

Efficacy of Adjunctive High Frequency Repetitive Transcranial Magnetic Stimulation of Right Prefrontal Cortex in Adolescent Mania: A Randomized Sham-Controlled Study

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Objective: To examine the efficacy of adjunctive right prefrontal high-frequency repetitive transcranial magnetic stimulation (rTMS) treatment in adolescent mania patients as compared to sham stimulation.

Methods: Twenty six right handed patients aged 12–17 years diagnosed with bipolar mania were randomized to receive daily sessions of active or sham rTMS (20 Hz, 110% of motor threshold, 20 trains, 10 s intertrain interval) over the right dorsolateral prefrontal cortex for 10 days. Mania was rated using Young Mania Rating Scale (YMRS) and Clinical Global Impression (CGI) at baseline, and after 5th and 10th rTMS.

Results: For YMRS scores, repeated measures analysis of variance (ANOVA) showed a significant main effect ($F=44.49$, degree of freedom [df]=1,2/29,29, $p<0.001$, Greenhouse–Geisser corrected, effect size $\eta^2=0.65$), but the interaction effect was not significant ($F=0.03$, $df=1,2/29,29$, $p=0.912$, Greenhouse–Geisser corrected). For CGI–Severity, repeated measures ANOVA showed a significant main effect ($F=24.49$, $df=1,42/34,21$, $p<0.001$, Greenhouse–Geisser corrected, effect size $\eta^2=0.51$), but the interaction effect was not significant ($F=0.06$, $df=1,2/29,29$, $p=0.881$, Greenhouse–Geisser corrected).

Conclusion: High-frequency right prefrontal rTMS was found to be ineffective as add-on to standard pharmacotherapy in adolescent mania.

KEY WORDS: Adolescent; Bipolar disorder; Mania; Prefrontal cortex; Repetitive transcranial magnetic stimulation.

INTRODUCTION

Bipolar disorder affects young people with a lifetime prevalence of 1% among 14 to 18 year-olds.¹⁾ The therapeutic options available are limited by variable response, adverse effects and are not adequate for many patients. Transcranial magnetic stimulation (TMS) is a noninvasive method in which magnetic field over the surface of the head depolarizes underlying superficial neurons. Repetitive TMS (rTMS) has been found to inhibit or activate cortical areas which is frequency dependent; low-frequency rTMS (< 1 Hz) has an inhibitory effect on cortical excitability and decreases blood flow, whereas high-frequency rTMS (> 5 Hz) may lead to activation of cortical areas and in-

crease blood flow.²⁾

There are very few studies that have examined the efficacy of rTMS in children and adolescents, most of them have focused on depression, and some involves the treatment of the attention deficit hyperactivity disorder (ADHD), autism and schizophrenia.³⁻⁵⁾ There are no major adverse events reported in these studies. High frequency rTMS has been studied for treatment of mania in adults in which improvements were reported after stimulating right prefrontal cortex. Grisaru *et al.*⁶⁾ conducted a double-blind, controlled trial of right vs. left prefrontal rapid rTMS in 16 bipolar mania adult patients and found an improvement in manic symptoms with right rTMS and a worsening with left rTMS. In contrast, another controlled study by Kaptan *et al.*⁷⁾ using right prefrontal rapid rTMS in 19 bipolar mania patients, reported lack of therapeutic effect when compared to sham rTMS. Praharaj *et al.*⁸⁾ in a randomized controlled study on a larger sample ($n=41$) found high-frequency supra-threshold right prefrontal rTMS was well tolerated and effective as

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add-on to standard pharmacotherapy in bipolar, mania patients. There are no published studies on the efficacy of rTMS in adolescent mania patients. Therefore, the current study was carried out to find the therapeutic efficacy and tolerability of add-on right prefrontal high-frequency (rapid) rTMS in adolescent mania patients.

METHODS

Participants

This was a prospective, hospital-based, single-blind, randomized, sham-controlled rTMS study carried out at the Centre for Cognitive Neurosciences, Central Institute of Psychiatry, Ranchi, India. The study was approved by the institutional review board. In this study, 26 right handed, normotensive patients of either sex, aged between 12-17 years with a diagnosis of bipolar disorder, mania according to Diagnostic Criteria for Research of International Classification of Diseases-10⁹) were included in the study. Written informed consent was obtained from the parents prior to the study. Subjects with current neurological or any comorbid psychiatric disorders or history of drug abuse, past history of epilepsy, significant head injury or any neurosurgical procedure, with cardiac pacemakers or other metal parts in the body, or who have received electroconvulsive therapy in past 6 months were excluded from the study. The selected 26 patients were alternatively assigned to receive either active rTMS (n=13) or sham stimulation (n=13), with first patient receiving active treatment.

Tools

A semi-structured pro-forma was used for recording demographic and clinical details. The Hindi version of Handedness Preference Schedule¹⁰ which has 15 items was used to assess hand preference. The 11-item clinician administered Young Mania Rating Scale (YMRS)¹¹ was used to assess severity of manic symptoms. Clinical Global Impression (CGI)¹² was used to assess overall illness severity.

rTMS Procedure

The motor threshold (MT) for the right abductor pollicis brevis was determined using a figure-of-eight shaped coil at 1 Hz frequency according to Rossini-Rothwell algorithm.¹³ According to this algorithm, MT was defined as the lowest intensity, which produced 5 motor evoked potential (MEP) responses of at least 50 μ V in 10 trials. The right prefrontal cortex rTMS stimulation site was de-

termined by measuring 5 cm anterior and in a parasagittal line from the point of maximum stimulation of contralateral abductor pollicis brevis muscle.¹⁴ Daily sessions of 20 Hz rTMS (at 110% of MT, 2 seconds/train, 20 trains/session, 10 seconds intertrain interval, 800 pulses/day) was administered after one week using Magstim Rapid device over the right dorsolateral prefrontal cortex (DLPFC) for 10 days. The sham group was administered rTMS after the first week of admission using same parameters with one wing of the coil at 45° angle with the head; in this position TMS does not produce MEPs but does produce scalp sensations.^{2,14} The stimulation sessions were performed as 'add on' to the ongoing medications as decided by the treating team. YMRS and CGI were administered at baseline (on day 7) and after 5th and 10th rTMS sessions by the first author, VP. The investigators were blind to the medications received by the patients during the study period which were solely decided by the treating team, who were blind to the treatment condition. The patients were blind to the treatment condition.

Statistical Analysis

The data obtained was analyzed using Statistical Package for Social Sciences-version 16.0 for Windows (SPSS Inc., Chicago, IL, USA). Socio-demographic and clinical variables were compared using independent *t*-test and chi-square test, for continuous and categorical variables, respectively. To see the effect of treatment, the mean YMRS and CGI-Severity (CGI-S) scores were compared between active and sham group using two way repeated measures ANOVA. Greenhouse-Geiser correction was applied considering violation of sphericity assumption. Effect sizes were calculated for the effect of treatment. The proportion of patients in each group that achieved remission was determined using chi-square test. Remission was defined as a score of 12 or less in YMRS as used by Tohen *et al.*¹⁵

RESULTS

Sample Characteristics

The socio-demographic and clinical profile of the active and sham group was comparable (Table 1). In the active group, 5 (38.5%) patients received lithium, 3 (23.1%) received carbamazepine, and 5 (38.5%) patients received valproate; whereas, in the sham group, 9 (69.2%) received lithium, 2 (15.4%) received carbamazepine, and 2 (15.4%) patients received valproate. There was no difference between the two groups. The mean motor threshold in the ac-

Table 1. Sample characteristics

Characteristic	Group		t/ χ^2	p value
	Active (n=13)	Sham (n=13)		
Age (yr)	15.38±1.80	16.00±1.22	-1.02	0.319
Education (yr)	8.38±4.21	10.76±2.48	-1.75	0.092
Gender			0.25	0.619
Male	10 (76.9)	11 (84.6)		
Female	3 (23.1)	2 (15.4)		
Socioeconomic status			3.34	0.188
Lower	8 (61.5)	9 (69.2)		
Middle	5 (38.5)	2 (15.4)		
Upper	0	2 (15.4)		
Habitat			0.65	0.420
Rural	7 (53.8)	9 (69.2)		
Urban	6 (46.2)	4 (30.8)		
Family type			1.75	0.185
Nuclear	8 (61.5)	11 (84.6)		
Joint	5 (38.5)	2 (15.4)		
Age of onset of illness (yr)	14.04±2.56	15.31±2.13	-1.36	0.184
Duration of illness (yr)	1.34±1.84	0.73±1.30	0.98	0.335
Total number of episodes	1.38±2.56	0.38±0.51	1.37	0.181
Number of manic episodes	1.07±2.21	0.15±0.37	1.48	0.152
Number of depressive episodes	0.15±0.55	0.23±0.43	-0.39	0.698
Duration of current episode (day)	31.92±30.88	44.76±33.66	-1.01	0.321
Age at first hospitalization (yr)	15.53±2.02	15.15±4.03	0.31	0.762
Family psychiatric illness			0	1
Present	9 (69.2)	9 (69.2)		
Absent	4 (30.8)	4 (30.8)		

Values are presented as mean±standard deviation or number (%).
* $p < 0.05$ (2-tailed).

Table 2. Repeated measures ANOVA showing the effect of rTMS on YMRS and CGI-S in mania (n=26)

	Baseline	After 5th rTMS	After 10th rTMS	Pillai's trace F	p value
YMRS				44.49**	<0.001
Active	34.38±7.04	23.46±10.42	16.00±15.63		
Sham	34.38±5.91	23.69±7.71	16.84±10.92		
YMRS-group				0.03	0.912
CGI-S				24.49**	<0.001
Active	4.84±0.80	4.15±1.06	3.38±1.61		
Sham	4.92±0.64	4.07±0.86	3.38±1.55		
CGI-S-group				0.06	0.881

Values are presented as mean±standard deviation.

** $p < 0.001$ (2-tailed).

ANOVA, analysis of variance; rTMS, repetitive transcranial magnetic stimulation; YMRS: Young Mania Rating Scale; CGI-S: Clinical Global Impression-Severity.

tive group was 61.92 (standard deviation [SD] 5.36) and in the sham group was 59.53 (SD 4.66); there was no difference between the two groups.

Effect of rTMS

The effect of rTMS on YMRS and CGI-S scores is shown in Table 2. For YMRS scores, repeated measures ANOVA showed a significant main effect ($F=44.49$, degree of freedom [df]=1.2/29.29, $p < 0.001$, Greenhouse-Geisser corrected, effect size $\eta^2=0.65$), but the inter-

action effect was not significant ($F=0.03$, $df=1.2/29.29$, $p=0.912$, Greenhouse-Geisser corrected). For CGI-S, repeated measures ANOVA showed a significant main effect ($F=24.49$, $df=1.42/34.21$, $p < 0.001$, Greenhouse-Geisser corrected, effect size $\eta^2=0.51$), but the interaction effect was not significant ($F=0.06$, $df=1.2/29.29$, $p=0.881$, Greenhouse-Geisser corrected). Among patients receiving add-on active rTMS 8 (61.5%) achieved remission in comparison to 6 (46.2%) patients receiving sham rTMS; the difference was not significant ($\chi^2=0.62$,

$p=0.431$).

Adverse Effects of rTMS

There was no report of any serious side effect including seizure in patients receiving rTMS or sham treatment. The most common complaint of the patients receiving active treatment was pain during delivery of the train of stimulation which improved spontaneously after completion of the session. Transient headache was reported by 2 patients (15.4%) receiving active treatment following rTMS session, which lasted from less than an hour to four hours.

DISCUSSION

The findings in our study showed that high-frequency rTMS over right prefrontal cortex was not effective in bipolar mania in adolescents. This is in contrast to the findings from the studies in adults,^{6,8} which reported improvement in manic symptoms with similar stimulation parameters. It was hypothesized that there is a decreased anterior metabolism (hypofrontality) that is more pronounced on the right side and a relative increase in metabolism is present on the left side in patients with mania, which is the opposite of what is observed in depression.⁶ The improvements have been suggested to occur as a result of correcting the altered metabolism or blood flow that is associated with mania.⁸ The lack of effect in our study could possibly indicate that the pattern of abnormalities in blood flow or metabolism observed in adolescents be different than that of adults.¹⁶ Recent studies have found high-frequency rTMS to be effective in adolescent depression.¹⁷⁻¹⁹ Another reason for the lack of efficacy of rTMS in our study could be the use of lower doses (800 pulses/day) in the current study, as some of the recent studies have used 2,000 to 3,000 pulses/day,¹⁹⁻²¹ albeit for indications other than mania. Indeed, another strategy that have used 15,000 pulses/day over 2 days ('accelerated rTMS') in depressed patients found it to be both safe as well as effective,²² which suggests aggressive treatment with higher dose may be equally effective alternatives to traditional rTMS approaches.

In our study, rTMS was well tolerated without any emergent serious adverse effects such as seizure. It can be concluded from our study that rTMS can be administered safely in adolescents using similar parameters as in the adults. The sample size was larger than previous studies in adolescent population.^{3-5,18,19} As the rTMS parameters are not standardized yet, further studies need to be done using different parameters in adolescent mania population.

The limitations of the study included lack of double blinding which could lead to rater bias during the assessment of psychopathology. Alternative assignment of the patients to either treatment group does not represent true randomization is another limitation. The DLPFC of patients was located using the "5 cm rule", which does not take into consideration the shape and size of a person's head.²³ This may result in some variations in the exact site of stimulation in the prefrontal cortex. Further studies may be conducted with precise localization under neuro-imaging guidance.

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