Efficacy of Adjuvant High Frequency Repetitive Transcranial Magnetic Stimulation on Negative and Positive Symptoms of Schizophrenia: Preliminary Results of a Double-Blind Sham-Controlled Study

Nishant Goyal, D.P.M.
S. Haque Nizamie, M.D., D.P.M.
Pushpal Desarkar, M.D., D.P.M.

The potential effect of repetitive transcranial magnetic stimulation (rTMS) on core positive and negative symptoms in schizophrenia has not yet been clearly established. The aim of this study was to examine the efficacy of adjuvant 10 Hz, suprathreshold left prefrontal rTMS in negative symptoms of schizophrenia in a double-blind sham-controlled design. Additionally, our study also investigated the suitability of applying the same stimulus condition on positive symptoms. Ten right-handed schizophrenia patients received sham or active 10 Hz suprathreshold rTMS to the left dorsolateral prefrontal cortex with psychopathology, depression and global improvement ratings before and after rTMS sessions. Compared to sham, active rTMS significantly improved negative symptoms, irrespective of change in depressive symptoms.

(The Journal of Neuropsychiatry and Clinical Neurosciences 2007; 19:464–467)

Transcranial magnetic stimulation (TMS) is a promising new therapeutic tool that could benefit schizophrenia patients. However, the potential effect of transcranial magnetic stimulation (TMS) on core negative and positive symptoms of schizophrenia has not yet been clearly established. Negative symptoms in schizophrenia affect the course of the disease adversely and impair social functioning more than do positive symptoms. Successful control of negative symptoms constitutes a great clinical challenge. Several initial studies on negative symptoms have suggested that the condition seems to respond to high frequency (20 Hz, 10 Hz) repetitive transcranial magnetic stimulation (rTMS).[1–4] However, significant methodological limitations, including an open design, lack of predefined stimulation parameters and randomization, limited these earlier findings. Recently, one trial by Hajak et al.[5] documented the superiority of 10 Hz rTMS using a sham-controlled parallel design (110% of motor threshold, over left dorsolateral prefrontal cortex), and found statistically significant improvement in negative symptoms of schizophrenia patients. Interestingly, in this study, positive symptoms deteriorated from baseline. However, in another recent study with a similar controlled design, Jandl et al.[6] failed to find significant improvement. In the case of positive symptoms, several initial reports of rTMS have suggested that it may be able to modulate the intensity of persistent auditory hallucinations. Hoffman et al.[7] found that 1 Hz rTMS applied to the left temporoparietal cortex could reduce hallucination severity. However, McIntosh et al.[8] later failed to reproduce the same finding. Furthermore, three recent studies[9–11] using a double-blind, sham-controlled design have given inconsistent results. Significant improvement noticed by Hoffman et al.,[9] using 1 Hz rTMS, was not replicated by Fitzgerald et al.[10] and Saba et al.,[11] who failed to find such differences in their studies. Considering the fact that successful rTMS of schizophrenia may be linked to stimulation frequency and symptom profile, there is a need for further studies to investigate the suitability and efficacy of 10 Hz, suprathreshold rTMS on schizophrenic negative symptoms with a parallel design. Thus, the aim of this study was to examine the replicability of the efficacy of adjuvant 10 Hz, suprathreshold left prefrontal rTMS in negative symptoms of

Received May 30, 2006; revised June 29, 2006; accepted October 17, 2006. Drs. Goyal, Nizamie, and Desarkar are affiliated with the Adult Psychiatry Unit, Central Institute of Psychiatry, Ranchi, Jharkhand, India. Address correspondence to Dr. Desarkar, Department of Child and Adolescent Psychiatry, Central Institute of Psychiatry, Kanke (PO), Ranchi-834006, Jharkhand, India; pushpalds@yahoo.com (e-mail).

schizophrenia in a double-blind sham-controlled design. Our study also investigated the suitability of applying the same stimulus condition on positive symptoms.

METHOD

Ten right-handed male patients meeting ICD-10-DCR (International Classification of Disease, 10th revision, Diagnostic Criteria for Research) criteria for schizophrenia and hospitalized in the Central Institute of Psychiatry, Ranchi, entered the pilot study, which was conducted before a larger trial. Written informed consent was obtained after detailed explanation of the study in the presence of a first-degree relative. None of the patients had a history of brain trauma, seizures, or drug abuse (except nicotine and caffeine), and all had normal neurological and general physical examinations. Patients had been either drug-naïve or drug-free for at least 2 months. Upon entering the study, each consecutively selected patient was allocated to rTMS and sham treatment group alternately with the first patient receiving active rTMS. Patients were started on antipsychotic medications (both typical and atypical, depending on individual clinical need) after entering into the study and were kept on the same dose for the entire duration of the trial. PRN treatment included use of anticholinergic medications and benzodiazepines for both groups. The study strictly followed a double-blind paradigm as both patients and rater remained blind for the given mode of treatment throughout the duration of the study. Mean age of the active group (29.8 [SD = 10.89] years) did not differ from the comparison (26.2 [SD = 7.42] years) group (Mann-Whitney $U = 11.00$, $p = 0.753$). There were no significant group differences on any of the demographic and clinical variables, including duration of illness ($p = 0.341$), age of onset ($p = 0.753$) and the mean dose of antipsychotic drugs expressed in terms of chlorpromazine-equivalent mg/day (Active = 330.0 [SD = 139.64], Sham = 380.0 [SD = 83.66]; Mann-Whitney $U = 11.00$, $p = 0.743$). None of the patients underwent any additional individual psychotherapy except standard milieu therapeutic activities in a naturalistic manner. Magstim Rapid® magnetic stimulator (Magstim Company Ltd, Whiteland, UK) with a figure-eight coil was used for stimulation. Treatment protocol consisted of one daily session 5 days a week for 2 weeks. Each treatment session consisted of active high frequency (10 Hz) stimulation administered (4.9 seconds on and 30 seconds off) 20 times per 20-minute session at 110% of the motor threshold with the coil over the left prefrontal area (tangential to the midline) at a point 5 cm anterior to the scalp position at which the motor threshold had been determined. Determination of motor threshold was performed before each session in both groups using single pulse stimulation over the left primary motor cortex, which was assessed as the lowest intensity that could produce five visible movements of the right abductor pollicis brevis out of 10 stimulations. Sham treatment was administered at 10 Hz with one wing of the figure-eight coil in contact with the scalp and at a 45° angle with respect to the head. The Positive and Negative Syndrome Scale (PANSS)[12] and the Clinical Global Impression (CGI) scale[13] were used to assess schizophrenic symptoms. Clinical ratings were performed before the baseline assessment and then after the last treatment session. Before each session, we specifically asked patients for side effects, and recorded all adverse events spontaneously reported or noted. We used the Calgary Depression Scale for Schizophrenia (CDSS)[14] to assess depressive symptoms and to disentangle them from negative symptoms in both groups before and after treatment. All 10 patients (five rTMS and five sham) completed the 2-week treatment protocol.

Statistics

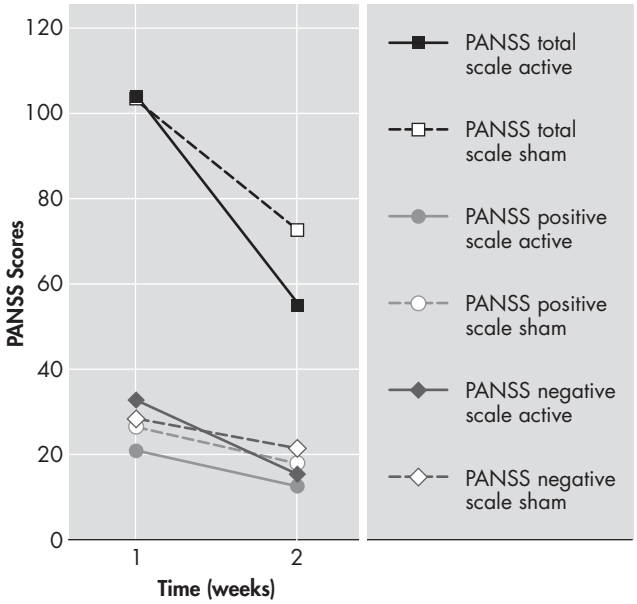
We used chi-square and Mann-Whitney U tests to compare the demographic and clinical characteristics of the two groups. To compare the overall effect of treatment over time for the two groups, we employed a set of multivariate repeat measures analysis of variance (ANOVA), with treatment as the between-group factor and time as the within-subject factor. Because of small sample size, we checked for sphericity assumptions using Mauchly's test of sphericity. Analysis revealed violation of the sphericity rule. Consequently, we performed the Greenhouse-Geisser correction. We used Spearman's rho to see the correlation between negative and depressive symptoms, and analyzed data using the Statistical Package for Social Sciences (SPSS, Inc., Chicago) version 11.0.

RESULTS

Two rTMS patients reported moderate headaches that lasted a few hours after treatment and responded to an-

algesics. No serious adverse effect was reported. Three (60%) patients showed much improvement in the active group compared with sham, where three (60%) patients showed minimal improvement per the CGI-Improvement scale. Repeat measure ANOVA with treatment as the between-group factor revealed that there was significant negative symptoms × group interaction, where improvement was seen more in the active rTMS group at the end of the treatment (Pillai's Trace $F = 12.402$, $p = 0.008$)(Figure 1). Positive scores (Pillai's Trace $F = 0.023$, $p = 0.884$) and PANSS total scores (Pillai's Trace $F = 4.108$, $p = 0.077$) did not show significant interaction with group, though there was a trend in the latter. Depressive symptoms showed a trend toward improvement in the active group (mean CDSS score pretreatment = 3.2 [SD = 4.43]; posttreatment score = 0.00 [SD = 0.00]; Wilcoxon $Z = 1.841$, $p = 0.066$), but not in the sham group (mean CDSS score pretreatment = 3.000 [SD = 3.535]; posttreatment score = 0.800 [SD = 0.836]; Wilcoxon $Z = 1.604$, $p = 0.109$). However, negative symptom scores both before and at the end of treatment did not correlate with corresponding CDSS scores (pretreatment Spearman's $\rho = -0.463$, $p = 0.178$; posttreatment Spearman's $\rho = 0.202$, $p = 0.575$). Furthermore, there was no relationship between changes of negative symptoms and CDSS scores (Spearman's $\rho = 0.308$, $p = 0.614$).

FIGURE 1. Changes of PANSS Scores With Treatment



DISCUSSION

The most robust finding in the present study was that active rTMS showed superiority over sham treatment in treating negative symptoms and this treatment efficacy is not attributable to improvement in depressive symptoms as both negative and depressive symptoms were independent of each other in our study. Interestingly, in our study, PANSS positive score did not improve with active stimulation. The differential efficacy of suprathreshold left prefrontal 10 Hz rTMS on negative symptoms and not on positive symptoms validates Hajak et al.'s[5] report of the efficacy of this stimulation parameter in controlling negative symptoms of schizophrenia and also indicates the nonsuitability of these rTMS stimulation parameters for controlling positive symptoms. As described earlier, significant reduction of negative symptoms in our study could be ascribed to correction of dysfunctional dopaminergic neurotransmission, which is thought to be associated with negative symptoms by suprathreshold, high frequency left prefrontal rTMS.[15] However, use of the same coil to administer sham stimulation along with small sample size comprising only the male population may limit our findings.

References

1. Feinsod M, Sreinen B, Chistyakov A: Preliminary evidence for a beneficial effect of low frequency, repetitive transcranial magnetic stimulation in patients with major depression and schizophrenia. Depress Anxiety 1998; 7:65–68
2. Cohen E, Bernardo M, Masana J, et al: Repetitive transcranial magnetic stimulation in the treatment of chronic negative schizophrenia; a pilot study. J Neurol Neurosurg Psychiatry 1999; 67:129–130
3. Rollink JD, Huber TJ, Mogk H, et al: High frequency repetitive transcranial magnetic stimulation (rTMS) of the dorso-lateral prefrontal cortex in schizophrenic patients. Neuroreport 2000; 11:4013–4015
4. Hoffman RE, Boutros NN: Transcranial magnetic stimulation studies of schizophrenia. Epilepsy Behav 2001; 2:S30–S35
5. Hajak G, Marienhagen J, Langguth B, et al: High-frequency repetitive transcranial magnetic stimulation in schizophrenia: a combined treatment and neuroimaging study. Psychol Med 2004; 34:1157–1163
6. Jandl M, Bittner R, Sack A, et al: Changes in negative symptoms and EEG in schizophrenic patients after repetitive transcranial magnetic stimulation (rTMS): an open-label pilot study. J Neural Transm 2005; 112:955–967
7. Hoffman RE, Boutros NN, Hu S, et al: Transcranial magnetic stimulation and auditory hallucinations in schizophrenia. Lancet 2000; 355:1073–1075
8. McIntosh AM, Semple D, Tasker K, et al: Transcranial magnetic

stimulation for auditory hallucinations in schizophrenia. Psychiatry Res 2004; 127:9–17
9. Hoffman RE, Hawkins KA, Gueorguieva R, et al: Transcranial magnetic stimulation of left temporoparietal cortex and medication resistant auditory hallucinations. Arch Gen Psychiatry 2003; 60:49–56
10. Fitzgerald PB, Benitez J, Daskalakis JZ, et al: A double-blind sham-controlled trial of repetitive transcranial magnetic stimulation in the treatment of refractory auditory hallucinations. J Clin Psychopharmacol 2005; 25:358–362
11. Saba G, Verdon CM, Kalalou K, et al: Transcranial magnetic stimulation in the treatment of schizophrenic symptoms: a double blind sham controlled study. J Psychiatr Res 2006; 40:147–152
12. Kay SR, Fiszbein A, Opler LA: The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13:261–276
13. Guy W, Bonato RR (eds): Manual for the ECDEU Assessment Battery, revised edition. Chevy Chase, Md, National Institute of Mental Health, 1970
14. Addington D, Addington J, Maticka-Tyndale E: Specificity of the Calgary Depression Scale for schizophrenia. Schizophrenia Res 1994; 11:239–244
15. Keck ME, Welt T, Muller MB, et al: Repetitive transcranial magnetic stimulation increases the release of dopamine in the mesolimbic and mesostriatal system. Neuropharmacology 2002; 43:101–109