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Research Article

To Evaluate the Efficacy of Repetitive Transcranial Magnetic Stimulation (rTMS) For Treatment of Negative Symptoms in Patients with Schizophrenia

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ABSTRACT

Introduction: The therapeutic use of rTMS (Repetitive Transcranial Magnetic Stimulation) across the dorsolateral prefrontal cortex in the management of negative symptoms of schizophrenia has recently emerged. This study was done to determine the effectiveness of high frequency rTMS over the left DLPFC (Dorsolateral Prefrontal Cortex) in reducing negative symptoms of schizophrenia.

Aim: To determine the efficacy of high frequency rTMS (20 Hz, 110 MT, 3000 pulses/day) over left dorsolateral prefrontal cortex as an augmentation treatment in negative symptoms of schizophrenia.

Materials and methods: 50 Patients with Schizophrenia diagnosed as per ICD-10 (International Classification of Diseases) having predominantly negative symptoms that fulfilled the inclusion and exclusion criteria were recruited for study. All patients were assessed on SANS (Scale for Assessment of Negative Symptoms) for negative symptoms, CDSS for depressive symptoms and Clinical Global Impression scale CGI for overall clinical improvement. The patients were then divided into active group and a sham group by chit method.

Results: There was significant improvement in the total SANS score between active and sham group after intervention. Total SANS scores reduced significantly after intervention in both active (78.52 ± 11.58 to 45.68 ± 5.52, $p<0.001$) and sham (74.64 ± 7.99 to 50.80 ± 4.77, $p<0.001$) rTMS arms on fractional measure ANOVA test but post interventional scores were significantly lesser in those who receive active rTMS as compared to those who receive sham.

Conclusion: Our study found a significant reduction in negative symptoms and overall clinical global improvement in patients with negative symptoms. This study adds to the existing literature with its robust design and large sample size as compared to previous studies despite few limitations and paves the path for future research regarding administration of high frequency rTMS. This protocol can be used as standard protocol for patients with negative symptoms of schizophrenia as there was significant improvement in all 5 subdomains of SANS scale which was not shown by previous studies.

Keywords: Schizophrenia; Negative symptoms; rTMS; Scale for Assessment of Negative Symptoms (SANS)

INTRODUCTION

Schizophrenia is a severe mental disorder with heterogeneous etiologies and characterized in general by fundamental and characteristic distortions of thinking and perception, and by inappropriate or blunted affect. Clear consciousness and intellectual capacity are usually maintained, although certain cognitive deficits may evolve in the course of time [ICD 10]. In India, according to National Mental Health Survey 2015-2016, the current prevalence rate of schizophrenia and other psychotic disorder is 0.5% and life time prevalence is 1.4%. The rate among males was slightly higher than female (0.5% in male *vs*. 0.4% in females).

In patients with schizophrenia, negative symptoms are now recognized to be one of the core symptom domains with a consistent course and to be an independent predictor of poor functional outcome. Negative symptoms are consisting of five essential components, which can be further divided into two separate factors: decreased expression and avolition/apathy [1]. (1) Anhedonia; (2) Avolition (apathy); (3) Social withdrawal; (4) Alogia; (5) Emotional (affective) flattening.

The negative symptoms of schizophrenia are difficult to treat with currently available treatment option including pharmacological and non-pharmacological interventions. The newer modalities for the treatment of negative symptoms of schizophrenia are Deep Brain Stimulation (DBS), Trans-cranial Direct Current Stimulation (tDCS), Electro Convulsive Therapy (ECT). These

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function by invasive or non-invasive application of electric current to brain areas. The finding of multifunctional neuro imaging and neurophysiologic studies have consistently reported hypo activity in Dorso-Lateral Prefrontal Cortex (DLPFC), as well as impaired fronto-parietal and fronto-striatal brain network connectivity to be associated with negative symptoms of schizophrenia [2].

The therapeutic use of rTMS across the dorsolateral prefrontal cortex in the management of negative symptoms of schizophrenia has recently come to light. According to research conducted in India by Swarndeep Singh et al, using adjunctive higher frequency (20-Hz) rTMS over Lt-DLPFC with more powerful stimulation settings (100% MT and 40000 pulses) may be a useful augmentation method for the treatment of negative symptoms [3].

There is a need to optimize rTMS settings that are beneficial for treating negative symptoms because the results of different rTMS protocols employed in different research have inconsistent results. Numerous research using high frequency rTMS (10 Hz, 15 Hz, and 20 Hz) revealed that higher frequencies were more effective in treating the negative symptoms of schizophrenia. To determine the effectiveness of high frequency rTMS over the left DLPFC in reducing negative symptoms of schizophrenia, we therefore planned to conduct this study using a more robust protocol. A comparison with sham controls was made over a period of 4 weeks.

To determine the efficacy of high frequency rTMS (20 Hz,110 MT,3000 pulses/day) over left dorsolateral prefrontal cortex as an augmentation treatment in negative symptoms of schizophrenia. To determine the efficacy of high frequency rTMS in reducing depressive symptoms. To find co-relation between number of sessions of rTMS with CDSS/SANS score. To standardize a treatment protocol for negative symptoms of schizophrenia.

MATERIALS AND METHODS

This is a hospital based open label randomized sham-controlled study in which 50 Patients with Schizophrenia diagnosed as per ICD-10 having predominantly negative symptoms who fulfilled the inclusion and exclusion criteria were recruited from the psychiatry OPD/IPD of JNMCH, Aligarh during the study period. Written informed consent was taken from each patient/patient's caregiver. The patients were assessed using a semi-structured proforma, which included socio-demographic details, clinical history, physical examination and mental status examination. All patients were assessed on Scale for Assessment of Negative Symptoms (SANS) for negative symptoms, Calgary Depression Scale for Schizophrenia (CDSS) for depressive symptoms and Clinical Global Impression scale (CGI) for overall clinical improvement. The patients were then divided into active group and a sham group by chit method. The active groups were given high frequency rTMS at 20 Hz, 110% motor threshold and total pulses 3000 per day. Total 20 sessions of rTMS at a rate of 5 sessions per week was given. The sham groups were given treatment by the same coil but in perpendicular position over the left dorsolateral prefrontal cortex. Patients in both groups were assessed on SANS, CDSS and CGI at the end of 2nd week and 4th week respectively. The rTMS machine used in this study was medstim-MS 30 waveform types are biphasic, full sine. Pulse width is 225 μs-320 μs (as per coil chosen), Pulse modes are single and repetitive. Output energy range is 30% to 100%, Magnetic field: 32 kT/sec. (coil surface), Maximum power is 2200 VA. Figure of 8 coils was used to give stimulus and localization of dorsolateral prefrontal cortex is done by providing TMS pulses to the relevant motor cortex inducing muscle twitches in the contralateral hand muscle, usually the Abductor Pollicis Brevis (APB). The coil was then placed for treatment 5 cm forward from this spot in a sagittal plane.

Inclusion criteria includes patients aged between 18 years and 60 years, patients from both gender, patient/patient's caregivers who gave written informed consent for the study, patients stable on medication for about 6 weeks prior to participating in study. Exclusion criteria includes patients aged<18 years and>60 years, patients with other co-morbid psychiatric disorders, patients with a diagnosis of neurological disorder or head injury or loss of consciousness in past, patients with a diagnosis of seizure disorder, patient/patient's caregivers who did not give consent for the study, patient who had pacemaker in place and/or any metallic implant in body.

Statistical analysis

Data analysis was done using SPSS version 26.0. Descriptive statistics were used to tabulate demographic and clinical characteristics of sample. The baseline demographic and clinical characteristics between two treatment groups were compared by using chi-square test and independent t-test for normally distributed continuous variables. Significant value was set to be at 0.05 changes of scores within group were examined *via* repeated measure ANOVA test and scores between the groups were examined using independent t-test. Post hoc Bonferroni correction was performed to compare scores obtained at baseline. All people who were assigned to experimental arms at baseline were included in the analysis regardless of whether they followed the research protocol or discontinued it. This is known as an intention-to-treat analysis. Missing values were assumed based on the most recent observation.

RESULTS

Table 1 shows most participants (72%) in the active group were in the age range of 20 years-30 years followed by 28% aged between 31 years-40 years. Likewise, most participants (60%) in the sham group were in the age range of 20 years-30 years followed by 40% aged between 31 years-40 years. The mean age was found to be 27.36 years ± 4.52 years and 27.92 years ± 4.15 years in the active and sham groups respectively.

Table 1: Sociodemographic and clinical profile.

Age (in years)	Group	
	Active	Sham
20-30	18 (72%)	15 (60%)
31-40	7 (28%)	10 (40%)
41-50	0 (0%)	0 (0%)
Mean Age	27.36 ± 4.52	27.92 ± 4.15

Table 2 with 13 males (52%) and 12 females (48%), the gender distribution seemed comparable in the active group. However, males (56%) clearly outnumbered females (44%) with regard to gender distribution in the Sham group. The active and sham groups were comprised of 25 participants each. Most study participants were single in both active (n=18) and sham (n=16) groups. Married individuals accounted for 28% and 36% of the active and sham groups respectively. Majority of the participants in both active and sham groups were either illiterate or received religious education. None of the participants were graduates in the sham group compared to 4% of graduates in the active group. Most

participants (44%) in the active group were unemployed (doing nothing, begging) followed by students (20%), homemakers (16%), and unskilled workers (16%). In the sham group, most subjects (36%) were unemployed (doing nothing, begging) followed by unskilled workers (24%), homemakers (16%), and students (20%). Most participants (60%) in the active group had a nuclear family followed by those living in a joint family setup (40%). Likewise, most participants (56%) in the sham group resided in a nuclear family followed by 44% in the joint family setup.

Most participants (52%) in the active group and (48%) in the sham group had an illness duration between 1-4 years. Nearly 1/5th of participants in both groups had illness duration between 9 years-12 years. The mean illness duration in the active and sham group was found to be 4.76 years ± 3.13 years and 4.96 years ± 2.71 years respectively. Only those patients who were maintained on antipsychotics for at least 6 weeks duration were recruited for this study. Most patients in the active group were maintained on Amisulpride (36%) followed by Clozapine (32%) and Olanzapine (24%) respectively. However, most patients in the sham group were maintained on Clozapine (36%) followed by Amisulpride (32%) and Olanzapine (20%). Mean SANS total score at baseline in the active and sham groups was found to be 78.52 ± 11.58 and 74.64 ± 7.99 respectively. Higher mean scores for affective flattening and avolition were noted in the active group compared to the sham group. Higher mean scores for alogia and attention impairment were noted in the sham group compared to the active group. However, mean scores for anhedonia were found to be comparable in both the groups.

Table 2: The gender distribution between active group and sham group.

Educational status	Group		Test of significance (χ^2)	p-value
	Active N=25 (n%)	Sham N=25 (n%)		
Graduate	1 (4%)	0 (0%)	1.244	0.941, NS
Intermediate	3 (12%)	3 (12%)		
Matric	2 (8%)	2 (8%)		
Middle	5 (20%)	4 (16%)		
Illiterate	7 (28%)	8 (32%)		
Others (Religious education)	7 (28%)	8 (32%)		
Occupational status	**Group**		**Test of Significance (χ^2)**	**p-value**
	Active N=25 (n%)	**Sham N=25 (n%)**		
Homemaker	4 (16%)	5 (20%)	1.711	0.887, NS
Student	5 (20%)	4 (16%)		
Unskilled	4 (16%)	6 (24%)		
Skilled	1 (4%)	1 (4%)		
Unemployed	11 (44%)	9 (36%)		
Family type	**Group**		**Test of Significance (χ^2)**	**p-value**
	Active N=25 (n%)	**Sham N=25 (n%)**		
Joint	10 (40%)	11 (44%)	0.082	0.774, NS
Nuclear	15 (60%)	14 (56%)		
Residence	**Group**		**Test of Significance (χ^2)**	**p-value**
	Active N=25 (n%)	**Sham**		
Rural	11 (44%)	11 (44%)	0.056	1.000, NS
Urban	14 (56%)	14 (56%)		
Duration of illness	**Group**		**Test of Significance (t)**	**p-value**
	Active N=25 (n%)	**Sham N=25 (n%)**		

1-4 years	13 (52%)	12 (48%)	0.241	0.810, NS
5-8 years	6 (24%)	8 (32%)		
9-12 years	5 (20%)	5 (20%)		
Mean illness duration	4.76 ± 3.13	4.96 ± 2.71		

Antipsychotic medication	Group		Test of Significance (χ^2)	p-value
	Active N=25 (n%)	Sham N=25 (n%)		
Clozapine	8 (32%)	9 (36%)	0.408	0.938, NS
Amisulpride	9 (36%)	8 (32%)		
Olanzapine	6 (24%)	5 (20%)		
Others (Risperidone, Aripiprazole, antidepressants)	2 (8%)	3 (12%)		

SANS (Baseline)	Mean scores	
	Active N=25 (n%)	Sham
Total score	78.52 ± 11.58	74.64 ± 7.99
Affective flattening	23.60 ± 6.37	20.84 ± 4.13
Alogia	14.60 ± 2.32	15.72 ± 2.09
Anhedonia	17.84 ± 2.95	17.84 ± 2.42
Avolition	13.20 ± 3.02	10.72 ± 1.42
Attention impairment	9.24 ± 1.12	9.40 ± 1.04

Symptomatology profile of patients

Mean SANS Total score at baseline in the active and sham groups was found to be 78.52 ± 11.58 and 74.64 ± 7.99 respectively. Higher mean scores for affective flattening and avolition were noted in the active group compared to the sham group. Higher mean scores for alogia and attention impairment were noted in the sham group compared to the active group. However, mean scores for anhedonia were found to be comparable in both the groups shown in Table 3.

Table 3: Baseline symptomatology profile (Active and Sham group).

SANS	Mean scores		Test of significance (χ^2)	p-value
	Active N=25 (n%)	Sham N=25 (n%)		
Total score	78.52 ± 11.58	74.64 ± 7.99		
Affective flattening	23.60 ± 6.37	20.84 ± 4.13		
Alogia	14.60 ± 2.32	15.72 ± 2.09	2.212	0.81
Anhedonia	17.84 ± 2.95	17.84 ± 2.42		
Avolition	13.20 ± 3.02	10.72 ± 1.42		
Attention impairment	9.24 ± 1.12	9.40 ± 1.04		

Table 4 and 5 shows total SANS scores reduced significantly after intervention in both active (78.52 ± 11.58 to 45.68 ± 5.52, p<0.001) and sham (74.64 ± 7.99 to 50.80 ± 4.77, p<0.001) rTMS arms on repeated measure ANOVA test. The Total SANS scores at baseline was found to be comparable in both active and sham groups. However, post-intervention SANS total scores were significantly lesser among subjects who received active rTMS compared to the sham rTMS group (a difference of 32.84 from baseline SANS score to 4 weeks post-intervention SANS scores in the active group as compared to a difference of 23.84 from baseline SANS score to 4 weeks post-intervention in the sham group).

Table 6 Fractional measure ANOVA revealed a significant group by time interaction among the SANS subdomains. The difference in post-intervention scores between active and sham groups was statistically significant in avolition (p-value<0.003), anhedonia (p-value<0.027) and attention (p-value<0.004) sub domains. Post-treatment, no significant difference between the two groups for any SANS subdomain except avolition (p-value<0.027) was seen after 2 weeks. Significant improvement was observed in anhedonia, attention, avolition and SANS total score in active group compared to the sham group after 4 weeks of intervention.

The mean CGI severity index (CGI-S) score at baseline was comparable between both the groups. However, a statistically significant reduction in CGI-S score was seen post-intervention (p-value=0.021) in the active group compared to the sham group shown in Table 7.

No statistically significant difference in CDSS scale scores in terms of depressive symptoms at any point of measurement was found between both the groups (p-value=0.227)

Table 4: Comparison of mean SANS total score (Active group).

Assessment timeline	Mean SANS total score	Change within groups	
		Pair	p-value
Baseline	78.52 ± 11.58	1 *vs.* 2	<0.001**
2 weeks	61.40 ± 7.85	2 *vs.* 3	<0.001**
4 weeks	45.68 ± 5.52	1 *vs.* 3	<0.001**

Table 5: Comparison of mean SANS total score (Sham group).

Assessment timeline	Mean SANS total score	Change within groups	
		Pair	p-value
Baseline	74.64 ± 7.99	1 *vs.* 2	<0.001**
2 weeks	60.36 ± 4.60	2 *vs.* 3	<0.001**
4 weeks	50.80± 4.77	1 *vs.* 3	<0.001**

Table 6: Mean SANS subdomain score comparison (Active and Sham group).

SANS	Mean scores						F-value	p-value
	Active			Sham				
	Baseline	2 weeks	4 weeks	Baseline	2 weeks	4 weeks		
Total score	78.52	61.4	45.68	74.64	60.36	50.8	9.818	0.001
Affective flattening	23.6	17.6	12.04	20.84	15.68	10.2	0.603	0.478
Alogia	14.6	11.08	7.84	15.72	12.44	9.8	1.612	0.211
Anhedonia	17.84	9.88	6.76	17.84	8.68	6.04	7.296	0.003
Avolition	13.2	15.04	12.72	10.72	15.32	14	3.965	0.027
Attention impairment	9.24	7.52	6.28	9.4	7.96	7.2	3.712	0.044

Table 7: Assessment of Cgi-S and Cdrs scales.

Scale	Active group			Sham group			Time × Group	
	Baseline	2 weeks	4 weeks	Baseline	2 weeks	4 weeks	F-value	P-value
SCDRS	3.64	2.88	1.72	4.24	3.28	2.4	1.368	0.227NS
CGI -S	5	3.84	3.32	4.88	3.92	3.6	4.176	0.021*

DISCUSSION

This randomized, sham-controlled study sought to determine the impact of adjunctive 20 Hz rTMS treatment over the left dorsolateral prefrontal cortex (Lt-DLPFC) on negative symptoms in schizophrenia patients receiving standard treatment. It found that the intervention had a positive impact on symptoms overall and improved quality of life and illness severity. Both active and sham participants got a total of 3000 pulses during one session, all at 110% motor threshold and with a 27-second inter-train delay. After rTMS intervention, significant differences between the active and sham treatment groups were observed in our study as determined by the SANS scale.

There were few studies published assessing effect of 20 Hz rTMS on Lt-DLPFC for negative symptoms of schizophrenia. Most of the studies published on 10 Hz rTMS and there are suggestions from literature that rTMS intervention with frequencies greater than 10 Hz might lead to better improvement in negative symptoms and this study provides further validation to these findings.

This study had two main components that might be viewed as improvements over the previous two studies and make the findings

of the present study more applicable: The highest number of pulses ever administered over one hemispheric of the brain to treat negative symptoms in schizophrenia was given to participants during each rTMS treatment course-60,000 pulses-under careful control with a sham coil. Additionally, negative symptoms were thoroughly evaluated using SANS and CDSS, which are intended to assess and distinguish depression from negative symptoms in patients with schizophrenia.

In the present study, the mean age of patients in active group and sham group were 27.36 ± 4.51 and 27.92 ± 4.15 respectively. Similar kind of studies done by Kumar N et al, in which the mean age of patients was 32 ± 9.20 and 30.8 ± 9.34 in active and sham group respectively [2]. In a study done by W.X Quan et al, the mean age of patients was 46.87 ± 7.87 and 46.87 ± 9.07 in active and sham group respectively which is not comparable with present study [4].

In the ongoing study, there were no sexual differences between the active and sham groups that were clinically meaningful. In our study, 56% of men and 44% of women were recruited in the active group, while 52% of men and 48% of women were included in the sham group. Singh et al. conducted a study that was identical to this one, enrolling 60% men and 40% women in the sham group and 54% men and 46% women in the active group [3].

Our study most of patient were unmarried. In active group 70% patients were unmarried and in sham group 64% patients were unmarried. Similar kind of study was done by Singh et al in which 54% patients were unmarried in both sham and active group. Another study done by Kumar N et al, in which 62% patients in both active and sham group were unmarried [2].

The majority of patients in the current study's active and sham groups were illiterate or merely receiving religious education, making up 56% and 64% of each group, respectively. Similar to a research by Kumar N et al, where 22% of the patients had uncertain educational status. According to a research by W. Quan et al, the average amount of education was 10 years. Wen et al. conducted a study in which the mean number of educational years was 9. Similar to studies by Kumar N et al. and Singh et al., the majority of patients in the current study-around 80% and 72% of patients in the active and sham groups, respectively-were unemployed. In the continuing study, the employment status of 44% of patients in the active group and 36% of patients in the sham group was unknown.

Majority of the patients were from urban background (56%) in both groups. Most of the patients were Muslims; 60% and 52% in active and sham group and from a nuclear family. In a similar study by Kumar N et al, it was found that 92% and 94% patients were Hindu in active and sham group respectively which is not comparable with present study.

Patients in our study were stabilized on antipsychotics for 6 weeks before being enrolled in the study. The majority of patients were on Clozapine (32%), Amisulpride (36%), or Olanzapine (24%), with the remainder using different medications. The patients in a similar study by Quan et al. were stabilized on atypical, conventional antipsychotics, and clozapine. Dlabac et al, conducted a different study in which patients were stabilized using Clozapine, Risperidone, and olanzapine [5]. To the best of our knowledge, this was a pioneering study in which 36% of patients were on Amisulpride.

Participants who receive sham rTMS also had statistically significant improvements after the intervention. One may speculate a possible placebo-effect in such a situation, whereby the mere setting of rTMS application showed some improvement among the subjects. Nevertheless, a clear statistically significant advantage in the improvement in negative symptoms was seen among participants randomized to active group as compared to the control group.

In the present study, the mean age of patients in active group and sham group were 27.36 years ± 4.51 years and 27.92 years ± 4.15 years respectively. Similar kind of studies done by Kumar N et al, in which the mean age of patients was 32 years ± 9.20 years and 30.8 years ± 9.34 years in active and sham group respectively. In a study done by W.X Quan et al in 2015 the mean age of patients was 46.87 years ± 7.87 years and 46.87 years ± 9.07 years in active and sham group respectively which is not comparable with present study.

The majority of patients in the current study's active and sham groups were illiterate or merely receiving religious education, making up 56% and 64% of each group, respectively. Similar to a research by Kumar N et al., where 22% of the patients had uncertain educational status. According to a research by Qan et al, the average amount of education was 10 years. Wen et al, conducted a study in which the mean number of educational years was 9. Similar to studies by Kumar N et al. and Singh et al., the majority of patients in the current study-around 80% and 72% of patients in the active and sham groups, respectively-were unemployed. In the continuing study, the employment status of 44% of patients in the active group and 36% of patients in the sham group was unknown.

Our study, compared with sham-rTMS, augmentation of antipsychotic medication with 20 sessions of active 20-Hz rTMS applied over Lt-DLPFC showed a significant reduction in negative symptoms when evaluated using SANS. The total SANS score reduced significantly after intervention in both active (78.52 ± 11.58 to 45.68 ± 5.528, $p<0.001$) as well as sham (74.64 ± 7.99 to 50.80 ± 4.77, $p<0.001$) rTMS arms. In a similar kind of study done by Kumar N et al, there was also significant reduction in SANS score after intervention in both active and sham group (60.6 ± 11.75 to 43.9 ± 12.67, $p<.01$) as well as sham (61.5 ± 13.69 to 50.5 ± 14.11, $p<.01$). In a similar study done by Quan et al, there was also significant reduction in SANS negative symptom score (p-value=0.017) in the active group as compared to sham study. In a similar kind of study done by Zhao et al, in which patients were given 20 Hz rTMS over DLPFC (20 sessions) and there was significant improvement in SANS score (p-value=0.031). In a similar study done by Kaiming Zhuo et al, there was significant improvement in negative symptoms as compared to sham group (p=0.021) [6]. In another study done by Na Wen et al, 20 sessions of 10 Hz active/sham rTMS over DLPFC (20 minutes per session, five times per week) was given and the active rTMS group outperformed the sham group in terms of improving negative symptoms (p=0.002). Novak and colleagues in 2006, who administered 20 Hz, total of 20,000 pulses unilaterally, while Barr and colleagues in 2012 applied 20 Hz, 15,000 pulses to each hemisphere [7,8]. Both studies failed to find any significant improvement ion negative symptoms.

Our study in the sub domains of SANS difference in post intervention scores between active and sham group is statistically significant in anhedonia (p-value=0.027), avolition (p-value=0.003) and attention (p-value=0.04) but not others. In a similar kind of study done by Kumar N et al, there was also significant reduction in affective flattening (p-value=<0.05) and avolition (p-value=<0.05). In a similar kind of study done by W.X.Quan et al, in 2015 and it also showed significant improvement in volition abulia

(p-value<0.05) and anhedonia/interest- social lack (p-value<0.01). In our study there was also significant improvement in attention (p-value (p-value=0.04) also which was not observed in previous studies.

Due to their overlapping characteristics, depression is a frequent confounder for the negative symptoms of schizophrenia. Furthermore, rTMS over the left DLPFC has been shown to be effective in treating depression. Therefore, by screening patients for depression, we attempted to account for this confounder. Additionally, the CDSS, a scale designed specifically for measuring depressive symptoms in adults with schizophrenia, was used to gauge the degree of depressive symptoms at baseline and assess changes, if any, over time. In our study there was no significant difference in the scores obtained on CDSS score and the two groups of participants did not differ in terms of depressive symptom (p value= 0.227). Similar kind of result was obtained by Singh et al, in which there was no significant difference in the scores of CDSS (p- value= 0.74). In another study done by Kumar N et al, showed similar results and the two groups did not differ in terms of depressive symptom (p-value=1.00).

Our study there was also significant improvement observed in the overall clinical condition of patients in the active group compared to sham group at the end of 20 sessions of rTMS, evaluated using CGI scores for severity of illness and CGI scores after 4 week was statistically significant (p-value=0.021). In a similar study done by Singh et al in 2020 there was significant difference in CGI-S Scores between two groups after intervention (p-value=0.01). In another study done by Similar kind of Kumar N et al, also showed significant difference in CGI-S scores between the two groups (p-value=<0.01) study done by Quan et al showed no significant difference in the CGI-S scores (p-value=0.132)

Except for a slight headache, localized scalp discomfort, and brief dizziness, all research participants took rTMS treatment well. No major side effects or adverse events were noted. Participants in the current trial were taking clozapine, however there were no recorded seizure episodes. According to a recent systematic review, HF-rTMS over the DLPFC can be provided safely to patients receiving supplementary treatment with various brain stimulation modalities [9-12]. There were no seizures recorded in any of the three prior RCTs that evaluated the impact of HF-rTMS on negative symptoms and that also included a small number of schizophrenia patients taking clozapine [13-15].

Limitations

Researchers all over the world believe no research is final and conceded with some limitations also. In this context, the present research has certain limitations as well, which should be addressed in near future. Limitations of our study are as follows:

Our study's primary drawback was the manual measurements we used to pinpoint the DLPFC on the scalp. Studies have revealed that neuro navigational approaches are more accurate in locating the stimulation site even though the "5 cm rule" has long been a common practice. Additionally, as directed by their clinicians, each of our study participants continued to receive their customary pharmacological therapies during the study time. One could contend that this could cause some confusion of the results. However, we could not discover any distinction between the drugs given to active group participants and sham group participants at the baseline. Additionally, we only included patients who had been taking stable drug doses for at least six weeks without any recent dose or medication adjustments. Hence, the chances of medicines being a confounder are low. Although the current study had a larger sample size than two previous studies using 20 Hz rTMS for treatment of negative symptoms in schizophrenia, the sample size was of 50 patients and it was mainly because of havoc of pandemic COVID-19 which led to lockdown twice during the study period. So, the findings of this study are based on a modest sample size, resulting in lower statistical power of the study and limiting the generalizability of study findings. There was no follow-up, which leaves open the question of prospective effects of rTMS over time in terms of decline, stabilization, or amplification.

Future directions

Research studies, combining both quantitative and qualitative research approaches are recommended to develop more comprehensive and effective study. The sample size should be increased to replicate our findings from study population to make it generalized for the whole population. The localization of DLPFC should be done by more precise method of neuronavigation-guided localization of DLPFC. Long term follow up should be carried out to know the long-term effect of rTMS on the negative symptoms of schizophrenia. rTMS treatment should be combined with neuroimaging that will provide more information about neural effects.

CONCLUSION

Our work allows us to conclude that high frequency (20 Hz) rTMS at 110% motor threshold with 3000 pulses per session administered over left DLPFC for 20 sessions over 4 weeks might be an effective augmentation strategy for the treatment of difficult to treat negative symptoms of schizophrenia. Our study found a significant reduction in negative symptoms as well as clinically significant improvement in all subdomains of SANS scale and overall clinical global improvement in patients with negative symptoms. This study adds to the existing literature with its robust design and large sample size as compared to previous studies despite few limitations and provides the possibilities for future research regarding administration of high frequency rTMS. High frequency rTMS is safe and well tolerated in patient with no serious side effects. This protocol can be used as standard protocol for patients with negative symptoms of schizophrenia as there was significant improvement in all 5 subdomains of SANS scale which was not shown by previous studies.

DECLARATIONS

Ethics approval and consent to participate

Ethical clearance was taken from JNMCH, AMU ethical committee, Ref No: IECJNMC/540.

Competing interests

There was no conflict of interest.

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