6:1853-6.
4. Ormel J, Tiemens B. Depression in primary care. In: Honig A, van Praag HM, editors. Depression: Neurobiological, Psychopathological and Therapeutic Advances. Chichester, UK: John Wiley; 1997.
5. Murray, CJL, Lopez AD. The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Disease, Injuries, and Risk Factors in 1990 and Projected to 2020, Vol. 1. Cambridge MA: Harvard University Press; 1996.
6. Fava M. Diagnosis and definition of treatment-resistant depression. Biol Psychiatry 2003;53:649-9.
7. Nierenberg AA, Dececco LM. Definitions of antidepressant treatment response, remission, nonresponse, partial response, and other relevant outcomes: A focus on treatment-resistant depression. J Clin Psychiatry 2001;62:5-9.
8. Joffe RT, Levitt AJ, Sokolov ST. Augmentation strategies: Focus on anxiolytics. J Clin Psychiatry 1996;57:25-31.
9. Phillips KA, Nierenberg AA. The assessment and treatment of refractory depression. J Clin Psychiatry 1994;55:20-6.
10. Pascual-Leone A, Valls-Solé J, Wassermann EM, Hallett M. Responses to rapid-rate transcranial magnetic stimulation of the human motor cortex. Brain 1994;117:847-58.
11. Kimbrell TA, Little JT, Dunn RT, Frye MA, Greenberg BD, Wassermann EM, *et al.* Frequency dependence of antidepressant response to left prefrontal repetitive transcranial magnetic stimulation (rTMS) as a function of baseline cerebral glucose metabolism. Biol Psychiatry 1999;46:1603-13.
12. Menkes DL, Bodnar P, Ballesteros RA, Swenson MR. Right frontal lobe slow frequency repetitive transcranial magnetic stimulation (SF rTMS) is an effective treatment for depression: A case-control pilot study of safety and efficacy. J Neurol Neurosurg Psychiatry 1999;67:113-5.
13. Grisaru N, Chudakov B, Yaroslavsky Y, Belmaker RH. Transcranial magnetic stimulation in mania: A controlled study. Am J Psychiatry 1998;155:1608-10.
14. Pridmore S, Bruno R, Turnier-Shea Y, Reid P, Rybak M. Comparison of unlimited numbers of rapid transcranial magnetic stimulation (rTMS) and ECT treatment sessions in major depressive episode. Int J Neuropsychopharmacol 2000;3:129-34.
15. Herwig U, Schonfeldt-Lecuona C, Wunderlich AP, von Tiesenhausen C, Thielscher A, Walter H, *et al.* The navigation

of transcranial magnetic stimulation. Psychiatry Res 2001;108:123-31.
16. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56-62.
17. Epstein C, Figiel GS, Amazon-Leece J, Figiel L. Rapid-rate transcranial magnetic stimulation in young and middle-aged refractory depressed patients. Psychiatric Ann 1998;28:36-9.
18. Figiel GS, Epstein C, McDonald WM, Amazon-Leece J, Figiel L, Saldivia A, *et al.* The use of rapid-rate transcranial magnetic stimulation (rTMS) in refractory depressed patients. J Neuropsychiatry Clin Neurosci 1998;10:20-5.
19. Isenberg K, Downs D, Pierce K, Svarakic D, Garcia K, Jarvis M, *et al.* Low frequency rTMS stimulation of the right frontal cortex is as effective as high frequency rTMS stimulation of the left frontal cortex for antidepressant-free, treatment-resistant depressed patients. Ann Clin Psychiatry 2005;17:153-9.
20. Fleischmann A, Prolov K, Abarbanel J, Belmaker RH. The effect of transcranial magnetic stimulation of rat brain on behavioral models of depression. Brain Res 1995;699:130-2.
21. Stallings LE, Speer AM, Spicer KM, Cheng KT, George MS. Combining SPECT and repetitive transcranial magnetic stimulation (rTMS)-left prefrontal stimulation decreases relative perfusion locally in a dose dependent manner (abstract). Neuroimage 1997;5:S521.
22. Avery D, Holtzheimer PE, Fawaz W, Russo J, Neumaier J, Dunner D, *et al.* A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. Biol Psychiatry 2006;59:187-94.
23. Berman RM, Narasimhan M, Sanacora G, Miano AP, Hoffman RE, Hu XS, *et al.* A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. Biol Psychiatry 2000;47:332-7.
24. Klein E, Ben-Shachar D, Grisaru N. Effects of rTMS on brain monoamines, receptors and animal models of depression. Presented to Biological Psychiatry Conference, San Diego, CA: May 1997.

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