Original Article

Efficacy Of Adjunctive Rtms In Psychogenic Non-Epileptic Seizure In Children And Adolescents: A Randomized Double Blind Sham Controlled Study

Dr. Sanjay Kumar Pany[1] , Dr. Nishant Goyal[2] , Prof. S. Haque Nizamie[3] , Dr. Sanjay Kumar Pany (Corresponding author)[4]

[1]Assistant Professor, P.G Department of Psychiatry Hi-Tech Medical College and Hospital, Bhubaneswar Email: panydr@gmail.com
[2]Associate Professor, Department of Psychiatry, Central Institute of Psychiatry, Ranchi
Email: psynishant@gmail.com
[3]Professor of Excellence, Department of Psychiatry, Central Institute of Psychiatry, Ranchi Email: sh.nizamie@gmail.com
[4]Assistant Professor, P.G Department of Psychiatry Hi-Tech Medical College and Hospital, Bhubaneswar Email: panydr@gmail.com
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Abstract

Transcranial Magnetic Stimulation (TMS) is a non-invasive method of stimulating focal areas of brain, which was initially developed as a tool to study localization of brain, is increasingly been used in neuropsychiatric research and clinical psychiatry. The effects of rTMS depend on the stimulation parameters, such as frequency and intensity (Wassermann et al, 1996). High frequency repetitive transcranial magnetic stimulation (rTMS) induces activation and low frequency rTMS causes inhibition of cerebral cortex, modifying cortical excitability (Pascual-Leone et al, 1998).

Introduction

Psychogenic non-epileptic seizures (PNES) are episodes of paroxysmal impairment of self- control associated with a range of motor, sensory and mental manifestations, which represent an experiential or behavioral response to emotional or social distress (Reuber, 2008). They are grouped into the category of psycho neurologic illnesses (e.g. conversion disorder, somatization disorders) in which symptoms are psychiatric in origin but neurologic in expression (Bourgeois et al, 2002). PNESs are often considered to be physical manifestations of underlying psychological stressors, despite being perceived as involuntary (Reuber et al, 2000).

Functional imaging data suggest that neural circuits linking volition, movement and perception are disrupted in conversion disorder. Several lines of evidence support the hypothesis that a deviance in cerebral lateral organization and an altered interhemispheric processing of sensorimotor and cognitive information, which has been referred to as functional commissurotomy, play a crucial role in dissociation.

PNES is an illness that is only partially responsive to currently available pharmacological and psychological treatments (Reuber, 2008). So there is a pressing clinical need for the development of novel therapeutics for this illness. Evidence suggests that repetitive transcranial magnetic stimulation (rTMS) can provide alleviation of refractory conversion paralysis and somatization associated with posttraumatic stress disorder (Scho¨nfeldt-Lecuona et al, 2006). However, no studies to date have been done in PNES. Various studies using rTMS, as an adjunctive treatment, have been conducted at the Central Institute in Psychiatry (CIP) targeting disorders like affective disorders, Obsessive Compulsive Disorder (OCD) and schizophrenia (Goyal et al, 2007; Bagati et al, 2009; Praharaj et al, 2009; Sarkhel et al, 2010; Mishra et al, 2010; Nongpiur et al, 2011; Ray et al, 2011). But no study till date have been done in CIP to see the therapeutic effect of rTMS on Psychogenic nonepileptic seizure, so to see the effect on PNES it was done.

Materials and methods

The current research was a prospective, hospital-based, randomized, double-blind, parallel, sham-controlled transcranial magnetic stimulation study conducted with the aim to examine the efficacy of adjunctive rTMS in psychogenic non-epileptic seizures (PNES) in children and adolescents. The primary objectives were to assess the effect of adjuvant low frequency rTMS and the qualitative changes in parameters of Psychogenic non-epileptic seizures (PNES) in children and adolescents subjected to adjuvant low frequency rTMS as compared to sham stimulation. The study was conducted over a period of one year from December 2012 to October 2013 conducted at the K. S. Mani Centre of Cognitive Neurosciences and Erna Hoch center of child and adolescent psychiatry, Central Institute of Psychiatry (C.I.P), Ranchi, India. Central Institute of Psychiatry. Ethical clearance was taken from the Institutional Ethics Committee prior to the start of the study.

Patients of either sex, between 8 to 18 years of age, diagnosed with Dissociative convulsions (PNES) by Diagnostic Criteria for Research (DCR) of International Classification of Diseases - tenth edition (ICD-10; WHO, 1993), right handed, normotensive, with at least one dissociative convulsion (Psychogenic Nonepileptic Seizure) in the last one-month period were included in the study. Those having epilepsy or any organic brain disorder, with cardiac pacemakers or other metal parts in the body, history of any major medical illness or ECT within past six months, uncooperative patients or whose parents and guardians refuse to consent were excluded from the study. The sampling was done by purposive sampling technique.

In this study, 21 patients with a diagnosis of Dissociative convulsions (PNES) fulfilling the inclusion and exclusion criteria were taken up for the study. However, one patient dropped out due to unwillingness to continue treatment. Written informed consent was obtained from the parents or caretaker prior to the study after explaining the procedure in detail. For proper distribution of the sample across the two groups, subjects denoted with odd numbers received active and even numbers received sham stimulation. The rater was completely blind to treatment allocation, thereby ensuring double-blinding and eliminating rater bias.

A detailed physical examination along with qEEG and CT scan cranium were done to rule out any neurological disease or epilepsy. Socio-demographic and clinical data was collected. Patients were assigned to active (odd no) or sham (even no) for r TMS. Then rTMS or sham treatment was given for 5 sessions over a week for 2weeks. PNES Scales, CDI-2 (Children's Depression Inventory 2), DES for adolescence (Adolescent Dissociative Experiences Scale-II), HAM-A (Hamilton Anxiety Scale), CGI-S (Clinical Global Impression-Severity of illness), were applied at 0, 2wk and 4wk by another rater who was blind to the treatment protocol. During the study period changes in the pharmacotherapy and psychotherapy of the patients were entertained. The motor threshold (MT) for the left abductor pollicis brevis (APB) was determined using a round coil at 1 Hz frequency. One session of daily rTMS treatments was administered over the Supplementary motor area at 90% of MT with the figure eight coil placed at midline. 120 pulses/train and 10 trains per session through a 70mm figure 8 coil was given. A total of 10 sessions of rTMS treatments were administered over a 2week.Using similar parameters, rTMS was delivered to sham group using similar coil but tilted at an angle of 45° from the scalp.

Statistical Analysis

The results obtained were analyzed by using the computer software program, Statistical Package for Social Sciences-version 21.0 (SPSS-21.0) for Windows®, with different parametric and nonparametric measures being used, wherever applicable. Description of sample characteristics was done with descriptive statistics like percentage, mean and standard deviation. Group differences for sample characteristics were examined with independent t-test and chi-square test wherever applicable. To compare the overall effect of treatment over time for the two groups, a set of multivariate repeated measures analysis of variance was employed with treatment as the between-group factor and time as the within-subject factor. TPS, TAPS, TPNES, ADES, HAM-A, CDI and CGI scores were compared across socio-demographic and clinical variables using independent sample t-test. Pearson's correlation was done to see any correlation between various clinical variables with reduction in various scores with treatment. A level of significance (α) of <0.05 (two tailed) was taken to consider a result statistically significant.

Observations and Results

A total of 21 patients were evaluated. **Table 1** shows the socio demographic and clinical variables (categorical) between the active and sham groups. Active groups having higher female representation, greater proportion belonging to lower socio-economic status and from rural background, mostly educated till primary and are Hindu, showed no significant difference in any of the variables. Also there was no significant difference in past and family psychiatric history between the two groups.

Variable		**Active N=10 n (%)**	**Sham N=10 n (%)**	**2**	**df**	**p**
Sex	**Male**	2 (20)	6 (60)	.173	1	0.170
	Female	8 (80)	4 (40)			
Religion	**Hindu**	6(60)	9(90)	.417	1	0.303
	Others	4(40)	1(10)			
Education	**Primary**	4(40)	7(70)	1.030	1	0.116
	Secondary	6(60)	2(20)			
	Intermediate and above	0(0)	1(10)			
Socio-economic status	**Low**	8 (80)	7 (70)	0.100	1	1.000
	Middle & Above	2 (20)	3 (30)			
Habitat	**Rural**	7 (70)	6 (60)	6.088	1	1.000
	Suburban and Urban	3 (30)	4 (40)			
Drugs	**SSRI**	6(60)	9(90)	1.000	1	0.303
	Others	4(40)	1(10)			
Past psychiatric history	**Absent**	10 (100)	10 (100)	0.000	1	-
	Present	0 (0)	0(0)			
Past medical history	**Present**	1 (10)	1 (10)	0.784	1	1.000
	Absent	9 (90)	9 (90)			
Family psychiatric history	**Present**	2(20)	3(30)	0.107	1	1.000
	Absent	8(80)	7(70)			
Family history of medical illness	**Present**	2(20)	1(5)	1.307	1	1.000
	Absent	8(40)	9(45)			
Birth and Developmental history	**Significant**	1 (10)	0 (0)	0.835	1	1.000
	Non-significant	9 (90)	10 (100)			
Premorbid temperament	**Ill balanced**	1(10)	0(0)	0.275	1	1.000
	Well balanced	9(90)	10(100)			

Table-1: Comparison of Socio-demographic and clinical variables (categorical) between two groups
*Significance at p<.05 (2-tailed)

Table 2 shows the socio demographic and clinical variables (continuous) of the sample of patients that consists of the active group and the sham control group. No statistical difference was found in age, duration of illness, number and duration of attack between two groups.

Variables	Active N=10 Mean (SD)	Sham N=10 Mean (SD)	t	df	p
Age (In years)	13.8 (2.201)	12.3 (3.056)	1.259	18	0.224
Duration of illness (In months)	6.1 (4.094)	17.9 (20.376)	1.795	18	0.089
No. Of attack (last 1m)	38.8(40.342)	22.8(41.718)	0.839	18	0.412
No. of attack(last 1wk)	13.8(15.002)	5.9(9.694)	1.400	18	0.178
No. of attack (1wk post rTMS)	5.1(10.948)	4.1(8.047)	0.233	18	0.819
No. of attack (2^{nd} wk post rTMS)	3.1(8.799)	5.3(11.253)	0.487	18	0.632
No. of attack (3^{rd} wk post rTMS)	4.0(8.432)	5.0(9.237)	0.253	18	0.803
No. of attack (4^{th} wk post rTMS)	3.1(5.152)	4.4(9.766)	0.372	18	0.714
Duration of attack(last 1m)	25.5(28.880)	31.3(36.518)	0.394	18	0.698
Duration of attack(last 1wk)	21.5(28.060)	17.4(18.945)	0.383	18	0.706
Duration of attack(1^{st} wk post rTMS)	3.8(9.342)	6.2(10.379)	0.543	18	0.593
Duration of attack(2^{nd} wk post rTMS)	3.0(7.888)	6.2(10.643)	0.764	18	0.455
Duration of attack(3^{rd} wk post rTMS)	0.7(1.636)	6.4(10.265)	1.734	18	0.100
Duration of attack(4^{th} wk post rTMS)	2.1(3.034)	5.0(9.933)	0.883	18	0.389

Table-2: Comparison of Socio-demographic and clinical variables (continuous) between two groups *Significance at p<.05 (2-tailed)

Table 3 shows effect of treatment across Active (rTMS) and Sham (Control) Groups over Time: TPS, TAPS, TPNES, ADES, CDI, HAMA, CGI scores within Subjects. For all the parameters, a set of repeated measures analysis of variance showed significant main effect of treatment over time (Pillai_s trace, p< 0.001).

Variables		Pre-treatment (0 wk) (Mean ± SD)	After 10^{th}session (2 wks) (Mean ± SD)	Post rTMS Treatment (4^{th} wk) (Mean ± SD)	Pillai's Trace F (within Subjects)	P
Total phenomenology score(TPS)	**Active (N=10)**	58.4±9.912	17.2 ±22.986	28.7 ± 26.808	15.587	**<.001****
	Sham (N=10)	53.7 ± 15.158	23.0 ± 28.425	34.5 ±30.041		
	Active (N=10)	2.0 ± 0.666	0.6 ± 0.843	0.7 ± 0.823	13.287	**<.001****

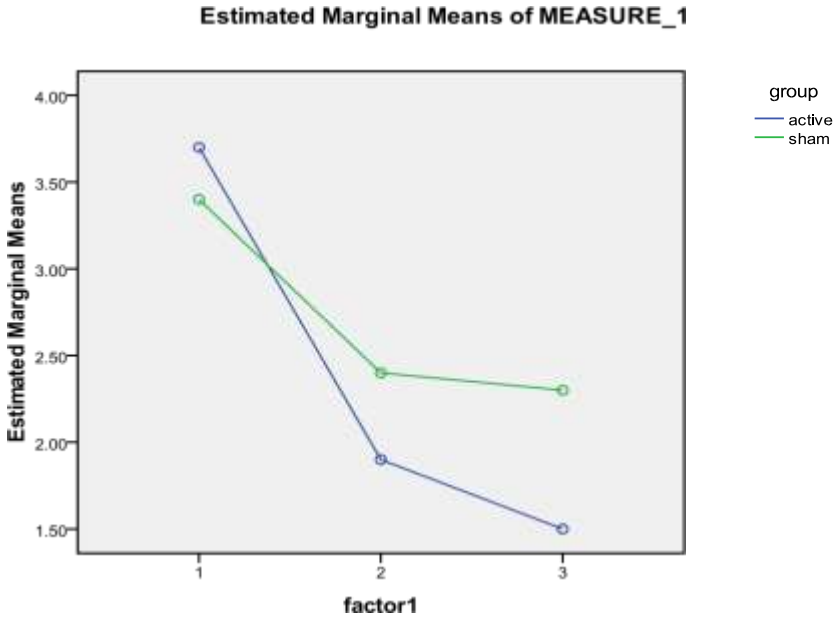
Total associated phenomena score(TAPS)	**Sham (N=10)**	1.5 ± 0.707	0.9 ± 1.100	0.9±0.875		
Total psychogenic nonepileptic seizure score(TPNSS)	**Active (N=10)**	60.3 ± 10.122	17.8 ± 23.733	29.4 ± 27.411	15.696	**<.001****
	Sham (N=10)	55.2 ± 15.288	23.9 ± 29.384	35.2 ± 30.705		
Adolescent dissociative experiences scale-II (ADES)	**Active (N=10)**	44.8 ± 38.694	23.1 ± 17.051	12.4 ± 11.529	16.331	**<.001****
	Sham (N=10)	33.2 ± 20.836	23.4 ± 14.531	18.0 ± 14.243		
Hamilton Anxiety Rating Scale (HAMA)	**Active (N=10)**	10.50± 5.254	5.5±4.196	4.0±4.944	55.759	**<.001****
	Sham (N=10)	12.6±4.742	9.1±3.784	6.1±3.348		
Childhood Depression Inventory- 2	**Active (N=10)**	39.6±9.674	35.8±9.162	33.5±8.276	14.343	**<.001****
	Sham (N=10)	41.0±9.498	38.7±7.008	34.7±5.677		
Clinical Global ImpressionSeverity Scale	**Active (N=10)**	3.7±1.418	1.9±1.100	1.5±0.849	45.576	**<.001****
	Sham (N=10)	3.4±0.966	2.4±0.843	2.3±0.823		

Table-3: Effect of Treatment across Active (rTMS) and Sham (Control) Groups over Time: Scores within Subjects **Significance at p<.01 (2-tailed)

Legend: TPS (Total phenomenology score), TAPS (Total associated phenomenology score), TPNES (Total psychogenic nonepileptic seizure score), ADES (Adolescent dissociative experiences scale-II), HAMA (Hamilton Anxiety Rating Scale), CDI (Childhood Depression Inventory) and CGI (Clinical Global Impression Severity Scale)

Furthermore, evaluation of interaction of both the groups with the change in the scores of various parameters across various clinical domains showed no significant difference in change in severity between the active and sham groups following rTMS, except in one parameter i.e. Clinical Global Impression Severity Scale score. There was statistically significant difference in the active group compared to the sham rTMS, in clinical global improvement with treatment over time (F=4.902, p= 0.021and effect size 0.366).

Figure-1: Profile plot of change in Clinical Global Impression Severity Scale (CGI) in active and sham group over time (n=20).



There were no major side effects but one patient (in active group) complained of headache, dull aching, mild to moderate in intensity soon after the rTMS session during initial 2-3 sessions and it subsided with addition of analgesics. Also five patients (four active and one sham) complained of sleepiness during initial three sessions but it subsided after few hours.

Discussion and conclusion

The present study examined the efficacy of adjunctive low frequency rTMS in Psychogenic nonepileptic seizure (PNES) patients. One case series has revealed the efficacy of Transcranial Magnetic Stimulation in Motor Conversion Disorder (Scho¨nfeldt-Lecuona et al, 2006). To the best of our knowledge so far, there are no studies have been done on the efficacy of rTMS in PNES. Hence, in our study adjunctive low frequency rTMS was used to observe any clinical effect in patients with PNES.

The current study had a sample size (N = 20). The mean age of patients was 13.8 (SD 2.201) years in the active group and 12.3(SD 3.056) years in the sham group which is comparable to a recent study (Wu et al, 2013). There was predominant female representation (12 – active and sham group). This could be explained by more female patients having dissociative disorder than male. In India female child having conflict present to society in the form of dissociation because of the restriction in our society (Szabo et al, 2012).

In our study, both active and sham groups have shown significant improvement (within the group) over time in TPS, TAPS, TPNES, ADES, HAMA, CDI and CGI over the study period of 4 weeks (table 3). This effect could be due to medication, rTMS intervention or even placebo response in active group and due to medication or even placebo response in sham group. Henceforth, repeated measures ANOVA between both the active and sham groups were conducted.

Repeated measures ANOVA for TPS, TAPS, TPNES, ADES, HAMA, CDI scores revealed significant improvement in active group compared to the sham group in group psychopathology interaction but CGI score revealed significant improvement in active group compared to the sham group in group psychopathology interaction (F=4.902, p=0.021, Effect Size=0.366).Our finding showed that stimulation at SMA lead to improvement in the clinical global severity in active group when compared to control group, though effect size

appears to be small like study by Enticott et al. (2012). There was no significant difference in the improvement of TPS, TAPS, TPNES scores between the active and sham groups. We know that SMA is implicated in psychogenic non epileptic seizure. In our study improvement was seen in both group till the rTMS session were given but it was not sustained after that. It can be due to the duration of rTMS sessions. Study by Scho¨nfeldt-Lecuona et al. (2006) found improvement in dissociative motor disorder after 5 weeks of treatment, but we give treatment for 2weeks so the effect was not sustained.

There was no significant difference in the improvement of CDI and HAMA scores between the active and sham groups. We know that parietal cortex is implicated in depression and anxiety disorders, with hypo activity in the former and hyperactivity in the latter. Also in individuals having depression with co-morbid anxiety disorders, either of the activity might be seen (Zimmerman et al, 2002). However, in our study, there was no significant improvement in the CDI and HAMA scores in all the subjects, although no difference was seen between the groups on repeated measures ANOVA (Machado et al, 2011). The intensity, frequency, duration and site of stimulation is a critical factor in the anxiolytic effect due to increase in extracellular serotonin in parietal cortex (5-HT) (Kanno et al, 2003; Ribeiro et al,2012). In our study we have given rTMS with frequency 1Hz and in the supplementary motor area which were not involved in the neurobiology of anxiety disorder, so improvement was not seen in our study. Similarly, poor response in depression can also be explained on the same basis as parietal cortex is involved in depression and we are giving rTMS in SMA (Bortolomasi et al, 2007; Bloch et al, 2008).

However, in our study, there was improvement in the TPNES, ADES, HAM-A and CDI scores in all the subjects, although no difference was seen between the groups on repeated measures ANOVA. This suggests that the improvement in the symptoms might be due to the effect of medications or placebo response. Placebo response in pychogenic nonepileptic seizure and is upto 75%. Placebo response rates in depression and trials range from 30 to 50% and drug/placebo differences are typically 18-25% (Brown, 1994; Trivedi and Rush, 1994; Schatzberg and Kraemer, 2000).

On the basis of the current study, it was concluded that low frequency SMA rTMS was found to be efficacious for global improvement in patients suffering from PNES. The improvement was more significant in patients with higher number and duration of the seizure attacks. However, the improvement was present till the rTMS session were given but the effect was not sustained after that.

Limitations

There were no normal controls in our study which could have given better comparative results. Most of the patients were receiving antidepressant during rTMS sessions, which could have altered the possible effects of rTMS. Futher studies with a larger sample size and longer duration of treatment can throw a light in this direction.

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