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A Comparative study to assess the effect of active versus sham rTMS treatment in female inpatients of Dissociative Disorder of Movement and Sensation

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Abstract
Introduction: *Psychogenic motor dysfunction (PMD) is common term used to describe increased, decreased, or abnormal movement that is not attributable to any organic cause. Dissociative Disorder of Movement and Sensation is described under F44.4- 44.7 in ICD-10. Our centre is located in Western Rajasthan, where a large number of female patients are presented with the dissociative disorder of movement and sensation. An emerging treatment modality called repetitive Transcranial Magnetic Stimulation (rTMS) noninvasively creates a brief, powerful magnetic field to induce electric current within a targeted brain region.*
Aims and Objectives: *1) to study the presentation of patients, 2) The comparison of treatment effect in between the three groups, 3) To find out the effectiveness of rTMS treatment and 4) To assess the tolerability of rTMS.*
Study design: *A Prospective study was conducted among female in patients with dissociative disorder of movement and sensation from the age group between 15-40 years. Total 52 female inpatients that fulfill selection criteria's of the study were recruited in the study. The recruited participants were allotted in the three study groups with the help of systemic random sampling method. First study group was Pharmacotherapy group, Second group was pharmacotherapy with sham rTMS treatment group and third one was pharmacotherapy with active rTMS group. Clinical Global Impression (CGI) Severity and Improvement scales were used. Illness Severity assessment was done at the time of admission in the study. Improvement with treatment was assessed at the end of 1 week period and follow up assessment was done at the end of 2 weeks period.*
Results: *In all three study groups, majority were in age between 20-30 years, housewife by occupation belongs to Hindu religion and lived in joint families. Common clinical presentations were convulsion or unresponsive spells (64.44%), tremors in limbs (20%), and sensory loss/Burning sensation (20%). In all three study groups the rTMS treatment group has been shown statistically significant improvement at the end of 1 week and 2 week on CGI-I score.*
Conclusion: *Important finding of this study is that rTMS can be used effectively and safely in dissociative disorder of movement and sensation.*
Key words: *Active rTMS, sham rTMS, dissociative disorder, CGI, ICD-10*

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I. Introduction

Psychogenic motor dysfunction (PMD) is common term used to describe increased, decreased, or abnormal movement that is not attributable to any organic cause. Most neurologist after excluding organic disease, refer these patients to psychiatry in the hope that treatment of a presumed underlying psychological disturbance will resolve symptoms [1]. Dissociative Disorder of Movement and Sensation is described under F44.4- 44.7 in ICD-10. F44.4- Dissociative motor disorders, F44.5- Dissociative convulsions, F44.6- Dissociative anesthesia and sensory loss, F44.7- Mixed dissociative [conversion] disorders [2]. Diagnosis and management of PMDs remains challenging. Symptoms can mimic the full range of organic abnormal involuntary movements— psychological or psychiatric disturbances being not always obvious. The outcome is often poor, since only half of the patients improve after 3 years of follow-up with a significant related disability, similar to that seen in neurodegenerative conditions [3].

In the past years, various treatment strategies have been tested in Functional Weakness related symptoms, including different forms of physiotherapy , pharmacotherapy , behavioral therapy and

hypnotherapy . The reported symptom recovery is very heterogeneous and varies depending on the treatment strategy and study. A large amount of new studies reported marked short-term improvements, mostly in the region of a 60–70% symptom reduction . However, long-term outcome, especially in patients with a long duration of illness at presentation is invariably poor [4]. An emerging treatment modality called repetitive Transcranial Magnetic Stimulation (rTMS) noninvasively creates a brief, powerful magnetic field to induce electric current within a targeted brain region. Depending on the frequency and intensity of these magnetic pulses, rTMS can trigger increases or decreases cortical excitability [1].

rTMS and tDCS have been shown to induce long-lasting changes in cortical excitability in directly stimulated cortical areas and in deeper interconnected brain areas [4]. Low-frequency repeated Tran cranial Magnetic Stimulation (TMS) was recently proposed to treat psychogenic paralysis, showing encouraging results. A preliminary study also suggested its efficiency in psychogenic tremor [3]. To date, no trials of rTMS for motor conversion have directly compared rTMS to a sham control.

A recent systematic review of rTMS studies for motor conversion highlights the need for more clinically relevant trials, with an adequate control group, standardized stimulation protocols, and consistent outcome measures across trials, before this modality may be considered as an effective treatment strategy [1]. Two major theories on the pathophysiology of motor conversion have arisen from functional MRI (fMRI) data. The first hypothesizes that frontal and sub cortical motor circuits are suppressed by over activity in limbic areas such as the amygdale, involved in integrating emotional stimuli, and prefrontal areas involved in motor planning , interestingly; hypnosis-induced paralysis produces a similar pattern . The second theory proposes that patients have impaired 'motor imagination' [1].

fMRI studies have found normal activation in motor areas when patients try to move a nonorganically paralyzed limb, but abnormal activation in prefrontal areas when patients view limb movements. This theory emphasizes a functional dissociation between formulation of an internal movement plan and motor output, rather than active inhibition of motor output areas [1].

Our centre is located in Western Rajasthan where a large no of female patients are presented with dissociative disorder of movement and sensation. So we planned this study to find out a new and definitive treatment modality in these patients.

Aims and Objectives:

1) To study presentation of patients diagnosed with dissociative disorder of movement and sensation

2) To study the comparison of treatment effect between the three groups-pharmacotherapy group, pharmacotherapy with sham rTMS group and pharmacotherapy with active rTMS group,

3) To find out the effectiveness of active rTMS treatment over sham rTMS treatment

4) To assess the tolerability of rTMS treatment

II. Materials And Methods

Study design:

After getting approval by institutional Ethical Committee, a prospective study was conducted among female in patients who were diagnosed with dissociative disorder of movement and sensation from the age group between 15-40 years. Total 52 female inpatients that fulfill selection criteria's of the study were recruited in the study. We excluded the patients from study who were not willing to participate, who have co-morbid medical and neurological illness, history of substance abuse and history of co-morbid psychotic illness. Then the recruited participants were allotted in the three study groups with the help of systemic random sampling method. First study group was Pharmacotherapy group in which only supportive pharmacotherapy was given, Second study group was pharmacotherapy with sham rTMS treatment group in which supportive pharmacotherapy with sham rTMS was given and third one was pharmacotherapy with rTMS group in which supportive pharmacotherapy with rTMS was given.

The aim of the study and method adopted was explained to patients and their caregivers. A written consent was taken from all participants and complete confidentiality was assured. After this the socio demographic profile sheet, semi structured clinical proforma were filled. Semi structured clinical proforma included the clinical descriptions such as details of illness presentation, physical and psychological examination and diagnosis according to ICD-10. Semi structured side effects questionnaire was used to assess the tolerability of rTMS treatment. After that Clinical Global Impression severity and improvement scales were used. Illness Severity assessment was done at the time of recruitment in the study. Improvement with treatment was assessed at the end of 1 week period and follow up assessment was done at the end of 2 weeks period.

The CGI-Severity (CGI-S) is rated on the following seven-point scale: 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; 7=among the most extremely ill patients [5].

This rating is based upon observed and reported symptoms, behavior, and function in the past seven days. Clearly, symptoms and behavior can fluctuate over a week; the score should reflect the average severity level across the seven days.

Using the principles of the CGI-I scale for a nominal CGI-I score. The CGI-I score is a 7-point scale which is commonly used to describe changes of a patient's clinical overall improvement related to a specific treatment. CGI-I comprises the following categories: 1 = very much improved; 2 = much improved; 3 = minimally improved 4 = no change; 5 = minimally worse; 6 = much worse; 7 = very much worse [5].

rTMS Protocol:

In study group-2 (pharmacotherapy with sham rTMS) total five consecutive sham rTMS sessions were given to the patients.

In study group-3 (pharmacotherapy with rTMS) total five consecutive active rTMS sessions were given to the patients.

Patients who were presented with weakness or paralysis, psychological aphonia, anesthesia and sensory loss, special sensory symptoms, swallowing symptoms, the protocol of rTMS had following characteristics: 1 train of 10 Hz stimulation frequency and 5 seconds duration, so a total 50 pulses in a train. Each subject had received 36 trains with inter train pause of 25 seconds with a total 1800 pulses in one session. The stimulation site was motor cortex of left side of head.

The patients who were presented with abnormal movement, with attack or seizure the protocol of rTMS treatment was 1Hz stimulation frequency, 1 train with a total 1800 pulses at the motor cortex of left side of head.

Statistical Analysis:

Statistical evaluation was performed by using the SPSS software package (version 20) for data analysis.

III. Results

Out of 52 patients, 45 patients were completed the study. Seven patients were dropped out from the study because of irregular follow up, poor response to treatment and side effect of treatment.

Table 1 shows various Socio demographic and clinical variable like Age, Sex, Marital status, Occupation, Education, Income, Socioeconomic status, Family type, Religion, Locality and Total duration of illness of the study groups. The mean age and SD in study group 1, 2 and 3 are 27.47(±8.096), 24.93(±6.158), 26.33(±6.466) respectively. Most of patients are from young adult age group. Only female inpatients were recruited in study. Total 73.33% females were married, 82.22% were housewife or unemployed, 33.33% were illiterate, 28.88% were primary educated, 55.55% patients were belongs to upper lower class of socioeconomic status and 71.11% patients were belongs to joint family. In religion 86.66% were Hindu. The mean total duration of illness in study group 1, 2 and 3 were 31.33(±38.73), 30.86(±48.20), 17.74(±23.40) respectively.

Table 1: Sociodemographic and clinical variables of all three study groups

Variable		Group 1 N=15 (%)	Group 2 N=15 (%)	Group 3 N=15 (%)	X^2 /F value	P value
Age in years Mean (SD)		27.47 (8.096)	24.93 (6.158)	26.33 (6.466)	0.499	0.611
Sex	**Female**					
Marital Status	**Married** **Unmarried/Others**	13(86.7) 2 (13.3)	9(60.0) 6(40.0)	11(73.3) 4 (26.7)	2.72	0.255
Occupation	**Skilled worker** **Elementary occupation** **Unemployed/ House wife**	1(6.7) 1(6.7) 13(86.7)	3(20.0) 1(6.7) 11(73.3)	1(6.7) 1(6.7) 13(86.7)	1.816	0.769
Education	**Graduate** **Intermediate/Diploma** **High school certificate** **Middle sch. certificate** **Primary sch. certificate** **Illiterate**	1(6.7) 1(6.7) 2(13.3) 3(20.0) 3(20.0) 5(33.3)	1(6.7) 1(6.7) 0 3(20.0) 5(33.3) 5(33.3)	0 0 2(13.3) 3(20.0) 5(33.3) 5(33.3)	4.615	0.915
Income	**<6323** **6327-18949** **18953-31589** **31591-47262** **>47266**	0 11(73.3) 2(13.3) 0 2(13.3)	2(13.3) 9(60.0) 3(20.0) 1(6.7) 0	2(13.3) 12(80.0) 1(6.7) 0 0	4.837	0.774
Socio-economic	**Lower middle (3)**	2 (13.3)	3(20.0)	2(13.3)	0.76	0.943

Status	**Upper lower(4)** **Lower (5)**	9(60.0) 4(26.7)	7(46.67) 5(33.33)	9(60.0) 4(26.7)		
Family Type	**Nuclear** **Joint**	3(20.0) 12(80.0)	4(26.7) 11(73.3)	6(40.0) 9(60.0)	1.514	0.469
Religion	**Hindu** **Muslim**	14(93.3) 1(6.7)	13(86.7) 2(13.3)	12(80.0) 3(20.0)	3.150	0.207
Locality	**Urban** **Rural**	1(6.7) 14(93.3)	2(13.3) 13(86.7)	1(6.7) 14(93.3)	2.143	0.343
TDI in months (Mean & SD)		31.33 (38.73)	30.86 (48.20)	17.74 (23.40)	0.612	0.547

Table 2 shows the various clinical presentations of the patients. Most common presentation were convulsion or unresponsive spells (64.44%), tremors in limbs (20%), sensory loss/Burning sensation (20%).

As per ICD-10, the most common diagnosis was F44.5 (Dissociative convulsions) found in 22 patients (48.88 %), followed by F44.7 (Mixed dissociative [conversion] disorder 17(37.77 %), and less common were F44.4(Dissociative motor disorder) 4 (8.88 %) and F44.6 (Dissociative anaesthesia and sensory loss) 2 (4.44 %).

Table 2: Clinical presentations of study patients

S. No.	Clinical presentation	Number of Patients (n)	Percent (%)
1.	Convulsion / Unresponsive spells	29	64.44
2.	Tremors in limbs	9	20
3.	Sensory loss/Burning sensation	9	20
4.	Dystonic movements	6	13.33
5.	Ataxia(Unable to stand unaided)	5	11.11
6.	Dysphonia/ Slurred speech	4	8.88
7.	Hiccup	3	6.66
8.	Swallowing symptoms	2	4.44

At the base line, mean score of CGI-S in group 1, 2, and 3 was 4.67(±0.976), 4.67 (±0.816), and 4.87 (±0.834) respectively. All the three groups were comparable on CGI-S score at the end of 1 week and all the three groups shows improvement. The comparison of three groups on CGI-I is statistically significant (p value<0.05) which shows the highest improvement in study group 3. (Table 3)

At the end of 2 week, the comparison of CGI-I score was done in all three groups which shows statistically significant improvement in group 3. This table also shows the persistence of response with rTMS treatment.

Table 3: Comparison of CGI-S, CGI-I scores at 1 week and 2 week in all three groups

Variable	Group 1 Mean (SD)	Group 2 Mean (SD)	Group 3 Mean (SD)	F value	P value
CGI-S	4.67 (0.976)	4.67(0.816)	4.87(0.834)	0.259	0.773
CGI-I at 1 Week	2.80(0.414)	2.73(0.458)	2.20(0.561)	7.000	0.002
CGI-I at 2 Week	2.47(0.990)	2.27(0.704)	1.40(0.506)	8.346	0.001

Table 4 shows Post HOC analysis in between groups of all three groups at the end of 1 week and 2 week. At the end of 1 week the comparison between group 1 and group 3 and comparison between group 2 and group 3 were statistically significant (p value<0.05) which shows highest improvement due to group 3. Similar findings were also found at the end of 2 week. There is no statistically significant difference in between comparison of group 1 and 2 at the end of 1 week and 2 week. (p value > 0.05).

Table 4: Post HOC analysis of CGI-I in between all three groups at 1 and 2 weeks duration

Variable	Mean Difference	Std. error	P value
CGI-I at 1 Wk			
1. Grp1-Grp2	0.067	0.176	0.924
2. Grp1-Grp3	0.600	0.176	0.004
3. Grp2-Grp3	0.533	0.176	0.011
CGI-I at 2 Wk			
1. Grp1-Grp2	0.200	0.278	0.753
2. Grp1-Grp3	1.067	0.278	0.001
3. Grp2-Grp3	0.867	0.278	0.009

Table 5 Shows the Intragroup Comparison of CGI-I score between 1 week and 2 week in the all three study groups.In this comparison study group 2 and study group 3 shows statistically significant improvement in between 1 week and 2 week CGI-I scores. (p value<0.05)

Table 5: Intra-group Comparison of CGI-I score between 1 week and 2 weeks duration

Group	CGI-I	Mean difference	S.D. difference	T score	P value
1	1 wk- 2 wk	0.333	0.816	1.581	0.136
2	1 wk- 2 wk	0.467	0.516	3.500	0.004
3	1 wk- 2 wk	0.800	0.561	5.527	0.000

Table 6 shows side effects (rTMS treatment related) in study group 2 and study group 3.One patient shows local pain over scalp in study group 2. In study group 3 one patient has muscular contraction, one patient has anxiety and two patients were complained of headache.

Table 6: rTMS treatment related Side effects in Study group 2 and Study group 3

S.No.	Side effect	Study Group 2 (n=15)	Study Group 3 (n=15)
1.	Skeletal muscle:- Pain, muscle contraction, arthralgia.	0	1
2.	Psychiatric:- anxiety, dysphoria, attack of laughter(Broca`s area stimulation), suicidal ideation, induced mania.	0	1
3.	Neurological:- local pain on the scalp muscles, headache, seizure, tremor.	1	2

IV. Discussion

This is a prospective study which was conducted among female inpatients dissociative disorder of movement and sensation. A total 52 patients who had been fulfilled the selection criteria's of the study were recruited in the study after an informed consent. In this study total 7 patients were discontinue during the study. In study group 1 four patients drop out due to poor treatment response and one patient discontinue due to irregular follow up. In study group 2 one patient discontinue due to poor treatment response. In study group 3 one patient discontinue due to headache. Remaining 45 patients were completed the study.

The various rTMS protocol has been used in previously conducted similar studies. Beatrice Garcin et al (2013) used 0.25 Hz frequency, 20 stimulus, 120 % of motor threshold [3]. Another study did by M.Broersma et al (2014) used 15 Hz frequency over the contralateral motor cortex, in two periods of 5 days, for 30 minutes a day at 80% of motor threshold, with a train length of 2 seconds and intertrain interval of 4 seconds [6].

Mean age and age of illness onset was comparable with the previous studies. In a study done by Mazhar Malik et al (2010), the average onset of age of Dissociative disorders was 25.9±7.5, where majority were young, females, formally educated, rural residents, unmarried, unemployed with no family history of mental illness [8]. In a study of Thapa R (2014, the mean age of participants was 21.23(±7.227) years [7]. One other study by M.Broersma et al 2014 had been taken age group 34-65 years old [6].

In this study, the most common diagnoses of patients were Dissociative convulsions, Dissociative motor, and less common were dissociative anaesthesia and mixed conversion disorder. Similar to this study, a previous study done by Mazhar Malik et al (2010) also found the similar diagnoses pattern and frequency [8].

The baseline illness severity score (CGI-S) were comparable in all three groups. After treatment all the three study groups have been shown improvement (CGI-I). In study group 3 highest improvement has been shown in which the mean CGI-S score at baseline 4.87, at the end of 1 week CGI-I score 2.20 and at the end of 2 week CGI-I score 1.40. In all three study groups the study group 3 (rTMS treatment group) has been shown statistically significant improvement at the end of 1 week and 2 week.

One study conducted by Schonfeldt-Lecuona et al (2006) in which patients received 2 weeks, 5 sessions per week of rTMS in supra-threshold 110 % total 4000 pulses per day after this 72 % patients have CGI-I score of 1 (very much improved),17% patients have CGI-I score 2 (much improved) at the end of 2 weeks period [4].

Post HOC analysis intergroup assessment shows that the end of 1 week there is statistically significant improvement in intergroup 1-3, and intergroup 2-3 comparison. These findings were persistent at the end of 2 week duration.

Intragroup comparison of study group 2 and study group 3 shows statistically significant improvement in CGI-I scores in between the 1 week and 2 week duration.

In study group 2 (sham rTMS treatment) the statistically significant improvement shows that this effect may be due to assurance given before treatment, possible psychological effect [9], blind selection and placebo effect as sham TMS coils can be positioned exactly like an active TMS coil resulting in a very good approximation of the auditory effects [10].

Side effects (rTMS treatment related) profile (study group 2 and study group 3) was, one patient showed local pain over scalp in study group 2. In study group 3 one patient had complain of muscular contraction, one patient had anxiety and two patients were complained of headache.

The main limitation of study was small sample size; another was short term follow up so we do not conclude whether the rTMS response will be maintained after the initial improvement.

V. Conclusion

The most important finding of this study was that rTMS can be used effectively and safely in dissociative disorder of movement and sensation.

Disclosure statement:
No financial support and no other potential conflict of interest were present.

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